Small cell lung cancer

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Manchester Lung Cancer Group
Manchester Radiation Related Research Group

17th ESO-ESMO Masterclass
25th March 2018
Objectives

• Standard systemic treatment in stage IV SCLC
  • First line
  • Second line
  • Targeted agents and immunotherapy

• Radiotherapy
  • Thoracic radiotherapy (stage I-III and IV)
  • Combination with chemotherapy
  • PCI
  • Ongoing clinical trials
Introduction

- Incidence of SCLC is declining-less than 10-15% of all lung cancer cases *Govindan JCO 2006*
- One third present with limited stage disease
- Excellent responses to CT and RT but few patients will be long term survivors
- High risk of local relapse
- High risk of distant spread (brain)
How do we stage SCLC?

Veterans classification

Zelen. Cancer Chemother Rep 1973

Role of PET controversial. Thomson. Lung cancer 2010

TNM classification

8008 patients

Zelen. Cancer Chemother Rep 1973

Shepherd F. JTO 2007

Limited stage = T1-4 N0-3 M0
Systemic treatment

Background

Aggressive disease, excellent response to first-line but short-lived

2nd-line chemotherapy may produce tumour regression but the evidence for a clinical benefit is limited

Platinum-based rechallenge is commonly used for platinum-sensitive (TTP≥ 90d) disease

Standard of care
Cisplatinum-Etoposide

Meta-analysis 36 trials
- E vs P vs EP vs none
- EP better than other combinations

*Mascaux et al, Lung Cancer 2000*

Meta-analysis 29 trials 5530 patients (LS, ES)
- Platinum vs. no platinum
- No difference in 6, 12 or 24 month survival
- No difference OR rate
- Higher CR rate for platinum
- Higher toxicity rates with platinum

*Amarasena et al, Cochrane Library 2009*
The Christie NHS Foundation Trust

COCIS IPD meta-analysis
Carboplatin vs. cisplatin-based chemotherapy

- In poor prognosis &/or ES-SCLC
- Four eligible trials - total of 663 patients (329 cisplatin, 334 carboplatin)
- Median OS 9.6 months with cisplatin & 9.4 months with carboplatin (HR 1.08, 95% CI 0.92–1.27; p = 0.69)
- Haematological toxicity was higher with carboplatin, and non-haematological toxicity was higher with cisplatin
- Key conclusion: no survival difference between cisplatin- and carboplatin-based CT in this setting


Carboplatin- A reasonable alternative to cisplatin in patients with poor prognostic factors
Variations In Dose and Dose intensification

Variable: Standard vs. Experimental

Cumulative dose

DI

Number of cycles

Dose per cycle

Interval between cycles

No survival benefit

No survival benefit

modest survival benefit

Thatcher, JCO 2000

DI is used to define the drug dose delivered per time unit and is expressed as mg/m² per week

17th ESO-ECMO Masterclass Clinical Oncology
### Maintenance or consolidation therapy

- N = 3688, 14 RCTs
- All (n=21) HR 0.93 (0.87-1.00) p=0.05
- CT (n=11) HR 0.89 (0.81 0.98) p=0.02
- CT increased OS 1 yr by 9%, 2yr by 4%
- IFNα (n=4) HR 0.78 (0.64-0.96) p=0.02

> ‘Clinical impact of maintenance chemotherapy needs to be confirmed by further studies’

