Immune Checkpoint Inhibition in Mesothelioma

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Milano, November 29 2019
Mesothelioma: Timeline of research and legal milestones

1949 | Doll reports that asbestos exposure is associated with an increased risk of lung cancer

1955 | The UK Asbestos Regulations control asbestos exposure in the workplace

1956 | Selikoff reports excess incidence of lung cancer and mesothelioma in asbestos workers

1964 | The UK Chief Inspector of Factories reports more frequent lung cancer in cases of asbestosis

1965 | Wagner identifies a link between asbestos exposure and mesothelioma

1969 | Newhouse and Thompson report asbestos exposure in mesothelioma cases: wives washing work clothes of exposed husbands was an exposure mechanism

1970 | US Federal Clean Air Act identifies asbestos as a hazardous pollutant

1985 | IARC Working Group classifies asbestos into IARC Group 1, carcinogenic to humans

2003 | UK Control of Asbestos Regulations Act prohibits the use, supply and importation of all asbestos

2011 | MAPS phase III trial confirms benefit from addition of bevacizumab to pemetrexed and cisplatin

2015 | Familial mesothelioma risk is postulated from Turkish studies of environmental erionite exposure

2016 | BAP1 loss of function results in EZH2-dependent transformation. Phase II EZH2 inhibitor trial opens to test this hypothesis in 2016 (REF 79)

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).

**PFS**

- **Pemetrexed/Cisplatin**
- **Cisplatin**
- Log rank p value 0.008

**OS**

- **Pemetrexed/Cisplatin**
- **Cisplatin**
- Log rank p value 0.051

**Survival Time (Months)**

- **Pts at Risk**
  - Pemetrex/Cis: 168
  - Cis: 163

- **Survival Time**
  - Cis: 128
  - Mts: 131

**PFS**

- **Pts at Risk**
  - Pemetrex/Cis: 100
  - Cis: 63

- **Time to PD (Months)**
  - Pemetrex/Cis: 33
  - Cis: 24

**Vogelzang, JCO 2003**
MAPS trial: Cisplatin/pemetrexe 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
- Malignant Pleural Mesothelioma (MPM)
- Histologically proven
- PS: 0-2
- No cardiovascular comorbidity
- Chemonaive

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

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

Median PFS: 7.48 mo, 95%CI: [6.79-8.13]
Median PFS: 9.59 mo, 95%CI: [8.49-10.59]

Median OS: 16.07 mo, 95%CI: [14.00-17.93]
Median OS: 18.82 mo, 95%CI: [15.90-22.62]
Nintedanib plus pemetrexed/cisplatin in patients with malignant pleural mesothelioma: Phase II results from the randomized, placebo-controlled LUME-meso Trial

All histologies

Epitheloid only

Grosso, JCO 2017
Nintedanib + pemetrexed/cisplatin in patients with unresectable MPM: Phase III results from the LUME-meso trial
Mesothelioma – low mutational load and high T-cell inflamed microenvironment

Bueno, Nat Gen 2016

Tremelimumab (CTLA4 antibody) in mesothelioma

- 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 as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial.

**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

![Graph showing overall survival comparison between Tremelimumab and Placebo](image)

- **Overall survival (%)**
- **Time since randomisation (months)**
- **Number at risk (number censored)**
  - Tremelimumab: 382 (0), 300 (5), 232 (11), 163 (13), 116 (13), 69 (29), 36 (48), 16 (63), 3 (72), 1 (74), 0 (75)
  - Placebo: 189 (0), 147 (3), 103 (6), 70 (9), 48 (10), 32 (14), 17 (26), 8 (29), 2 (34), 0 (35)

**SD in placebo arm 22%**

**Maio, Lancet Oncol 2017**
Summarizing available results on single agent immune checkpoint inhibition in mesothelioma second or later line

<table>
<thead>
<tr>
<th>Study</th>
<th>Keynote-028 + Pembrolizumab</th>
<th>NivoMes Nivolumab</th>
<th>MERIT Nivolumab</th>
<th>“Chicago” Pembrolizumab</th>
<th>Avelumab Unselected</th>
</tr>
</thead>
<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%)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>8 (24%)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>10 (29.4)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>14 (22%)&lt;sup&gt;2, 3&lt;/sup&gt;</td>
<td>5 (9%)&lt;sup&gt;1&lt;/sup&gt;</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>
</tr>
<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>

<sup>1</sup> Levels of PD-L1 expression did not correlate with response
<sup>2</sup> Higher responses in PD-L1 positive tumors
<sup>3</sup> Higher responses in sarcomatous mesothelioma

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Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial

RR 20%

Median PFS 5.5 months
Median OS 18 months
Summarizing available results on combined therapy with immune checkpoint inhibition in second or first line

