Malignant Pleural Mesothelioma – Current Developments

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Milano, 25.11.2016
Mesothelioma in Europe

- Peak incidence around 2020
- British mesothelioma register and male death rates for cancer of the pleura from 6 European countries
- Statistical modeling taking into account asbestos legislation and the long latency period

Peto, BJC 1999
Stopping asbestos exposure may not modify the subsequent risk of mesothelioma

Table 1  Observed and expected deaths from mesothelioma and lung cancer, and corresponding to age at first and last employment

<table>
<thead>
<tr>
<th></th>
<th>Person-years</th>
<th>Observed</th>
<th>Expected</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First and last employment &lt;30</td>
<td>30.366</td>
<td>25</td>
<td>0.4</td>
<td>6626.7 (4287.5–9807.5)</td>
</tr>
<tr>
<td>First employment &lt;30, last at age 30–39 years</td>
<td>6035</td>
<td>9</td>
<td>0.11</td>
<td>8019.0 (3672.7–15236.1)</td>
</tr>
<tr>
<td>First employment &lt;30, last &gt;40</td>
<td>2832</td>
<td>6</td>
<td>0.10</td>
<td>5896.0 (2163.8–12853.3)</td>
</tr>
</tbody>
</table>

CI, confidence interval; SMR, standardized mortality ratio.

"From Pira et al., 2007.

La Vecchia and Boffetta, J Cancer Prevention 2011
Diagnosis malignant pleural mesothelioma: Video-assisted pleural biopsy for histology and immunohistochemistry

Morphology:
Epithelial, sarkoid or mixed

IHC:
Calretinin, mesothelin, WT-1, podoplanin
Key therapeutic considerations (1)

- Mesothelioma presents usually in a locally advanced stage not amenable to curative therapy.
- Cis- or caboplatin combined with pemetrexed has emerged as the preferred chemotherapy based on one randomized trial.
- Multimodality therapies including chemotherapy, pleurectomy/decortications or extrapleural pneumonectomy with or without radiotherapy continue to be explored and remain a controversial issue.

Vogelzang; JCO 2003
Multimodality therapy of malignant pleural mesothelioma: The important questions

- EPP or no surgery?
  Impossible to answer in context of a randomized study. MARS feasibility trial failed
  Treasure, Lancet Oncol 2011

- PORT to hemithorax after neoadjuvant chemo and EPP:
  SAKK 17/04
  Stahel. Lancet Oncol 2015
MARS feasibility trial

24 randomly assigned to EPP (with radical radiotherapy)

- 5 EPP surgery not started
  - 3 patient refusal
  - 2 clinical decision

- 3 EPP surgery abandoned
  - 1 perioperative death
  - 2 unexpected disease progression

16 completed EPP surgery

- 11 postoperative complications
  - 1 reoperation plus cardiac plus pulmonary
  - 1 cardiac plus pulmonary plus infection
  - 1 cardiac plus pulmonary artery compression
  - 1 cardiac plus urine retention
  - 2 pulmonary plus other
  - 1 reoperation* 1 cardiac
  - 3 other

- 8 radical radiotherapy not received
  - 1 clinical decision
  - 2 toxicity
  - 2 disease progression
  - 3 died

Operative mortality of EPP 18%

Treasure, Lancet Oncol 2011
### Table: Prospective studies of trimodality therapy of malignant pleural mesothelioma including neoadjuvant chemotherapy, extrapleural pneumonectomy (EPP), and radiotherapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of patients</th>
<th>ITT median survival (95% CI)</th>
<th>EPP operative mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
<td>EPP</td>
</tr>
<tr>
<td></td>
<td>Weder and colleagues¹</td>
<td>T1-3, N0-2</td>
<td>19 (100%)</td>
</tr>
<tr>
<td></td>
<td>Weder and colleagues²</td>
<td>T1-3, N0-2</td>
<td>61 (100%)</td>
</tr>
<tr>
<td></td>
<td>Rea and colleagues³</td>
<td>T1-3, N0-2</td>
<td>21 (100%)</td>
</tr>
<tr>
<td></td>
<td>Batirel and colleagues⁴</td>
<td>T1-3, N0-2</td>
<td>20 (100%)</td>
</tr>
<tr>
<td></td>
<td>Krug and colleagues⁵</td>
<td>T1-3, N0-2</td>
<td>77 (100%)</td>
</tr>
<tr>
<td></td>
<td>Van Schil and colleagues⁶</td>
<td>T1-3, N0-2</td>
<td>59 (100%)</td>
</tr>
</tbody>
</table>

ITT - intention to treat. Median survival is in months.

