Current standard of care in SCLC, Mesothelioma and NSCLC

Rolf Stahel
University Hospital of Zürich

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Disclosures

Consultant or Advisory Role in the last two years
I have received honoraria as a consultant at advisory boards from Abbvie, AstraZeneca, Boehringer Ingelheim, MSD, Pfizer, Roche and Takeda.

Speaker Honoraria in the last two years
I have received honoraria as a speaker from Astra Zeneca, Boehringer Ingelheim, Lilly, MSD and Roche.

DMC in the last two years
Roche and Takeda

Financial Support of ETOP trials (president and scientific chair)
AstraZeneca, BMS, Boehringer Ingelheim, Genentech, MSD, Roche, and Pfizer.
THE NATURE OF THE "OAT-CELLED SARCOMA"
OF THE MEDIASTINUM.

W. G. BARNARD.

University College Hospital Medical School, London.

... It usually forms a large mass which replaces the lymphatic glands of the posterior and anterior mediastina and infiltrates the pericardium, whilst a relatively small mass occupies the hilum of one lung involving a bronchus; metastases are numerous and widely spread. Histologically the growth consists essentially of small oval cells with scanty cytoplasm which have been likened to oat grains. The purpose of this paper is to show that these tumours are primary carcinomata of the lung.

J. Path, 1926
Pathobiology of SCLC

1924 Oat cell carcinoma of the mediastinum (Bernard)
1961 Primary lung tumor (Watson)
1967 WHO entity
1968 Neurosecretory granules (Bensch)
1980 SCLC cell lines (Gazdar)
1981 Bombesin autocrine loop (Moody)
1982 3p deletion (Wang-Peng)
1983 Monoclonal antibodies (Mulshine)
1985 Myc amplification (Nau)
1988 Rb mutation (Harbour)
1992 p53 mutation (Mitsudomi)
1994 Bcl-2 hyperexpression (Ikegaki)
2002 Mouse model by conditional inactivation of Rb and p53 (Meuwissen)
Induction of SCLC by somatic inactivation of TP53 and Rb
Comprehensive genomic analysis of SCLC
Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors
Effect of stage, PS and weight loss on SCLC survival based on early VA study group trials

• Stage (placebo controls):
  LD MST 11.7 weeks, ED 5.0 weeks

• Karnofsky status (placebo controls)

• Weight loss 10 lbs (ED, placebo controls):
  Present MST 13.1 weeks, absent MST 18.7 weeks

Zelen, Cancer Chemotherapy Reports 1973
How 4-6 cycles of chemotherapy became the standard

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Cycles</th>
<th>Regimen</th>
<th>PFS</th>
<th>OAS</th>
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<tr>
<td>Cullen, 1986</td>
<td>309</td>
<td>6/14</td>
<td>CAV</td>
<td>N/A</td>
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<tr>
<td>Bleehan, 1989</td>
<td>256</td>
<td>6/12</td>
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<td>Spiro, 1989</td>
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<td>Lebean, 1992</td>
<td>320</td>
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<td>Giaccone, 1993</td>
<td>426</td>
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<td>CAE</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Sculier, 1993</td>
<td>91</td>
<td>6/6+12</td>
<td>IEA+EVi</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Bleehan, 1993</td>
<td>309</td>
<td>3/6</td>
<td>CMEV</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Cisplatin in small cell anaplastic bronchogenic carcinoma: A phase II study

*Dombernowsky, …, Hansen, Cancer Treat Rep 1979*

- Considering the severe refractory nausea and vomiting and minimal response rate […] we feel that cisplatin has no major role as single agent […].

Phase II study with cisplatin in small cell anaplastic carcinoma

*Cavalli, Goldhirsch, Eur J Cancer 1980*

- These data warrant the incorporation of cisplatin in combination with other agents for this disease
Cisplatin and etoposide as standard of care for SCLC

- Etoposide and cisplatin: an effective treatment for relapsed SCLC [after CAV]

<table>
<thead>
<tr>
<th>Disease Extent</th>
<th>No. of Patients Evaluable</th>
<th>Response (%)</th>
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<tr>
<td></td>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>LD</td>
<td>24</td>
<td>4 (17)</td>
</tr>
<tr>
<td>ED</td>
<td>54</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>6 (8)</td>
</tr>
</tbody>
</table>

