Updates in Malignant Pleural Mesothelioma and Small Cell Lung Cancer

Steven Kao
BHB MBChB PhD FRACP
Medical Oncology Staff Specialist
Conflicts of Interest

• **Served on Advisory Boards**: AstraZeneca; Pfizer; Boeringher

• **Honorarium to my institution**: MSD, BMS, Roche, AstraZeneca, Pfizer, Boeringher

• **Travel Support**: BMS, Roche, AstraZeneca
Outline

• Malignant pleural mesothelioma
  - Treatment strategies in unresectable/inoperable disease
  - Treatment strategies in resectable disease

• Small cell lung cancer
  - Extensive stage disease
  - Limited stage disease
Malignant Pleural Mesothelioma (MPM)
Epidemiology – Worldwide Trends

Not accounting for projections in Asia
Estimated future cases for Japan alone is 66,000 over 50 years
In China, the numbers will be substantially more*

Clinical Features – High Symptom Burden

- Insidious onset before chest pain (60%) or breathlessness (60%)
- Other symptoms: cough, weight loss, fever/sweats (<30%)
- Pleural effusion in up to 95%
- Mean time from symptoms to diagnosis: 2-3 months

Robinson et al. Lancet 2005;366:397
General Treatment Algorithm

Staging and Medical Work-Up

Stage I-III
- Multimodality Therapy
- Medically Inoperable
  - Systemic Therapy
    - First line:
      - Cisplatin + pemetrexed
      - Cisplatin + pemetrexed + bevacizumab
    - Second line:
      - Vinorelbine

Observation
- Non-bulky disease
- Minimal/no symptoms
- Epithelioid histology

Therapeutic clinical trials are optimal at all branches
Unresectable and/or Inoperable Disease

Staging and Medical Work-Up

Stage I-III
- Medically Inoperable

Stage IV
- Systemic Therapy
  First line:
  - Cisplatin + pemetrexed
  - Cisplatin + pemetrexed + bevacizumab
  Second line:
  - Vinorelbine

Three Trials Worth Remembering
Unresectable and/or Inoperable Disease

Staging and Medical Work-Up

Stage I-III
- Medically Inoperable

Stage IV
- Systemic Therapy
  - First line:
    - Cisplatin + pemetrexed
  - Second line:
    - Cisplatin+pemetrexed + bevacizumab
  - Vinorelbine

EMPHASIS Trial
The Trial That Changed Our Outlook on Chemotherapy

456 patients

- **Pemetrexed** 500 mg/m² q 21D
- Cisplatin 75 mg/m² q 21D

- **Primary objective:** OS (HR = .67)

- **Placebo** q 21D
- Cisplatin 75 mg/m² q 21D

**Stratification:** Performance status, histology, gender, WBC, disease measurability, baseline homocysteine

Vogelzang et al. JCO 2003
Cisplatin + Pemetrexed Improves Overall Survival

Median cycles of cisplatin/pemetrexed received was 6

Vogelzang et al. JCO 2003
Cisplatin/Pemetrexed Improves QoL

Unresectable and/or Inoperable Disease

Staging and Medical Work-Up

Stage I-III
Medically Inoperable

Stage IV

Systemic Therapy

First line:
- Cisplatin + pemetrexed
- Cisplatin+pemetrexed + bevacizumab

Second line:
- Vinorelbine

MAPS Study
MAPS (the Mesothelioma Avastin Cisplatin Pemetrexed Study)

Open-label, multi-centre randomized phase II-III trial

- Malignant Pleural Mesothelioma (MPM)
- Histologically proven
- PS= 0-2
- No cardiovascular comorbidity
- Chemonaive

Without cross-over allowed

Group A

Pemetrexed 500 mg/m² D1
Cisplatin 75mg/m² D1
6 cycles, Q21D

Group B

Pemetrexed 500 mg/m² D1
Cisplatin 75mg/m² D1
Bevacizumab 15 mg/kg D1
6 cycles, Q21D