Weder, Lancet Oncol 2011

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**Letter responding to MARS**

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Rare adult solid cancers
Superior results of P/D and EPP in epithelial malignant mesothelioma

- Non-randomized prospective study comparing EPP (22 pts) and P/D (17 pts)
- 25 received neoadjuvant therapy, 17 adjuvant radiotherapy

Lang-Lazdunski, JTO 2012
Does surgery improve survival of patients with malignant pleural mesothelioma?: A multicenter retrospective analysis of 1365 consecutive patients

Survival curves according to the treatment (nonsurgical treatment versus EPP versus P/D) considering only patients with favorable prognostic factors.

Bovolato, JTO 2014
Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>14</td>
</tr>
<tr>
<td>M</td>
<td>137</td>
</tr>
<tr>
<td>T Stage (clinical):</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>45</td>
</tr>
<tr>
<td>T2</td>
<td>61</td>
</tr>
<tr>
<td>T3</td>
<td>45</td>
</tr>
<tr>
<td>N Stage:</td>
<td></td>
</tr>
<tr>
<td>N0/1</td>
<td>130</td>
</tr>
<tr>
<td>N2 (mediastinoscopy)</td>
<td>21</td>
</tr>
<tr>
<td>Histologic type:</td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>124</td>
</tr>
<tr>
<td>Mixed histology</td>
<td>18</td>
</tr>
<tr>
<td>Sarcomatous</td>
<td>9</td>
</tr>
</tbody>
</table>

RR 34%

Stahel, Lancet Oncol 2015
• 125/151 patients underwent surgery, of whom 113 had extrapleural pneumonectomy as intended; 12 patients had thoracotomy but no radical resection.
• 96 (64%) of 151 patients achieved complete macroscopic (R0 and R1) resection.
• Five patients had died 30 days after surgery (two with pulmonary embolism and right heart failure, one with cardiac arrest, one with diaphragmatic patch failure, and one with septic multiorgan failure), a further five had died by 60 days (three had rapid tumour progression, one had cerebrovascular insult, and one had septic multiorgan failure)
SAKK 17/04: Survival from registration

All patients:
RR 30%
Median OS 15 (12.1-19.3) months

Patients randomized:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20.8</td>
<td>14.4-27.8</td>
</tr>
<tr>
<td>B</td>
<td>19.3</td>
<td>11.5-21.8</td>
</tr>
</tbody>
</table>

Stahel, Lancet Oncol 2015
SAKK 17/04: locoregional relapse free survival from surgery

Stahel, Lancet Oncol 2015
136 patients underwent macroscopic complete resection by extrapleural pneumonectomy after induction chemotherapy for MPM. We analysed 106 patients who presented with recurrent disease until October 2014.

Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma

ECOG performance status of 0 to 2, with good pulmonary function tests, a new histological diagnosis of MPM previously untreated, clinical stage T1-3N0M0, suitable for combined modality therapy,

Perrot, J Thorac Cardiovasc Surg 2016
Key therapeutic considerations (2)

- 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.
- Occasional responses occur with multitargeted TKIs.

Zalcman, Lancet Oncol 2016
MAPS trial: Cisplatin/pemetrexed 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

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

**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)

Zalcman, Lancet Oncol 2016
Vinca alkaloids in the therapeutic management of malignant pleural mesothelioma

Cerersoli, Cancer Treatment Rev 2015
Sunitinib in second line for mesothelioma

- 53 patients, median of 26-weeks cycles
- 6 (12%) PRs
- Median time to progression 3.5 months
- 40% required dose reduction, fatigue most common side effect

Nowak, JTO 2012
Other clinical investigations

NGR-hTNF:
• Phase III in previously treated mesothelioma
  *Gafaar, ASCO 2015*

Trabectidine, lubinectidine:
• 7/17 41% (95% CI 18-67%) patients with biphasic or sarcomatoid mesotheliomas with PFS 12 weeks on trabectidine
  *Cortinovis, ASCO 2015*
• Lubinectidine phase II including all histologies with PE PFS at 3.5 months under Lurbinectidine monotherapy according to RECIST criteria modified for malignant mesothelioma
Key areas of therapeutic research

• Antibody-drug conjugates targeting mesothelin

• Immune checkpoint inhibitors
Comprehensive genomic analysis of malignant pleural mesothelioma

Bueno, Nat Gen 2016
Key molecular features of malignant mesothelioma

- Arises from mesothelial cells of the pleural, pericardial, and peritoneal cavities.
- Often associated with asbestos exposure. Asbestos carcinogenesis is linked to chronic inflammation that may lead to malignant mesothelial cell transformation after decades long latency.
- Consistent molecular features include:

BAP-1 mutation in mesothelioma

- Genetic alterations in BAP1 gene have been identified in 23% of MPM specimens. 
  