#### Table

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Maintenance n/N</th>
<th>Follow-up n/N</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>01 Chemotherapy</td>
<td></td>
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</tr>
<tr>
<td>Cullen 1969</td>
<td>12/16</td>
<td>14/16</td>
<td>0.48 (0.26 - 0.81)</td>
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<tr>
<td>Cullen 1969</td>
<td>25/29</td>
<td>29/32</td>
<td>0.47 (0.29 - 0.81)</td>
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<tr>
<td>Anonymous 1989</td>
<td>131/131</td>
<td>134/134</td>
<td>0.87 (0.69 - 1.11)</td>
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<tr>
<td>Byrne 1989</td>
<td>28/34</td>
<td>22/30</td>
<td>1.74 (1.00 - 3.03)</td>
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<tr>
<td>Ellinger 1990</td>
<td>24/25</td>
<td>21/25</td>
<td>1.67 (0.87 - 2.82)</td>
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<td>Ellinger 1990</td>
<td>18/18</td>
<td>17/18</td>
<td>1.77 (0.91 - 3.44)</td>
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<tr>
<td>Giaccone 1993</td>
<td>203/219</td>
<td>206/215</td>
<td>1.04 (0.86 - 1.26)</td>
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<tr>
<td>Johnson 1993</td>
<td>55/72</td>
<td>53/79</td>
<td>0.46 (0.32 - 0.67)</td>
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<tr>
<td>Beth 1996</td>
<td>56/65</td>
<td>52/64</td>
<td>0.94 (0.65 - 1.34)</td>
</tr>
<tr>
<td>Studier 1996</td>
<td>36/43</td>
<td>41/46</td>
<td>0.89 (0.57 - 1.39)</td>
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<tr>
<td>Schiller 2001</td>
<td>100/112</td>
<td>103/111</td>
<td>0.99 (0.75 - 1.30)</td>
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<tr>
<td>Hanna 2002</td>
<td>65/72</td>
<td>70/72</td>
<td>0.73 (0.52 - 0.93)</td>
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<tr>
<td>Han 2008</td>
<td>17/21</td>
<td>16/24</td>
<td>0.79 (0.40 - 1.60)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>775/859</td>
<td>770/856</td>
<td>0.89 (0.61 - 1.26)</td>
</tr>
</tbody>
</table>

| 02 Interferon-alpha   |                 |               |             |
| Mattson 1992          | 62/91           | 66/87         | 0.70 (0.50 - 0.98) |
| Kelly 1995            | 50/64           | 51/68         | 0.94 (0.64 - 1.39) |
| Tumenski 1997         | 12/14           | 11/12         | 0.92 (0.53 - 1.59) |
| Leblanc 1999          | 66/84           | 56/66         | 0.81 (0.55 - 1.17) |
| **Subtotal (95% CI)** | 190/253         | 184/235       | 0.78 (0.61 - 0.96) |

| 03 Interferon-gamma   |                 |               |             |
| Jaff 1994             | 49/51           | 36/49         | 1.20 (0.76 - 1.89) |
| Van Zandwijk 1997     | 64/65           | 54/62         | 1.03 (0.71 - 1.49) |
| **Subtotal (95% CI)** | 96/115          | 68/111        | 1.09 (0.82 - 1.46) |

| 04 Other biological agents |     |               |             |
| Shepherd 2002          | 194/268        | 197/286       | 1.01 (0.83 - 1.23) |
| Giaccone 2005          | 196/257        | 183/236       | 1.19 (0.96 - 1.46) |
| Arnold 2007            | 53/53          | 52/54         | 1.01 (0.66 - 1.69) |
| Pudil 2007             | 26/49          | 20/43         | 0.74 (0.49 - 1.12) |
| **Subtotal (95% CI)**  | 427/625        | 402/612       | 1.06 (0.92 - 1.26) |

| Total (95% CI)         | 1522/1835      | 1522/1835     | 0.93 (0.87 - 1.00) |
Second line chemotherapy

- Relapse >6 months post chemotherapy
  → re challenge with carboplatin - etoposide

- Relapse <3-6 months post chemotherapy
  → Anthracycline based chemotherapy (CAV)

- Relapse < 3 months post chemotherapy (‘refractory disease’)
  → RT or clinical trials