Maintenance Bevacizumab
15 mg/kg D1, Q21D
until progression

Surveillance

Stratification: center, histology (epithelioid vs. sarcomatoid/mixed), PS (0-1 vs. 2), smoking status (active vs. never-smoker)

Zalcman et al. Lancet 2016;387:1405
Addition of Bevacizumab Improves Overall Survival (1° Endpoint)

Median 18.8 v 16.1 mo
Unresectable and/or Inoperable Disease

Staging and Medical Work-Up

Stage I-III
- Medically Inoperable
  - Systemic Therapy
    - First line:
      - Cisplatin + pemetrexed
      - Cisplatin + pemetrexed + bevacizumab
    - Second line:
      - Vinorelbine

Stage IV

MS01 Trial (extrapolation)
MS01 Trial (Total of 840 Pts Planned)

409 patients randomised

136 assigned to ASC
132 died
4 alive
136 analysed for primary outcome of overall survival

137 assigned to ASC+MVP
Chemotherapy received:
5 received 0 cycles
11 received 1 cycle
16 received 2 cycles
16 received 3 cycles
85 received 4 cycles
4 data outstanding
137 analysed for primary outcome of overall survival

136 assigned to ASC+V
Chemotherapy received:
4 received 0 cycles
31 received 1–3 cycles
26 received 4–6 cycles
7 received 7–9 cycles
68 received 10–12 cycles
136 analysed for primary outcome of overall survival

MVP = mitomycin, vinblastine, cisplatin
V = vinorelbine 30mg/m² weekly for 12 weeks

Muers et al. Lancet 2008
Overall Survival

Median OS: 7.6 vs. 9.5 months (ASC vs. ASC + V) HR=0.8, p=0.08

Muers et al. Lancet 2008
Unresectable and/or Inoperable Disease

Staging and Medical Work-Up

Stage I-III

Medically Inoperable

Stage IV

Systemic Therapy

First line:
- Cisplatin + pemetrexed
- Cisplatin + pemetrexed + bevacizumab

Second line:
- Vinorelbine

Therapeutic clinical trials are optimal at all branches
Unresectable and/or Inoperable Disease

Staging and Medical Work-Up

Stage I-III

Stage IV

Medically Inoperable

Systemic Therapy

First line:
- Cisplatin (carboplatin) + pemetrexed
- Cisplatin + pemetrexed + bevacizumab

Second line:
- Vinorelbine

 Carboplatin
Equivalence
## Expanded Access Programme Results

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>843</td>
<td>861</td>
</tr>
<tr>
<td>RR</td>
<td>26%</td>
<td>21.7%</td>
</tr>
<tr>
<td>1 year survival</td>
<td>63%</td>
<td>64%</td>
</tr>
<tr>
<td>TTP</td>
<td>7 months</td>
<td>6.9 months</td>
</tr>
<tr>
<td>Grade III/IV neutropenia</td>
<td>24%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Carboplatin is a reasonable choice of platinum partner, particularly where cisplatin is contraindicated

Unresectable and/or Inoperable Disease

Staging and Medical Work-Up

Stage I-III

Medically Inoperable

Stage IV

Systemic Therapy

First line:
• Cisplatin (carboplatin) + pemetrexed x 6C
• Cisplatin+pemetrexed + bevacizumab

Second line:
• Vinorelbine
Retrospective Experience in 2\textsuperscript{nd} Line Setting from Memorial Sloan Kettering Cancer Centre