  Bott, Nature Genetics 2011
BAP-1 mutation in mesothelioma

- BAP1 was initially identified in lung cancer cell lines as a protein that binds to BRCA1
  *Jensen, Oncogene 1989*
- Germline BAP1 mutations have been detected in families with a high incidence of MPM
  *Testa, Nature Genetics 2011*
- Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers
  *Abdel-Rahman, Nature Genetics 2011*
- The Prevalence of BAP1 germline mutation in sporadic malignant pleural mesothelioma is estimated around 1-2%
  *Rusch, Lung Cancer 2014*
Vorinostat in second line malignant pleural mesothelioma

Krug, Lancet Oncol 2015
Genetic/epigenetic changes present in mesothelioma offer different possibilities for therapeutic intervention.
Deaminase deprivation with pegylated arginine deiminase in patients with argininosuccinate synthetase 1-deficient malignant pleural mesothelioma

Szlosarek, JAMA Oncol 2016
A phase I study of GSK2256098, a focal adhesion kinase inhibitor, in patients with advanced solid tumors

- In the 29 patients with recurrent mesothelioma, the median PFS was 12 (95% CI 9.1, 23.4) weeks
- (23.4 weeks merlin negative, n = 14; 11.4 weeks merlin positive, n = 9)

Soria, Ann Oncol 2016
A phase I study of apitolisib (CDC-0980), a dual PI3K and mTOR inhibitor in patients with advanced solid tumors

Of the 27 MPM patients treated at 30 mg 28/28 schedule, 26 were evaluable by modified RECIST-independent review. Median time on study was 4 months (range, 0.5–38.9) with 8 patients (29.6%) on study for more than 6 months, including 2 patients (7.4%) for more than 12 months.

Dolly, CCR 2016
Targeting mesothelin with monoclonal antibodies and immunoconjugates

- Amatuximab, a chimeric monoclonal antibody
  - Combination with cisplatin/pemextrexed:
  - PRs in 33/89 (40%) and SD in 42 (51%).
  - Six month-PFS rate was 51%, median PFS 6.1 months (95% CI: 5.8, 6.4).
    Hassan, CCR 2014

- Immunotoxin SS1P (Recombinant antibody FV and pseudomonas exotoxin)
    Weldon, Mol Cancer Therapeutics 2013
Targeting mesothelin with monoclonal antibodies and immunoconjugates

- Ametumab ravtansine (maytansinoid tubulin inhibitor)

- Preclinical activity in mesothelioma
  Golfier, Mol Cancer Ther 2014

- Phase I in patients with metastatic mesothelioma
  Hassen, WCLC 2015
Phase 3 trial anetumab ravtansine plus pemetrexed and cisplatin in first line malignant pleural mesothelioma
### PD-L1 expression in malignant pleural mesothelioma

<table>
<thead>
<tr>
<th></th>
<th>Mansfield et al&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Cedrés et al&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Thapa et al&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Combaz-Lair&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>106</td>
<td>77</td>
<td>311</td>
<td>58</td>
</tr>
<tr>
<td>Antibody used</td>
<td>5H1-A3- mouse monoclonal</td>
<td>E1L3N- Rabbit IgG</td>
<td>E1L3N- Rabbit IgG (cell signalling)</td>
<td>E1L3N- Rabbit IgG (cell signalling)</td>
</tr>
<tr>
<td>Criteria of positivity</td>
<td>&gt;5% membranous and/or cytoplasmic staining</td>
<td>≥ 1% membranous and/or cytoplasmic staining</td>
<td>≥ 5% membranous staining</td>
<td>≥ 1% membranous staining</td>
</tr>
<tr>
<td>PD-L1 positivity</td>
<td>All 40%</td>
<td>20.7%</td>
<td>41.7%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Epitheloid 33%</td>
<td>20%</td>
<td>33%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>Non-epitheloid 38%</td>
<td>73%</td>
<td>42%*</td>
<td>37%</td>
</tr>
</tbody>
</table>

*Strong positivity predominantly in non-epitheloid tumors

<sup>1</sup>Mansfield, JTO 2014, <sup>2</sup>Cedres, Plos One 2015, <sup>3</sup>Thapa, ASCO 2016, <sup>4</sup>Combaz-Lair, Human Pathol 2016
Whole-exome sequencing on DNA from 22 MPMs and matched blood samples. Identification of 517 somatic mutations across 490 mutated genes

Mesothelioma contain an average of 24 protein coding alteration per sample, a rate considerably lower than other types malignancies

*Bueno, Nat Gen 2016*
T-cell inflamed microenvironment by tumor entity across TCGA solid tumors