<table>
<thead>
<tr>
<th>Study</th>
<th>MAPS-2</th>
<th>INITIATE</th>
<th>NIBIT</th>
<th>DREAM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo</td>
<td>Ipi/Nivo</td>
<td>Ipi/Nvo</td>
<td>Tremi/Durma*</td>
</tr>
<tr>
<td>Patient Number</td>
<td>54</td>
<td>54</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>PR</td>
<td>19%</td>
<td>29%</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>
</tr>
<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% 57% (ns)</td>
</tr>
</tbody>
</table>
Nivolumab or nivolumab plus ipilimumub 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

RR 19%

RR 28%
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

Median PFS
4.0 months
5.6 months

Median OS
11.9 months
15.9 months

Scherpereel, Lancet Oncol 2019
Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study

Median OS 16.6 months

RR 28%

Median response duration 16.1 months

Median PFS 5.7 months
DREAM: Final results of a phase 2 trial of durvalumab with first line chemotherapy in mesothelioma

**Trial design – Single-arm, multicentre phase II trial with a safety run-in, N=56**

**Population**
- 1st line MPM
- Non-surgical
- No prior RT to measurable disease
- ECOG PS 0-1
- No PD-L1 selection

**Induction**
- Cisplatin 75mg/m² + Pemetrexed 500mg/m² + Durvalumab 1125mg q3w

**Maintenance**
- Durvalumab 1125mg q3w x 52 w

**Outcomes**
- PFS6*
- OTRR (CR + PR)*
- Toxicity
- PFS
- OS
- mRECIST for MPM, mirRC

**Statistical considerations**
- 2-stage Simon’s design: 31 in stage 1, additional 23 in stage 2, for total n=54
- 6 patients in an initial safety run-in using a 3+3 design
- The hypothesis was that the regimen would be worthy of pursuit if the true PFS6 rate was 65% or higher, but not if it was 45% or lower
- 90% power with a one-sided type 1 error rate of 5%

*Nowak, WCLC 2017
DREAM: Final results of a phase 2 trial of durvalumab with first line chemotherapy in mesothelioma

Objective tumour response

<table>
<thead>
<tr>
<th></th>
<th>Confirmed response mRECIST (%)</th>
<th>Confirmed response IREIST (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>26 (48)</td>
<td>27 (50)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20 (37)</td>
<td>20 (37)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (15)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

Nowak, WCLC 2017
Key eligibility criteria

- Malignant pleural mesothelioma (all histologies)
- Progression after previous platinum-based chemotherapy
- ECOG PS 0-1
- Measurable or evaluable disease according to RECIST 1.1 criteria
- Adequate haematological, renal, and liver function
- Availability of tumour tissue for translational research

Institutional choice

Chemotherapy
- Pembrolizumab: 200 mg fixed dose *i.v.* day 1 of each 3-week cycle (q3w)
- Gemcitabine 1000 mg/m^2^ d1/8 q3w *i.v.*
- Vinorelbine 30 mg/m^2^ d1/8 q3w *i.v.*
- Vinorelbine 60/80 mg/m^2^ d1/8 q3w *p.o.*

Pembrolizumab

200 mg fixed dose *i.v.* day 1 of each 3-week cycle (q3w)

Primary endpoint:
Progression-free survival (PFS) assessed by blinded independent central review (BICR)

Secondary endpoints:
- Objective response rate (ORR)
- Time to treatment failure (TTF)
- Overall survival (OS)
- Investigator assessed (IA) PFS
- Adverse events

Correlative endpoints:
- Outcome by PD-L1 status

Treatment until progression by RECIST 1.1, max 2 years*
* beyond PD allowed in case of clinical benefit

RECIST 1.1 Assessment:
Every 9 weeks for the first 6 months and 12 weeks thereafter

Cross-over to pembrolizumab allowed at progression

*Stratification factor
Histological subtype: Epithelioid vs. Non-epithelioid

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**Design:** Phase III, randomised 1:1

**Stratification factors:** Histological subtype (epithelioid vs. non-epithelioid)

**Assumption:** median PFS with standard chemotherapy 3.5 months

**Target:**

- detect an increase of **median PFS to 6 months under pembrolizumab** (80% power at an one-sided significance level of 2.5%)
- HR=0.58 (6-month PFS: 30% for chemotherapy and 50% for pembrolizumab)
- a total of 110 events needed