Evans, JCO 1985
Cisplatin and etoposide as standard of care for SCLC

- Randomized trial of cyclophosphamide, doxorubicin, and vincristine vs cisplatin and etoposide vs alternation of these regimens  *Fukuoka, JNCI 1991*

- Randomized study of cyclophosphamide, doxorubicin, and vincristine vs etoposide and cisplatin vs alternation [...] in extensive disease SCLC  *Roth, JCO 1992*
IPD meta-analysis: carboplatin vs cisplatin-based chemotherapy

- In poor prognosis &/or ED-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

Rossi, JCO 2012
IPD meta-analysis: carboplatin vs. cisplatin-based chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Events</th>
<th>Median OS (months)</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>328</td>
<td>293</td>
<td>9.64</td>
<td>8.72 to 10.7</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>335</td>
<td>296</td>
<td>9.41</td>
<td>8.75 to 10.7</td>
</tr>
</tbody>
</table>

Rossi, JCO 2012
Randomized phase II–III study of bevacizumab in combination with chemotherapy in previously untreated ED SCLC: results from the IFCT-0802 trial†
Carboplatin and etoposide with or without palifosfamide in untreated extensive-stage SCLC: A multicenter, adaptive, randomized phase III study (MATISSE)
Randomized phase II trial of cisplatin and etoposide in combination with veliparib or placebo for ED SCLC: ECOG-ACRIN 2511 Study

Owonikoko, JCO 2018
Phase 3 studies of immune checkpoint inhibitors as first line therapy of extensive disease SCLC
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: Trial design

**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

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

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

**Survival follow-up**

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Liu, WCLC 2018; Horn, NEJM 2018
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: Response

- **Response (%)**
  - **CR**
    - Atezolizumab + CP/ET: 2.5
    - Placebo + CP/ET: 1.0
  - **CR/PR**
    - Atezolizumab + CP/ET: 60.2
    - Placebo + CP/ET: 64.4
  - **SD**
    - Atezolizumab + CP/ET: 20.9
    - Placebo + CP/ET: 21.3
  - **PD**
    - Atezolizumab + CP/ET: 10.9
    - Placebo + CP/ET: 6.9

- **Duration of response**
  - **Median duration, months (range)**
    - Atezolizumab + CP/ET (N = 121): 4.2 (1.4 to 19.5)
    - Placebo + CP/ET (N = 130): 3.9 (2.0 to 16.1)
  - **HR (95% CI)**
    - Atezolizumab + CP/ET: 0.70 (0.53, 0.92)
  - **6-month event-free rate — %**
    - Atezolizumab + CP/ET: 32.2
    - Placebo + CP/ET: 17.1
  - **12-month event-free rate — %**
    - Atezolizumab + CP/ET: 14.9
    - Placebo + CP/ET: 6.2
  - **Patients with ongoing response — no. (%)**
    - Atezolizumab + CP/ET: 18 (14.9)
    - Placebo + CP/ET: 7 (5.4)

*Liu, WCLC 2018; Horn, NEJM 2018*
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: OS
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: PFS

Liu, WCLC 2018; Horn, NEJM 2018
First-line atezolizumab plus chemotherapy in extensive-stage SCLC: Adverse events

Clinical data cutoff date: April 24, 2018.

Liu, WCLC 2018; Horn, NEJM 2018
Prophylactic cranial irradiation in ED SCLC

Selection:
• Any type of response
• No evident CNS or leptomeningeal disease

Radiotherapy:
• 20 Gy in 5 or 8
• 24 Gy in 12
• 25 Gy in 10
• 30 Gy in 10 or 12 fractions

HR 0.27
HR 0.68

Slotman, NEJM 2007
Prophylactic cranial irradiation versus observation in patients with extensive-disease SCLC: a multicentre, randomised, open-label, phase 3 trial

Selection:
- absence of brain metastases confirmed by within 4 weeks before enrolment
- absence of tumour regrowth confirmed by thoracoabdominal CT within 4 weeks before enrolment

Radiotherapy:
- 25 Gy in 10 fractions
Prophylactic cranial irradiation versus observation in patients with extensive-disease SCLC: a multicentre, randomised, open-label, phase 3 trial