MESOT-TREM-2008 and 2012: Tremelimumab in mesothelioma

- Tremelimumab 15 mg/kg q12 ws
- 29 patients with chemotherapy resistant disease
- 2 patients with durable partial responses lasting 6 and 18 months
- Disease control in 31%
- Median PFS and OS 6.2 and 10.7 months

- Tremelimumab 10 mg/kg q4ws
- 29 patients with chemotherapy resistant disease
- Disease control in 31%
- Median Ir PFS and OS 6.2 and 11.3 months;

Tremelimumab in second or third line versus placebo in malignant mesothelioma

**DETERMINE Study Design**

Global, Randomized, Double-Blind, Placebo-Controlled, Phase 2b Trial

- N=571
  - Pleural/peritoneal MM
  - ECOG PS 0–1
  - 1–2 prior regimens (including a platinum)
  - Measurable disease
- 2:1 randomization
- Stratification:
  - Pleural vs. peritoneal
  - 2nd vs. 3rd line
  - EORTC low vs. high risk
- Tremelimumab i.v.
  - 10 mg/kg q4w x 7 doses, then q12w
  - n=382
- Placebo i.v.
  - n=189

**Primary endpoint:** Overall survival (OS)

Key secondary endpoints: 18-month OS, PFS, overall response rate and duration, disease control rate (DCR), durable DCR, safety

**Statistics:** 90% power to detect an overall HR of 0.71 (increase in median OS from 7 to 9.3 mo) using a 2-sided 0.05 level test

**DETERMINE: Overall Survival (ITT Population)**

- Events, n (%): 307 (80.4%) vs. 154 (81.5%)
- Median OS (mo): 7.7 vs. 7.3
- 18-mo survival: 17.4% vs. 18.2%

Analysis with 2 stratification factors (EORTC status and line of therapy)*

OS HR = 0.92

95% 2-sided CI: 0.76, 1.12
2-sided p-value = 0.408

* p-value for OS derived from stratified log-rank test; HR and its CI derived from stratified Cox regression. With 2 q-q loss of death with tremelimumab.

Kindler ASCO 2016
KEYNOTE-028: Pembrolizumab mesothelioma cohort, PD-L1 positive

**PD-L1 Screening: MPM Cohort**
- Patients Screened: n = 84
- Samples Evaluable for PD-L1: n = 80
- PD-L1-Positive Tumors: n = 38
- Patients Enrolled: N = 25

**Change From Baseline in Tumor Size**
- 60.9% with decrease from baseline

**Treatment Exposure and Response Duration**
- Objective response rate: 28.0% (95% CI, 12.1–49.4)
- Disease control rate: 76.0% (95% CI, 54.9–90.6)

Alley, WCLC 2015
Summarizing available results on immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Keynote-028 PD-L1+</th>
<th>NivoMes Unselected</th>
<th>Avelumab Unselected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Number</td>
<td>25</td>
<td>18</td>
<td>53</td>
</tr>
<tr>
<td>PR</td>
<td>7 (28%)</td>
<td>5 (27%)</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td>SD</td>
<td>12 (48%)</td>
<td>4 (22%)</td>
<td>27 (47.2%)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (16%)</td>
<td>9 (50%)</td>
<td>18 (34%)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>2 (8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Level of PD-L1 expression in Keynote-028 did not correlate with response. Both PD-L1 positive and negative patients responded to Avelumab. Response to Avelumab was not associated with TIL or tumour PD-L1 staining.
PROMISE-meso: Pembrolizumab in advanced pretreated malignant pleural mesothelioma

Study design:
- Multicentre, randomised, phase III trial, ETOP sponsored

Primary objectives:
- To assess safety and efficacy of pembrolizumab versus standard chemotherapy in MPM

Primary endpoint:
- Progression-free survival (based on independent radiological review)

Sample size:
- 142 randomized patients
CA209-743: A phase III, randomized, open label trial of nivolumab in combination with Ipilimumab versus pemetrexed with cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma

Study design:

- **Key eligibility criteria**
  - Unresectable untreated pleural mesothelioma
  - Available tumor sample
  - PS 0-1
  - No prior Chemotherapy for pleural mesothelioma

- **Ipiilimumab 1 mg/kg Q6 weeks + Nivolumab 3 mg/kg Q2 weeks (up to progression/toxicity*)

- **Stratification Factors**
  - Histology (epithelioid vs. sarcomatoid or mixed histology subtypes)
  - Gender

- **Cisplatin 75mg/m2 or Carboplatin AUC 5 + Pemetrexed 500 mg/m2 in 21 day cycles for up to six cycles**

- **Treatment beyond initial investigator assessed progression according to mRECIST specific to mesothelioma, will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.**

**ClinicalTrials.gov Identifier: NCT02899299**