- New drugs
  - Topotecan vs BSC positive
  - Pico platinum vs BSC negative
  - Amrubicin vs topotecan (ACT1) positive RR and PFS, not OS
## New chemotherapy in SCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Drug</th>
<th>Design</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>JCOG 9511</td>
<td>Topoismerase</td>
<td>Irinotecan</td>
<td>PE vs PI*</td>
<td>Positive</td>
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<tr>
<td>SWOG 0124</td>
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<td>PE vs PI</td>
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<tr>
<td>HOG S0124</td>
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<td>PE vs P</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PE vs PI</td>
<td>Negative</td>
</tr>
<tr>
<td>Socinski</td>
<td>TS</td>
<td>Pemetrexed</td>
<td>PE vs Pem</td>
<td>Negative</td>
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<tr>
<td>Von Pawel</td>
<td>Topoisomerase</td>
<td>Topotecan</td>
<td>Topo vs CAV</td>
<td>Positive</td>
</tr>
<tr>
<td>O’Brien</td>
<td>Topoisomerase</td>
<td>Topotecan</td>
<td>Topo vs BSC</td>
<td>Positive</td>
</tr>
<tr>
<td>Fink</td>
<td>Topoisomerase</td>
<td>Topotecan</td>
<td>PE vs TE</td>
<td>Negative</td>
</tr>
<tr>
<td>SPEAR</td>
<td>Platinum</td>
<td>Picoplatin</td>
<td>Pico vs BSC</td>
<td>Negative</td>
</tr>
<tr>
<td>EORTC 08062</td>
<td>Anthracycline</td>
<td>Amrubicin</td>
<td>Amb vs AmbC vs PE</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Meta-analysis PI vs PE (significant heterogeneity between studies)

- Jiang et al. JTO 2010  PI vs PE (better RR and OS)
- Shao J Thor Oncol 2012 (updated ) PI vs PE (better OS)
# SCLC & anti-angiogenics

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Agent</th>
<th>Design</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>NCI-C/EORTC</td>
<td>MMP</td>
<td>Marimastat</td>
<td>+/- Maintenance</td>
<td>Negative</td>
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<tr>
<td>BAYER</td>
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<td>BAY 12-9566</td>
<td>+/- Maintenance</td>
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<tr>
<td>ECOG CALGB</td>
<td>VEGF</td>
<td>BEV (B)</td>
<td>Chemo + B</td>
<td>Positive</td>
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<tr>
<td>HOG</td>
<td></td>
<td></td>
<td>Chemo + B</td>
<td>Negative</td>
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<tr>
<td></td>
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<td>Chemo + B</td>
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<tr>
<td>LLCG</td>
<td>Vascular stabilizer</td>
<td>Thalidomide</td>
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<tr>
<td>NCI-C</td>
<td>VEGFR TKi</td>
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<tr>
<td>NCI</td>
<td>VEGFR TKi</td>
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# SCLC & targeted therapy

<table>
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<th>Target</th>
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</tr>
<tr>
<td>Langer</td>
<td>Bcl-2</td>
<td>Obatoclax</td>
<td>Chemo +/-</td>
<td>Negative</td>
</tr>
<tr>
<td>ECOG</td>
<td>mTOR</td>
<td>CCI-779</td>
<td>+/- Maintenance</td>
<td>Negative</td>
</tr>
<tr>
<td>HOG</td>
<td>EGFR</td>
<td>gefitinib</td>
<td>Monotherapy</td>
<td>Negative</td>
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<tr>
<td>Johnson</td>
<td>Kit</td>
<td>Imatinib</td>
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<td>Negative</td>
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<tr>
<td>Krug</td>
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<tr>
<td>Dy</td>
<td></td>
<td></td>
<td>Monotherapy</td>
<td>Negative</td>
</tr>
<tr>
<td>EORTC</td>
<td>GD-3</td>
<td>BEC2/BCG</td>
<td>+/- Maintenance</td>
<td>Negative</td>
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<tr>
<td>SWOG</td>
<td>Proteosome</td>
<td>Bortezomib</td>
<td>Monotherapy</td>
<td>Negative</td>
</tr>
<tr>
<td>SWOG</td>
<td>RAS/VEGF</td>
<td>Sorafenib</td>
<td>Monotherapy</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Sharp. EJC 2016
NSCLC and SCLC are highly mutated

Lung Cancers from smokers have 10x somatic mutations vs non-smokers

Immune Checkpoint Blockade
Ipilimumab (anti-CTLA4 monoclonal antibody)

- n = 130
- Chemo naive
- Carboplatin + taxol +/- ipilimumab 10mg/kg
- 1:1:1 phased, concurrent or control
- Median OS 12.9 vs. 9.1 vs. 9.9 months (HR=0.75; p=0.13)
- grade 3/4 immune related AEs 17 vs 21 vs 9%