Takahasi, Lancet Oncol 2017
Thoracic radiotherapy for extensive SCLC: the CREST study

27

Primary endpoint:
• 1- survival (improvement by 10%)
Secondary endpoint.
• PFS

Slotman, Lancet 2014
Thoracic radiotherapy for extensive SCLC: the CREST study

OS at 1 year was 33% (95% CI 27–39) in the thoracic radiotherapy group versus 28% (95% CI 22–34) in the control group (p=0.066)

Slotman, Lancet 2014
Thoracic radiotherapy for extensive SCLC: the CREST study

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

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

Grade 3+ toxicity < 5%
Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: A secondary analysis of the phase III CREST trial

Effect of thoracic radiotherapy and site and number of metastases.

<table>
<thead>
<tr>
<th></th>
<th>Progression free survival HR (95% CI); ( p )-value</th>
<th>Overall survival HR (95% CI); ( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver metastases</td>
<td></td>
<td></td>
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<tr>
<td>present</td>
<td>1.22 (0.75–1.76) ( p = 0.28 )</td>
<td>0.90 (0.62–1.31) ( p = 0.57 )</td>
</tr>
<tr>
<td>absent</td>
<td>1.74 (1.23–2.46) ( p = 0.001 )</td>
<td>1.38 (0.96–1.98) ( p = 0.08 )</td>
</tr>
<tr>
<td>Bone metastases</td>
<td></td>
<td></td>
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<tr>
<td>present</td>
<td>1.60 (1.08–2.38) ( p = 0.02 )</td>
<td>0.94 (0.63–1.41) ( p = 0.76 )</td>
</tr>
<tr>
<td>absent</td>
<td>1.36 (0.98–1.87) ( p = 0.06 )</td>
<td>1.19 (0.85–1.65) ( p = 0.32 )</td>
</tr>
<tr>
<td>Number of metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>2.02 (1.24–3.28) ( p = 0.003 )</td>
<td>1.55 (0.93–2.58) ( p = 0.09 )</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>1.25 (0.93–1.66) ( p = 0.14 )</td>
<td>0.94 (0.70–1.27) ( p = 0.69 )</td>
</tr>
</tbody>
</table>

Slotman, Lung Cancer 2017
Standard chemo-radiotherapy for limited stage SCLC

Turrisi, N Engl J Med 1999
Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage SCLC (CONVERT): an open-label, phase 3, randomised, superiority trial

Faivre-Finn, Lancet Oncol 2017
Prophylactic cranial irradiation for patients with SCLC in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group

Auperin, NEJM 1999
Study design:
Multicentre, open label, randomized phase II trial, ETOP sponsored, collaboration with IFCT and other trial groups

Primary objectives:
PFS and OS

Sample size:
260 randomized patients
EGFR-mutant adenocarcinomas that transform to SCLC and other neuroendocrine carcinomas: Clinical outcomes

Patients
- 58 transforming on TKI
- 9 de novo SCLC or mixed

Median time to transformation:
- 17.8 (95%CI: 14.2-26.2) months

Evaluable with platinum/etoposide:
- RR 54% of 46
- Median PFS 3.4 (95%CI: 2.4-5.4) months

Evaluable with ICB:
- RR 0/17, best TTP 9 wks

Marcoux, JCO 2019
Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent SCLC

Overall survival

Log Rank
p-value: 0.772

Von Pawel, JCO 1999
Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed SCLC (JCOG0605): a multicentre, open-label, randomised phase 3 trial

Goto, Lancet Oncol 2016
KEYNOTE-158 Phase II study of pembrolizumab in second line ED SCLC
Phase 3 studies of immune checkpoint inhibitors in second line treatment or as maintenance in extensive disease SCLC

*Nivolumab Checkmate-331*
- SCLC second line
  - N=798
  - Nivolumab
  - Topotecan or Amrubicine
  - Primary endpoints: OS
  - OS negative

*Nivolumab Checkmate-451*
- SCLC ED after EP (SD or OR)
  - N=940
  - Nivolumab/ipilimumab
  - Placebo
  - Primary endpoints: PFS and OS
  - OS negative