N = 60

URGENT NEED TO IMPROVE TREATMENT OPTIONS in MPM

Zauderer et al. Lung Cancer 2014
## Single Agent PD1/PD-L1 Blockade in Mesothelioma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Keynote-028&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Uni of Chicago&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NivoMes&lt;sup&gt;3&lt;/sup&gt;</th>
<th>MERIT (Japan)&lt;sup&gt;4&lt;/sup&gt;</th>
<th>JAVELIN meso&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Avelumab</td>
</tr>
<tr>
<td>PD-L1 selection</td>
<td>≥ 1%</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>no of patients</td>
<td>25</td>
<td>64</td>
<td>34</td>
<td>34</td>
<td>53</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>92%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Responses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>22%</td>
<td>15%</td>
<td>29%</td>
<td>9.4%</td>
</tr>
<tr>
<td>SD</td>
<td>52%</td>
<td>41%</td>
<td>35%</td>
<td>39%</td>
<td>47.2%</td>
</tr>
<tr>
<td>PD</td>
<td>16%</td>
<td>?</td>
<td>50%</td>
<td>32%</td>
<td>?</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>5.4</td>
<td>4.1</td>
<td>3.6</td>
<td>6.1</td>
<td>3.9</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>18</td>
<td>11.5</td>
<td>Not reported</td>
<td>NR</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>

## Combination Immunotherapy in Mesothelioma

<table>
<thead>
<tr>
<th>Trial</th>
<th>MAPS-2(^1)</th>
<th>NIBIT-Meso(^2)</th>
<th>INITIATE(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Nivolumab + ipilimumab</td>
<td>nivolumab</td>
<td>Tremelimumab + durvalumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nivolumab + ipilimumab</td>
</tr>
<tr>
<td>PD-L1 selection</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No of patients</td>
<td>57</td>
<td>57</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>No</td>
<td>Some</td>
<td>no</td>
</tr>
<tr>
<td>Responses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>24.2%</td>
<td>17.5%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>SD</td>
<td>27.4%</td>
<td>22.2%</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47%</td>
</tr>
<tr>
<td>PD</td>
<td>37.1%</td>
<td>57.1%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not reported</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>5.6</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not reported</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not reported</td>
</tr>
</tbody>
</table>

1st Line Immunotherapy Trials

• DREAM\textsuperscript{1}
  - Phase 2 single arm
  - Cisplatin 75mg/m\textsuperscript{2} + pemetrexed 500mg/m\textsuperscript{2} + durvalumab 1125mg Q3w x6 cycles followed by durvalumab 1125mg Q3w x52 w
  - N=54
  - PFS6 = 57%

• CheckMate-743\textsuperscript{2}
  - Randomised phase 3, 2 arms
  - Nivolumab + ipilimumab vs. pemetrexed and cisplatin or carboplatin
  - N=600
  - Co-primary endpoint: OS, PFS

• CCTG Trial\textsuperscript{3}
  - Randomised phase 2, 3 arms
  - Cisplatin/pemetrexed vs cisplatin/pemetrexed + pembrolizumab vs pembrolizumab
  - N=126
  - Primary endpoint: PFS

1. Nowak et al. World Lung 2018; 2. NCT02899299; 3. NCT02784171
Resectable Disease

Staging and Medical Work-Up

Stage I-III

Multimodality Therapy

Therapeutic clinical trials are optimal at all branches
## International Prospective Studies in Extrapleural Pneumonectomy (EPP)

<table>
<thead>
<tr>
<th>Author</th>
<th>Stage</th>
<th>Number of patients</th>
<th>Induction Chemo</th>
<th>EPP</th>
<th>RT</th>
<th>ITT Median survival (months)</th>
<th>EPP operative mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weder, 2004</td>
<td>T1-3 N0-2</td>
<td>19 (cis/gem x3)</td>
<td>16 (84%)</td>
<td>13 (68%)</td>
<td>23</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Weder, 2007</td>
<td>T1-3 N0-2</td>
<td>61 (cis/gem x4)</td>
<td>45 (74%)</td>
<td>36 (59%)</td>
<td>19.8</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>Rea, 2007</td>
<td>T1-3 N0-2</td>
<td>21 (carbo/gem x4)</td>
<td>17 (81%)</td>
<td>15 (71%)</td>
<td>25.5</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Flores, 2006</td>
<td>T-43 N0-2</td>
<td>19 (cis/gem x4)</td>
<td>9 (47%)</td>
<td>8 (42%)</td>
<td>19</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Krug 2009</td>
<td>T1-3 N0-2</td>
<td>77 (cis/pem x4)</td>
<td>57 (74%)</td>
<td>44 (57%)</td>
<td>16.8</td>
<td>3.7%</td>
<td></td>
</tr>
<tr>
<td>Van Schil, 2010</td>
<td>T1-3 N0-1</td>
<td>59 (cis/pem x3)</td>
<td>42 (73%)</td>
<td>38 (64%)</td>
<td>18.4</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td>256</td>
<td>186 (73%)</td>
<td>154 (60%)</td>
<td>17-25.5</td>
<td>0-5%</td>
<td></td>
</tr>
</tbody>
</table>