Suggest further investigation of ipilimumab in ED-SCLC

Reck et al Annals Oncol 2013
Ipilimumab in ES SCLC

N = 1132
Chemo naïve
Platinum/etoposide
+/- ipilimumab/placebo 10mg/kg x4 (cycle 3-6) → ipi/placebo maintenance every 12 w

No difference in OS (11 vs 10.9 mos)

No difference in PFS (4.6 vs 4.4 mos)

Anti-CTLA-4 antibody plus chemotherapy does NOT WORK

Reck et al, JCO 2016
Key inclusion criteria
- SCLC
- Progressive disease
- ≥1 prior therapy including first-line platinum-based therapy
- Unselected by PD-L1 expression (n=128)

Primary endpoint
ORR

- Grade 3-4 adverse events: 15% (NIVO) vs 34% (NIVO+IPI (3 mg/kg))
- ORR was 15% (NIVO) and 25% (NIVO+IPI) for evaluable pts

Pembrolizumab in Patients With ES SCLC: Phase Ib KEYNOTE-028

Study objective
- To assess the efficacy and safety of pembrolizumab, an anti-PD-1 monoclonal antibody, in patients with PD-L1+ SCLC

Key patient inclusion criteria
- SCLC
- PD-L1 positivity
- Failure of standard therapy
- ≥1 measurable lesion
- ECOG PS 0 or 1
- Absence of autoimmune disease or interstitial lung disease
(n=20)

Primary endpoints
- ORR per RECIST v1.1, safety

Secondary endpoints
- PFS, OS, duration of response

1Defined as membranous PD-L1 expression in ≥1% of cells in tumour nests or positive strands in stroma.
2Every 8 weeks for the first 6 months, every 12 weeks thereafter.

Progression-Free Survival (%)

Overall Survival (%)

Ott. JCO 2017
Ongoing trials (recruiting or in FU) 
TO UPDATE

• With RT
  • NCT02402920 -Phase I Trial of Pembroluzimab and Concurrent CTRT for the Elimination of Small Cell Lung Cancer (LS and ES)

• First line
  • NCT02580994- Pembrolizumab in Untreated Extensive SCLC (REACTION)
  • NCT02763579-Atezolizumab in Untreated Extensive SCLC

• Second line
  • NCT02481830-Efficacy Study of Nivolumab or Chemotherapy (Topotecan or Amrubicin) in Relapsed Small-cell Lung Cancer (CheckMate 331)

• Maintenance
  • NCT02359019-Phase II Pembrolizumab in ES SCLC After Completion of Combination Chemotherapy
Conclusions

• Platinum based therapy remains a standard of care
• Many newer combinations as good, but none convincingly better
• Topotecan licensed for 2nd line treatment
• Treatment remains palliative
  • Improve QOL, control symptoms
  • Minimise toxicity
• Immunotherapy - a game-changer in SCLC?
  • Need data on selection of patients
Radiotherapy
The Christie NHS Foundation Trust

• 75 year old male
• PMH HBP, mild COPD, ex smoker 30 PY
• PS1, MRC RS 1

Presented with a cough and SOB on exertion

• FEV1 55% predicted, KCO 46% predicted

• Bronchoscopy—tumour obstructing the L main bronchus

• CT thorax & abdomen

Mass LUL Station 4R, 4L, 5 and 7 lymph nodes

• CT brain clear

Stage I-III SCLC - clinical case

Treatment options

• Sequential CTRT
• Concurrent CTRT
• Dose fractionation
  – 40 Gy/15F
  – 45/30F BD
  – 50-55 Gy/20F
  – >60 Gy/30+F
• 3DRT or IMRT?
• PCI?
Current evidence

• CTRT > CT (Pignon, Warde)

• Concurrent CTRT > sequential CTRT (Takada)

• Early RT > late RT (Fried, Cochrane review)

• Best survival results achieved with early BD concurrent CTRT (Turrisi, Jeremic, Faivre-Finn)

• Cisplatin Etoposide is the standard chemotherapy in combination with RT. Can be delivered at full dose with thoracic RT with an acceptable toxicity profile
Role of thoracic radiotherapy
Meta-analyses