*Reck, ESMO IO 2018, press release November 2018*
Randomized phase 3 study of nivolumab monotherapy versus chemotherapy in relapsed SCLC: Results from CheckMate 331
WNT pathway activation in recurrent SCLC

Relapse associated changes in genes regulating WNT signaling in 24/30 paired samples, i.e APC

APC knockdown increase WNT signaling in H1694

Etoposide resistance by APC deletion in H82

Wanger, Nat Comm 2018
Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent SCLC: a first-in-human, first-in-class, open-label, phase 1 study

Main adverse events grade III/IV:
- Fatigue (5%)
- Thrombocytopenia (15%)
- Rash (5%)
- Edema (3%)

Rudin, Lancet Oncol 2017
What can we conclude for the first line therapy of small-cell lung cancer

- Four to 6 cycles of platinum-etoposide are standard of care since 30 years
- For selected patients with extensive disease consolidation with thoracic radiotherapy should be considered, in particular for patients with less than 3 metastatic sites and absence of liver metastases
- Prophylactic cranial irradiation is recommended for responding patients with limited disease, its use is controversial in patients with extensive disease
- Combining atezolizumab with platinum-etoposide provides a survival advantage for patients with extensive disease
Mesothelioma: Timeline of research and legal milestones

- **1949**: Doll reports that asbestos exposure is associated with an increased risk of lung cancer.
- **1955**: Selikoff reports excess incidence of lung cancer and mesothelioma in asbestos workers.
- **1956**: The UK Asbestos Regulations control asbestos exposure in the workplace.
- **1956**: US Federal Clean Air Act identifies asbestos as a hazardous pollutant.
- **1965**: Wagner identifies a link between asbestos exposure and mesothelioma.
- **1966**: Newhouse and Thompson report asbestos exposure in mesothelioma cases: wives washing work clothes of exposed husbands was an exposure mechanism.
- **1969**: The UK bans import and use of crocidolite and amosite.
- **1970**: The UK bans asbestos and importation of all asbestos.
- **1975**: IARC Working Group classifies asbestos into IARC Group 1, carcinogenic to humans.
- **1980**: Second IARC working group concludes that asbestos is carcinogenic.
- **1985**: UK Control of Asbestos at Work Regulations introduce statutory control procedures.
- **1987**: Familial mesothelioma risk is postulated from Turkish studies of environmental erionite exposure.
- **2003**: Bap1 loss of function results in EZH2-dependent transformation. Phase II EZH2 inhibitor trial opens to test this hypothesis in 2016.
- **2006**: MAPS phase III trial confirms benefit from addition of bevacizumab to pemetrexed and cisplatin.
- **2009**: Randomized phase III trial confirms benefit from pemetrexed and cisplatin combination chemotherapy.
- **2011**: Bap1 mutations are associated with increased sensitivity to asbestos in a mouse model.
- **2016**: Arginine deprivation with ADI-PEG20 improved PFS in patients with ASS1-deficient mesothelioma.
- **2017**: The PD1 inhibitor pembrolizumab appears to be well tolerated and might confer anti-tumour activity in patients with PDL1-positive malignant pleural mesothelioma.

*Yap, Nat Rev Cancer 2017*
Cisplatin and pemetrexed versus cisplatin in malignant pleural mesothelioma (fully vitamin supplemented patients)
MAPS trial: Cisplatin/pemetrexede with or without bevacizumab

**IFCT-GFPC-0701 trial: MAPS**
*Mesothelioma Avastin cisplatin Pemetrexed Study*

IFCT-sponsored, open-label, multi-centre randomized phase II-III trial
Roche supplied bevacizumab

- **A**
  - Pemetrexed 500 mg/m² D1
  - Cisplatin 75 mg/m² D1
  - 6 cycles, Q21D
  - Surveillance

- **B**
  - Pemetrexed 500 mg/m² D1
  - Cisplatin 75 mg/m² D1
  - Bevacizumab 15 mg/kg D1
  - 6 cycles, Q21D
  - Maintenance Bevacizumab 15 mg/kg D1, Q21D until progression

CT-scan Q. 3 cycles in both arms.
Response assessed with modified RECIST criteria for mesothelioma