Randomised EPP Trial

Median survival:
14.4 months (EPP arm) vs. 19.5 months (no EPP arm)
HR between EPP and no EPP groups = 1.9, p=0.082
Extended Pleurectomy/Decortication (P/D)

- MARS2 (ClinicalTrials.gov NCT02040272)
  - Feasibility study comparing extended PD vs no extended PD following cisplatin/pemetrexed chemotherapy
    - Ability to randomise 50 patients within the first 24 months or to recruit 25 patients within any 6 month period

- EORTC 1205 (ClinicalTrials.gov NCT02436733)
  - Primary endpoint: Rate of success to complete the full treatment at 20 weeks
    - Full protocol treatment
    - Alive and no PD No persisting G3/4 toxicities (CTCAE V 4.0)
Practice Points in MPM in 2018

• Resectable disease
  - No high level evidence – ? EPP or extended P/D
  - Multimodal therapy incorporating chemotherapy and surgery - a reasonable option in highly selected patients
  - Ideally in the setting of clinical trial; otherwise highly specialist surgical centres

• Unresectable disease
  - First line setting:
    • 6 cycles of cisplatin (carboplatin) + pemetrexed without maintenance
    • 6 cycles of concurrent cisplatin/pemetrexed + bevacizumab followed by maintenance bevacizumab
  - Second line setting: No optimal regimen
    • Vinorelbine the default option
    • Pembrolizumab seems promising – reasonable alternative to vinorelbine

• Watch the space:
  - Immunotherapy combo or chemotherapy/immunotherapy combo
Small Cell Lung Cancer (SCLC)
Introduction

• Accounts for 10-15% of newly diagnosed lung cancer
  - Incidence declining
• Majority (>95%) associated with tobacco smoking
• 1/3 present with limited stage only
• Rapid doubling times and early propensity to metastasise
• Initial sensitivity to chemotherapy with 60-80% RR
• 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

• Limited vs. Extensive

• Based on encompassable radiation field

TNM Classification

• Limited stage = T1-4 N0-3 M0
Treatment Algorithm in SCLC in 2018

SCLC

Limited Stage

Chemoradiation

- Very Fit: Concurrent Cisplatin + etoposide with BD RT
- Fit: Concurrent Cisplatin + etoposide with daily RT
- Less Fit: Sequential Platinum + etoposide followed by RT

PCI in (near) CR

Extensive Stage

Platinum/etoposide x4-6

- Thoracic RT if residual thoracic disease
- PCI if no gross progression

Platinum/etoposide x4-6

- Thoracic RT if residual thoracic disease
- MRI brain monitoring

Carboplatin/etoposide/atezolizumab x4

Followed by maintenance atezolizumab ± PCI

2nd Line options
- Topotecan
- CAV

3rd line: nivolumab (if no previous immunotherapy)
Treatment Algorithm in ES-SCLC in 2018

SCLC

→ Extensive Stage

Platinum/etoposide x4-6

→ Thoracic RT if residual thoracic disease + PCI if no gross progression

Platinum/etoposide x4-6

→ Thoracic RT if residual thoracic disease + MRI brain monitoring

Carboplatin/etoposide/atezolizumab x4

Followed by maintenance atezolizumab ± PCI

2nd Line options
- Topotecan
- CAV

3rd line: nivolumab (if no previous immunotherapy)
History of chemotherapy in SCLC