  - 13 randomised trials
  - 2140 patients
  - 3 year survival
    - 8.9% CT alone
    - 14.3% CT+RT
  - Thoracic RT benefited more younger patients
    - RR of death in the CTRT as compared with CT group
      - 0.72 for patients < 55 years old (0.56-0.93)
      - 1.07 (0.70-1.64) for patients over 70
  - 14% reduction in risk of death, p = 0.001

- Warde et al. *JCO* 1992

- Limitations
  - Response to treatment assessed on CXR
  - Dated RT techniques (2D)
### Timing of thoracic RT with chemotherapy

7 RCTs
Advantage of early (<9 weeks) radiotherapy

<table>
<thead>
<tr>
<th></th>
<th>2 yr %</th>
<th>NNT for benefit</th>
<th>P</th>
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<tbody>
<tr>
<td>All (1524)</td>
<td>+5.2 [0.6-9.7]</td>
<td>20</td>
<td>0.03</td>
</tr>
<tr>
<td>Platinum</td>
<td>+9.8 [3.8-15.9]</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>Platinum+ HART</td>
<td>+16.7 [9.4-26]</td>
<td>6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Fried et al. J Clin Oncol 2004*
Standard of care for LS-SCLC
Intergroup 0096

Once daily Thoracic Irradiation
D1  D3  D22 D24  D43 D45  D64 D66
RT 45Gy/33D/25F

Twice daily Thoracic Irradiation
D1  D3  D22 D24  D43 D45  D64 D66
RT 45Gy/19D/30F

CR → PCI

If < CR
No PCI

Registration
Randomisation
Limited Stage Small Cell Lung Cancer
Restage

Complication and no. of radiation treatments per day

P < 0.001 by log-rank test

CONVERT

multinational, phase III randomised study

RT 45Gy/30F/19D
Twice-daily (BD) thoracic RT

RT 66Gy/33F/45D
Once-daily (OD) thoracic RT

Chemotherapy
4 to 6 cycles
Cisplatin 25mg/m² D1-3 or
75mg/m² D1
Etoposide 100mg/m² D1-3

Stratification factors
Centre
No. of cycles chemo: 4 vs. 6
PS: 0,1 vs. 2

Registration
Randomisation

Limited Stage Small Cell

RTP after randomisation
RT started on D22 cycle 1
3DCRT or IMRT
No ENI
QA programme

PS 0-2
No age limit

SD, PR, CR → PCI

547 patients
8 countries
75 centres

If <SD → no PCI

Chemotherapy
Radiotherapy

17th ESO-ESMO Masterclass Clinical Oncology
Overall survival

Median follow-up: 45 months

- Primary objective: overall survival
- Trial hypothesis
  - Expected survival BD arm 44%
  - Projected survival OD arm 56%

<table>
<thead>
<tr>
<th>Overall survival (n=543)</th>
<th>BD</th>
<th>OD</th>
<th>Log-rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>30 (24-34)</td>
<td>25 (21-31)</td>
<td>p=0.14</td>
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<tr>
<td>1-year</td>
<td>83% (78-87)</td>
<td>76% (71-81)</td>
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<tr>
<td>2-year</td>
<td>56% (50-62)</td>
<td>51% (45-57)</td>
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<tr>
<td>3-year</td>
<td>43% (37-49)</td>
<td>39% (33-45)</td>
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<tr>
<td>5-year</td>
<td>34% (27-41)</td>
<td>31% (25-37)</td>
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</table>