Stratification: center, histology (epithelial vs. sarcomatoid/mixed), PS (0-1 vs. 2), smoking status (ever smoker vs. never-smoker)
Nintedanib + pemetrexed/cisplatin in patients with unresectable MPM: Phase III results from the LUME-meso trial
Summarizing available results on single agent immune checkpoint inhibitors in mesothelioma second or later line

<table>
<thead>
<tr>
<th>Study</th>
<th>Keynote-028 Pembro</th>
<th>NivoMes Nivolumab</th>
<th>MERIT Nivolumab</th>
<th>“Chicago” Pembrol</th>
<th>Avelumab Unselected</th>
</tr>
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<tbody>
<tr>
<td>Patient Number</td>
<td>25</td>
<td>34</td>
<td>34</td>
<td>64</td>
<td>53</td>
</tr>
<tr>
<td>PR</td>
<td>5 (20%)(^1)</td>
<td>8 (24%)(^1)</td>
<td>10 (29.4)(^2)</td>
<td>14 (22%)(^2,3)</td>
<td>5 (9%)(^1)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (52%)</td>
<td>8 (24%)</td>
<td>13</td>
<td>26 (41%)</td>
<td>27 (47%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.5 months</td>
<td>2.6 months</td>
<td>6.1 months</td>
<td>4.1 months</td>
<td>4.1 months</td>
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<tr>
<td>Median OS</td>
<td>18 months</td>
<td>11.8 months</td>
<td>17.3 months</td>
<td>11.5 months</td>
<td>10.7 months</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Safety</td>
<td>DCR12w 40%: 48%</td>
<td>PFS</td>
<td>RR &gt;25% NR</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) PD-L1 positive only
\(^1\) Levels of PD-L1 expression did not correlate with response
\(^2\) Higher responses in PD-L1 positive tumors
\(^3\) Higher responses in sarcomatous mesothelioma
Summarizing available results on combined agent immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>MAPS-2</th>
<th>INITIATE</th>
<th>NIBIT</th>
<th>DREAM</th>
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<td>Ipi/Nivo</td>
<td>Ipi/Nvo</td>
<td>Tremi/Durva*</td>
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<tr>
<td>Patient Number</td>
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<td>54</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>PR</td>
<td>18.5%</td>
<td>25.9%</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td>SD</td>
<td>25.9%</td>
<td>24.1%</td>
<td>38%</td>
<td>35%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4 months</td>
<td>5.6 months</td>
<td>6.2 months</td>
<td>5.7 months</td>
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<tr>
<td>Median OS</td>
<td>11.9 months</td>
<td>15.9 months</td>
<td>&gt;12.7 months</td>
<td>16.6 months</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>DCR12w 40%: 44%</td>
<td>DCR12w 40%: 52%</td>
<td>irR</td>
<td>PFS6m: 65%</td>
</tr>
</tbody>
</table>

*first line
Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial

Treatment duration in pts with OR

Scherpereel, Lancet Oncol 2019
What can we conclude for the first line therapy of small-cell lung cancer

- Cis- or caboplatin combined with pemetrexed have emerged as the preferred chemotherapy based on one randomized trial.
- Multimodality therapies including chemotherapy, pleurectomy/decoratication or extrapleural pneumonectomy with or without radiotherapy continue to be explored and remain controversial.
- Bevacizumab added to cisplatin/pemetrexed leads to an increase in progression-free survival and overall survival.
- There is no standard second line therapy, the most commonly used single agents are vinorelbine or gemcitabine.
- ICB has resulted in responses, some of them durable, however there is yet no randomized data.
What can we conclude for the first line therapy of advanced NSCLC without oncogenic driver mutation

- There is no single platinum-based doublet standard chemotherapy, however pemetrexed combinations are favoured in non-squamous cell NSCLC.
- If platinum-based chemotherapy is indicated, a combination with bevacizumab is a treatment option in eligible patients with non-squamous NSCLC. In this case, carboplatin/paclitaxel is the preferred combination.
- Pemetrexed maintenance therapy is an option for patients with non-squamous NSCLC without progression after first line therapy.
- Immune checkpoint inhibition with pembrolizumab is becoming an option for patients with tumors with strong PD-L1 expression.
- Current developments in first line immunotherapy are moving into chemotherapy/IO or IO/IO combinations.