- Cyclophosphamide combination (CAV, CAE, CDE, CEV) – 80s
- Etoposide/Cisplatin (EP) = CAV, less toxic – 90s
- Metaanalysis (36 studies)
  - EP better than other combinations
- Metaanalysis (19 studies, 4054 pts)
  - Cisplatin 4.4% survival benefit at 1 year

Accepted EP regimen:
- Cisplatin 80mg/m² IV D1 + etoposide 100mg/m² IV D1,2,3 Q3 weekly x 4-6 cycles
- Cisplatin 60mg/m² IV D1 + etoposide 120mg/m² IV Q1,2,3 Q3 weekly x 4-6 cycles

EP Efficacy:
ORR 70%
PFS 5.5 m
OS <10 m

Cisplatin or Carboplatin-Based?

Carboplatin- or Cisplatin-Based Chemotherapy in First-Line Treatment of Small-Cell Lung Cancer: The COCIS Meta-Analysis of Individual Patient Data

Accepted Regimen: Carboplatin AUC5 IV D1 + Etoposide 100mg/m² IV D1,2,3 Q3W x 4-6 cycles

Socinski et al. JCO 2009

Rossi et al. JCO 2012
Treatment Algorithm in ES-SCLC in 2018

SCLC

Extensive Stage

Platinum/etoposide x4-6
Thoracic Irradiation in ES- SCLC?

Slotman et al. Lancet 2014
Post hoc Analysis of CREST

Slotman et al. World Lung 2015
Treatment Algorithm in ES-SCLC in 2018

SCLC

Extensive Stage

Platinum/etoposide x4-6

Thoracic RT if residual thoracic disease
Prophylactic Cranial Irradiation (PCI) in ES-SCLC

- Median Overall Survival (OS): 6.7 vs. 5.4 months
- 1-year Survival: 27.1% vs. 13.3%
- Hazard Ratio (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 QL (alopecia, fatigue)

Slotman et al. NEJM 2007
Role of PCI with MRI Monitoring

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)
- Stratification
  - Age, ECOG PS, response, institution

Arm B
- Observation alone (n=79)

Primary endpoint
- OS

Takahashi T et al. Lancet Oncol 2017
Role of PCI with MRI Monitoring

Median OS for PCI: 11.6 mo (95% CI: 9.5-13.3)
Median OS for observation: 13.7 mo (95% CI: 10.2-16.4)

Takahashi T et al. Lancet Oncol 2017
Treatment Algorithm in ES-SCLC in 2018

SCLC

Extensive Stage

Platinum/etoposide x4-6

Thoracic RT if residual thoracic disease

+ PCI if no gross progression

Platinum/etoposide x4-6

Thoracic RT if residual thoracic disease

+ MRI brain monitoring
IMpower 133

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

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

Induction (4 x 21-day cycles)
- Atezolizumab (1200 mg IV, Day 1)
- Carboplatin
- Etoposide
- Placebo
- Carboplatin
- Etoposide

Maintenance
- Atezolizumab
- Placebo

Survival follow-up
- Treat until PD or loss of clinical benefit
- PCI per local standard of care

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

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

\(^a\) Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors.

Thoracic RT not allowed

Horn et al. NEJM 2018
IMpower 133: OS

**Overall survival (%)**

- **12-month OS**
  - Atezolizumab: 51.7%
  - Placebo: 38.2%

**Median OS, months (95% CI)**
- Atezolizumab + CP/ET (N = 201): 12.3 (10.8, 15.9)
- Placebo + CP/ET (N = 202): 10.3 (9.3, 11.3)