Faivre-Finn. Lancet Oncol 2017
# Acute Toxicity

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Arm</th>
<th>N</th>
<th>Median (Range)</th>
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<tbody>
<tr>
<td>Lung V5 (%)</td>
<td>BD</td>
<td>246</td>
<td>56.2 (7.2-88.5) 60.8 (7.0-91.6)</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>234</td>
<td></td>
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<tr>
<td>Lung V20 (%)</td>
<td>BD</td>
<td>252</td>
<td>23.2 (0.1-35.4) 28.8 (8.0-40.5)</td>
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<tr>
<td></td>
<td>OD</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Heart (% total dose)</td>
<td>BD</td>
<td>240</td>
<td>2.0 (0-45.3) 1.4 (0-36.2)</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>Spinal cord (max dose, Gy)</td>
<td>BD</td>
<td>251</td>
<td>32.0 (1.3-45.8) 41.7 (1.3-52.6)</td>
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<tr>
<td></td>
<td>OD</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>Oesophagus (max dose, Gy)</td>
<td>BD</td>
<td>248</td>
<td>45.7 (0.7-64.4) 65.9 (2.2-71.7)</td>
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<tr>
<td></td>
<td>OD</td>
<td>236</td>
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</tr>
<tr>
<td>Oesophagus V35 (%)</td>
<td>BD</td>
<td>246</td>
<td>34.0 (0-76.5) 38.8 (0-82.8)</td>
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<td>OD</td>
<td>230</td>
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</table>

<table>
<thead>
<tr>
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<th>BD (n=254)</th>
<th>OD (n=256)</th>
<th>p</th>
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<tbody>
<tr>
<td>AE (grade)</td>
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</tr>
<tr>
<td>1-2</td>
<td>1-2</td>
<td>1-2</td>
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<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
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<tr>
<td></td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td></td>
<td>n (%)</td>
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<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>159 (62.6)</td>
<td>46 (18.1)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>(max dose, Gy)</td>
<td></td>
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<tr>
<td></td>
<td>(18.1)</td>
<td>(0.4)</td>
<td></td>
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<tr>
<td>Pneumonitis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>51 (20.1)</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
<td>1</td>
</tr>
<tr>
<td>(max dose, Gy)</td>
<td></td>
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<tr>
<td></td>
<td>(1.2)</td>
<td>(0.4)</td>
<td>(0.4)</td>
</tr>
<tr>
<td></td>
<td>49 (19.1)</td>
<td>3 (1.2)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.4)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
</tbody>
</table>

1 patient in each arm not assessable for oesophagitis, 6 patients for pneumonitis
*1 patient in BD arm and 2 patients in OD arm (1 received sequential CTRT) died from radiation pneumonitis

Faivre-Finn. Lancet Oncol 2017
Conclusions

- Radiation-related toxicities were lower than expected likely due to the use of modern RT techniques
- Survival in both arms was higher than previously reported
- **BUT** OD RT did not result in a superior survival or worse toxicity than BD RT
- 45Gy in 30 # BD should continue to be regarded as standard of care because
  - CONVERT is not an equivalence trial
  - However OD RT (66 Gy in 33 fractions) can be considered an alternative regime BD RT cannot be delivered

Faivre-Finn. Lancet Oncol 2017
Targeted agents and RT

Phase II - 29 LS-SCLC patients recruited

Early trial closure

Two patients developed tracheoesophageal fistulae
One patient died from an aerodigestive hemorrhage

Spigel et al. J Clin Oncol 2010
The Christie NHS Foundation Trust

Chemo-Radiotherapy:
cis-/carboplatin + etoposide
4 cycles

Biomaterial for translational research:
Consolidation vs observation:
induction maintenance

max 1 year
combination nivolumab/ipilimumab
nivolumab
observation

LD SCLC

Screening:

RT (Thoracic Radiotherapy)
accelerated schedule preferred
start: day 1 of chemo cycle 1
day 1 of chemo cycle 2

Tumour evaluation:

cancer
PD no
PD yes
off

R

Week
from start of chemotherapy
3 6 9

Serum
Whole blood
Biopsy: FFPE block or slides

RT (Thoracic Radiotherapy)

FDG-PET-CT or CT

Brain MRI or CT

CT scans for tumour assessment:
- up to 18 months: every 9 weeks
- up to 2 years: every 12 weeks
- years 3 & 4: every 6 months
- at 5 years

At progression:

Voluntary re-biopsy?
FFPE block

11th ESO-ESMO Masterclass Clinical Oncology
Prophylactic cranial irradiation in LS -SCLC

- **Why PCI?**
  - Major risk of spread to brain-50 to 60%
  - Eradicates micrometastatic disease
  - PCI can reduce the risk of spread by 50%
  - PCI improves survival (6% @ 3 years)
    - *Auperin N Engl J Med 1999*

- **When?**
  - After concurrent CTRT
  - With consolidation thoracic RT if sequential CTRT is given
    - *Blanchard. Curr Opinion Oncol 2010*

- **Toxicity**
  - lethargy
  - raised ICP → steroids
  - scalp reaction, hair growth will be delayed
  - Late toxicity?