**HR (95% CI)**
- Atezolizumab + CP/ET: 0.70 (0.54, 0.91)
- Placebo + CP/ET: p = 0.0069

**Median follow-up, months**
- Atezolizumab + CP/ET: 13.9 months

---

Horn et al. NEJM 2018
**IMpower 133: OS in Key Subgroups**

<table>
<thead>
<tr>
<th>Population</th>
<th>Median overall survival (months)</th>
<th>OS hazard ratio&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atezolizumab + CP/ET</td>
<td>Placebo + CP/ET</td>
</tr>
<tr>
<td>Male (n = 261)</td>
<td>12.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Female (n = 142)</td>
<td>12.5</td>
<td>9.5</td>
</tr>
<tr>
<td>&lt; 65 years (n = 217)</td>
<td>12.1</td>
<td>11.5</td>
</tr>
<tr>
<td>≥ 65 years (n = 186)</td>
<td>12.5</td>
<td>9.6</td>
</tr>
<tr>
<td>ECOG PS 0 (n = 140)</td>
<td>16.6</td>
<td>12.4</td>
</tr>
<tr>
<td>ECOG PS 1 (n = 263)</td>
<td>11.4</td>
<td>9.3</td>
</tr>
<tr>
<td>Brain metastases (n = 35)</td>
<td>8.5</td>
<td>9.7</td>
</tr>
<tr>
<td>No brain metastases (n = 368)</td>
<td>12.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Liver metastases (n = 149)</td>
<td>9.3</td>
<td>7.8</td>
</tr>
<tr>
<td>No liver metastases (n = 254)</td>
<td>16.8</td>
<td>10.2</td>
</tr>
<tr>
<td>bTMB &lt; 10 mut/mb (n = 139)</td>
<td>11.8</td>
<td>9.2</td>
</tr>
<tr>
<td>bTMB ≥ 10 mut/mb (n = 212)</td>
<td>14.6</td>
<td>11.2</td>
</tr>
<tr>
<td>bTMB &lt; 16 mut/mb (n = 271)</td>
<td>12.5</td>
<td>9.9</td>
</tr>
<tr>
<td>bTMB ≥ 16 mut/mb (n = 80)</td>
<td>17.8</td>
<td>11.9</td>
</tr>
<tr>
<td>ITT (N = 403)</td>
<td>12.3</td>
<td>10.3</td>
</tr>
</tbody>
</table>


<sup>a</sup> Hazard ratios are unstratified for patient subgroups and stratified for the ITT.

Horn et al. NEJM 2018
Treatment Algorithm in ES-SCLC in 2018

SCLC

Extensive Stage

Platinum/etoposide x4-6

Thoracic RT if residual thoracic disease +
PCI if no gross progression

Platinum/etoposide x4-6

Thoracic RT if residual thoracic disease +
MRI brain monitoring

Carboplatin/etoposide/atezolizumab x4

Followed by maintenance atezolizumab ± PCI
Topotecan in 2nd Line

- Topotecan 1.5g/m² IV D1-5 Q3W vs. CAV (cyclophosphomide 1000mg/m², doxorubicin 45mg/m², vincristine 2mg D1 Q3W) for the treatment of recurrent SCLC (n=211)
- Progressive SCLC at least 60 days after completion of 1st line chemotherapy (78% had received platinum/etoposide)

Von Pawel et al. JCO 1999
Nivolumab after Platinum/Etoposide (2nd Line)

Bristol-Myers Squibb Announces Phase 3 CheckMate-331 Study Does Not Meet Primary Endpoint of Overall Survival with Opdivo Versus Chemotherapy in Patients with Previously Treated Relapsed Small Cell Lung Cancer

CATEGORY: CORPORATE/FINANCIAL NEWS
FRIDAY, OCTOBER 12, 2018 6:59 AM EDT

• CheckMate-331 (phase 3 trial)
  - Nivolumab vs SOC chemo in patients who relapsed following platinum-based chemotherapy
  - Failed to meet primary endpoint of OS
Atezolizumab in Relapsed SCLC (IFCT16-03)

Pujol et al. ESMO 2018

Eligibility
- ED or LD SCLC (VALG)
- Progressive disease
- PS 0-2
- Measurable disease (RECIST 1.1)
- No autoimmune disease
- No brain metastases
- No corticosteroids
- Informed consent

Stratification
Sensitive vs refractory disease
PS (0-1 versus 2)
Limited versus extensive disease
Gender

Endpoint: Response rate in the experimental arm at 6 weeks (confirmation needed at 12 weeks)

Post-hoc analyses
PD-L1 tumor staining (SP142)
NGS analysis of selected genes

Median follow-up [95% CI]: 13.7 months [12.7-NR]

HR (adjusted)$_{\text{Atezolizumab}}$ = 2.26 [1.30-3.93] ; p=0.004

6-months PFS rate for Atezolizumab group: 6.3% [0.0%; 13.1%]

HR (adjusted)$_{\text{Atezolizumab}}$ = 0.84 [0.45-1.58]; p=0.60

Median OS, [95% CI]
- A - Chemotherapy: 9.4 [3.8-12.7]; n=20, 14 events, 6 censored
- B - Atezolizumab: 11.4 [3.7-15.3]; n=43, 24 events, 19 censored

1-year OS rate for Atezolizumab group: 42.5% [26.9%; 58.2%]

ATZ : Atezolizumab 1,200 mg q3w
CT: oral or IV topotecan q3w or [carboplatin – etoposide] q3w (investigators’ choice).
Treatment Algorithm in ES-SCLC in 2018

SCLC

Extensive Stage

Platinum/etoposide x4-6

- Thoracic RT if residual thoracic disease
  - + PCI if no gross progression

Platinum/etoposide x4-6

- Thoracic RT if residual thoracic disease
  - + MRI brain monitoring

Carboplatin/etoposide/atezolizumab x4

Followed by maintenance atezolizumab ± PCI

2nd Line options
- Topotecan
- CAV
Nivolumab after Platinum/Etoposide (3\textsuperscript{rd} Line)

CheckMate-032

- 109 patients with SCLC who progressed after platinum-based chemotherapy and at least one other prior line of therapy included
- Nivolumab 3mg/kg IV every 2 weeks
- \(~65\%\) of patients had platinum-sensitive SCLC

<table>
<thead>
<tr>
<th>BICR-Assessed Overall Response Rate</th>
<th>OPDIVO (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>(6.5, 19.5)</td>
</tr>
<tr>
<td>Complete response</td>
<td>0.9%</td>
</tr>
<tr>
<td>Partial response</td>
<td>11%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BICR-Assessed Duration of Response, RECIST v1.1</th>
<th>(n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (months)</td>
<td>(3.0, 42.1)</td>
</tr>
<tr>
<td>% with duration (\ge) 6 months</td>
<td>77%</td>
</tr>
<tr>
<td>% with duration (\ge) 12 months</td>
<td>62%</td>
</tr>
<tr>
<td>% with duration (\ge) 18 months</td>
<td>39%</td>
</tr>
</tbody>
</table>

Treatment Algorithm in ES-SCLC in 2018

SCLC → Extensive Stage
- Platinum/etoposide x4-6
  - Thoracic RT if residual thoracic disease + PCI if no gross progression
- Platinum/etoposide x4-6
  - Thoracic RT if residual thoracic disease + MRI brain monitoring
- Carboplatin/etoposide/atezolizumab x4
  - Followed by maintenance atezolizumab + PCI

2nd Line options
- Topotecan
- CAV
- Platinum/etoposide Retreatment

3rd line: nivolumab (if no previous immunotherapy)
Treatment Algorithm in LS-SCLC in 2018

SCLC

Limited Stage

Chemoradiation

Very Fit
- Concurrent Cisplatin + etoposide with BD RT

Fit
- Concurrent Cisplatin + etoposide with daily RT

Less Fit
- Sequential Platinum + etoposide followed by RT

PCI in (near) CR
Chemotherapy in Limited Stage SCLC (LS-SCLC)

- Cisplatin is the best radiosensitiser – cisplatin plays a major role in the treatment of LS-SCLC

- Cisplatin/etoposide can be delivered at full dose with thoracic RT with an acceptable toxicity profile

- No change in systemic therapy in last 20 years
  - No role for anthracyclines/pemetrexed/irinotecan
  - No role for chemotherapy dose intensification
  - No role for targeted agents
Chemoradiation Better than Chemotherapy Alone

• Pignon et al. NEJM 1992
  - 13 randomised trials
  - 2140 patients
  - 3 year survival
    • 8.9% chemotherapy alone
    • 14.3% chemotherapy + radiation (sequential or concurrent)