- **Significant neurocognitive impairment prior to PCI (~50%)**

- **Multiple confounding factors interfering with the evaluation of late toxicity**

- **No reports of significant increased long term neurological sequelae in RCTs**
  - *Gregor. Eur J Cancer 1997*

- **Standard dose fractionation-25 Gy in 10 fractions**
Progress in stage I-III SCLC

CT alone  <10
Seq CTRT  10-15
ConCTRT  20-25
BD CTRT  25
CONVERT BD  34

5 year survival (%)

Median Survival (months)

17th ESO-ESMO Masterclass Clinical Oncology
Prophylactic cranial irradiation in stage IV SCLC
EORTC 08993-22993

Chemotherapy (4-6 cycles)

- No response
- Any response

Random

Brain imaging no mandated

PCI
20-30 Gy in 5-12 fractions

No PCI

< 5 weeks
4-6 weeks

PS 0-2
Age ≤75

N=286

**Prophylactic cranial irradiation in stage IV SCLC**

**EORTC 08993-22993**

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**Symptomatic brain metastases**

- **1 year**: 14.6% vs. 40.4%
- **HR**: 0.27 (0.16-0.44)  \( p < 0.001 \)

**Overall survival**

- **1 year**: 27.1% vs. 13.3%
- **HR**: 0.68 (0.52-0.88)  \( p = 0.003 \)

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Immune Checkpoint Blockade

Ipilimumab (anti-CTLA4 monoclonal antibody)

- Rationale-The T cell attack can be turned off by stimulating the CTLA4 receptor

- n = 130
- Carboplatin + taxol +/- ipilimumab 10mg/kg
- 1:1:1 phased, concurrent or control
- Median OS 12.9 vs. 9.1 vs. 9.9 months (HR=0.75; p=0.13)
- grade 3/4 immune related AEs 17 vs 21 vs 9%

Reck et al Annals Oncol 2013
Japanese PCI-study ES SCLC

Primary endpoint: Overall survival
Planned n=330 (299 deaths)
Trial closed after interim analysis after 50% inclusion
111 out of 299 (37%) deaths observed (n=224)
Trial was stopped due to futility (<0.1% showing OS benefit)

Japanese PCI-study ES SCLC


- 1-year cumulative incidences of BM were 32.9% and 59.0%
- Salvage brain-directed radiotherapy for BM was employed in 46% and 83%

Limited QoL and neurocognitive function data
Thoracic radiotherapy in stage IV SCLC-CREST study

ES-SCLC, WHO PS 0-2, no upper age limit

4-6 platinum-based chemotherapy

Any response

Stratification:
- Centre
- Presence of intrathoracic disease

RANDOMIZE

TRT (30 Gy in 10 Fr)

PCI

PCI

No TRT

PCI

PCI

N=498

Slotman. Lancet 2014
Thoracic radiotherapy in stage IV SCLC-CREST study

Median follow up 24 months

12 months (95% CI)
Thoracic RT : 33% (27–39)
No Thoracic RT : 28% (22–34)
HR = 0.84 (95%CI 0.69-1.01)
p=0.066

24 months (95% CI)
Thoracic RT : 13 (8.8 – 18.7)
No Thoracic RT : 3 (1.5 – 7.6)
p=0.004

Survival difference @
18 Months: p=0.03
24 Months: p=0.004

Grade 3+ toxicity<5%
SUMMARY

- For clinical guidelines: ESMO Ann Oncol 2010 and 2013
  NCCN Thorax 2013

- Platinum etoposide is still standard
- Some newer drugs appear as effective as platinum, but none are better
- No clear role for dose intensification or maintenance
- A breakthrough for targeted therapy is still awaited…..
- Immunotherapy - a game changer?

- Progress has been made with RT!!
- Results of CONVERT confirm BDRT as standard of care