14% reduction in risk of death, p=0.001
Concurrent ChemoRT Better than Sequential ChemoRT

Takada et al. JCO 2002

<table>
<thead>
<tr>
<th></th>
<th>Median OS (mo)</th>
<th>5-yr OS (%)</th>
<th>Severe Oesophagitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent</td>
<td>27</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Sequential</td>
<td>20</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>

Takada et al. JCO 2002
Standard of Care RT for LS-SCLC: Intergroup 0096

Turrisi et al. NEJM 1999
CONVERT Study: Superiority Trial

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

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

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

PS 0-2
No age limit
SD,PR,CR→PCI

547 patients
8 countries
75 centres

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

Faivre-Finn et al. Lancet Oncol 2017
45G BD Radiotherapy Remains the SOC

Median OS: 30 mo (95% CI: 24-34) in BD group vs 25 mo (95% CI: 21-31) in once-daily group

2-year OS: 56% in BD group vs 51% in once daily group

Toxicity similar between arms

Faivre-Finn et al. Lancet Oncol 2017
Treatment Algorithm in LS-SCLC in 2018

SCLC

Limited Stage

Chemoradiation

Very Fit

Concurrent Cisplatin + etoposide with BD RT (45G; 30#)
Treatment Algorithm in LS-SCLC in 2018

SCLC

Limited Stage

Chemoradiation

Very Fit

Concurrent Cisplatin + etoposide with BD RT (45G; 30#)

Fit

Concurrent Cisplatin + etoposide with daily RT (66G; 33#)
Treatment Algorithm in LS-SCLC in 2018

SCLC

Limited Stage

Chemoradiation

Very Fit

Concurrent Cisplatin + etoposide with BD RT (45G; 30#)

Fit

Concurrent Cisplatin + etoposide with daily RT (66G; 33#)

Less Fit

Sequential Platinum + etoposide followed by RT
PCI in LS-SCLC

PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

- 7 RCT; n=987 (88% in PCI group had LS-SCLC; 83% in control group)
- Complete remission with chemotherapy
- PCI delivered between 1977 to 1995

3 year OS improved from 15.3% to 20.7% (5.4% increase)

Auperin et al. NEJM 1999
Treatment Algorithm in LS-SCLC in 2018

SCLC

Limited Stage

Chemoradiation

Very Fit

Concurrent Cisplatin + etoposide with BD RT

Fit

Concurrent Cisplatin + etoposide with daily RT

Less Fit

Sequential Platinum + etoposide followed by RT

PCI in (near) CR
?The Future

STIMULI: A randomised phase 2 trial of consolidation with nivolumab and ipilimumab in limited-stage SCLC after chemoradiotherapy

Key Inclusion Criteria
- ≥18 years of age
- Untreated LS-SCLC
- ECOG PS 0–1
- Non PD after completion of CRT, PCI
- Adequate hematological, renal, hepatic and lung function
- Recovery of all AEs to Grade ≤1*

Induction:
- Ipilimumab 3 mg/kg+
- Nivolumab 1 mg/kg
- Q3W X4

Maintenance:
- Nivolumab 240 mg Q2w

Primary outcome measure: OS, PFS
N: 260

Observation
Practice Points in SCLC in 2018

• LS-SCLC
  - Concurrent chemotherapy (cisplatin+etoposide x4-6) with radiotherapy (45G/30# BD) starting early (1st or 2nd cycle of chemotherapy)
  - If near CR post chemoRT, PCI increases OS
  - Watch out for integration of immunotherapy

• ES-SCLC
  - Platinum/etoposide x4-6 cycles followed by sequential thoracic RT if residual thoracic disease + either PCI if no progression or MRI monitoring without PCI
  - Carboplatin + etoposide + atezolizumab x4 cycles followed by maintenance atezolizumab (± PCI) improves OS compared to carboplatin + etoposide
  - 2nd line options include topotecan or CAV
  - Refinement in use of immunotherapy likely
Thank you