**Expected accrual rate:** 2 pts per month for the first 6 months increasing to 10 thereafter

**Planned sample size:** **142 patients** (accrued over 19 months)
Patients registered in ETOP database N=151

Randomized N=144 (Sep17 – Aug18) Pts ineligible for inclusion n=7

Chemotherapy

Allocation

N=71

N=73

Follow-up

Still on follow-up N=34 Withdrawals n=2

Still on follow-up N=36 Withdrawals n=1

Treatment

Received ≥1 dose N=72
Still on treatment n=8
Off treatment n=64
Reasons: Progression n=56
Death n=5
Toxicity n=1
Patient decision n=1
Other n=2

Received ≥1 dose N=70
Germitigbinc: 12 (17%), Vinorelbine: 58 (83%)
Still on treatment n=5
Off treatment n=66
Reasons: Progression n=47
Death n=4
Toxicity n=6
Investigator decision n=6
Patient decision n=2
Other n=1

ITT analysis

N=73

N=71

- Accrual period:
  12 September 2017 – 13 August 2018
- Accrual rate: 13 pts/m, exceeding expected 10

- Patients by country:
  74% Great Britain, 19% Switzerland, 7% Spain

- Median Follow-up (Interquartile range):
  11.8 months (9.9-14.5)

45 (63%) chemotherapy patients crossed over to pembrolizumab at progression
Progression-Free Survival by BICR

<table>
<thead>
<tr>
<th></th>
<th>Events/N</th>
<th>Median PFS (95%CI)</th>
<th>6m PFS% (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>56/71</td>
<td>3.4 m (2.2, 4.3)</td>
<td>27.4% (17.1, 38.7)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>62/73</td>
<td>2.5 m (2.1, 4.2)</td>
<td>25.0% (15.5, 35.6)</td>
</tr>
</tbody>
</table>

HR* (95%CI): 1.06 (0.73, 1.53)
p* = 0.76

*Stratified by histological subtype

92% (91/99) BICR PDs were identified also by IA
PFS (BICR) for subgroups defined by variables of clinical interest

<table>
<thead>
<tr>
<th>Gender</th>
<th>Events/ N</th>
<th>Median PFS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>22/ 26</td>
<td>4.2</td>
<td>0.79 (0.33, 1.88)</td>
</tr>
<tr>
<td>Male</td>
<td>96/ 118</td>
<td>2.5</td>
<td>1.13 (0.75, 1.69)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>62/ 71</td>
<td>2.3</td>
<td>1.07 (0.64, 1.78)</td>
</tr>
<tr>
<td>≥70</td>
<td>56/ 73</td>
<td>4.1</td>
<td>0.95 (0.56, 1.63)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>28/ 35</td>
<td>3.7</td>
<td>1.10 (0.51, 2.39)</td>
</tr>
<tr>
<td>1</td>
<td>88/ 108</td>
<td>3.4</td>
<td>1.04 (0.68, 1.58)</td>
</tr>
<tr>
<td>EORTC score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good prognosis</td>
<td>77/ 99</td>
<td>4.1</td>
<td>0.97 (0.62, 1.53)</td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>41/ 45</td>
<td>2.0</td>
<td>1.04 (0.55, 1.95)</td>
</tr>
<tr>
<td>Histological Subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-epithelioid</td>
<td>14/ 16</td>
<td>3.4</td>
<td>1.76 (0.58, 5.33)</td>
</tr>
<tr>
<td>Epithelioid</td>
<td>104/ 128</td>
<td>3.2</td>
<td>0.99 (0.68, 1.47)</td>
</tr>
<tr>
<td>All patients</td>
<td>118/ 144</td>
<td>3.4</td>
<td>1.04 (0.72, 1.50)</td>
</tr>
</tbody>
</table>

*HRs unstratified, unadjusted

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### Best Overall Response – Duration of Response (DOR) by BICR

<table>
<thead>
<tr>
<th>Pembrolizumab N (%)</th>
<th>Chemotherapy N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td><em><em>Med. DOR</em> (95% CI)</em>*</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>22% (13%, 33%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>16 (21.9)</td>
</tr>
<tr>
<td>Progression of Disease (PD)</td>
<td>33 (45.2)</td>
</tr>
<tr>
<td>Not Evaluable (NE)</td>
<td>7 (9.6)</td>
</tr>
</tbody>
</table>

* Stratified p=0.004

**Median DOR* (95% CI)**

- Pembrolizumab: 4.6 months (2.2, 10.3) with 16 responders (7 PD and 4 deaths)
- Chemotherapy: 11.2 months (6.2, 15.3) with 4 responders (3 PD)
Overall Survival: ITT analysis

<table>
<thead>
<tr>
<th></th>
<th>Deaths/N</th>
<th>Median OS (95% CI)</th>
<th>6m OS% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>34/71</td>
<td>11.7 m (7.4, NE)</td>
<td>72.9% (60.8, 81.7)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>37/73</td>
<td>10.7 m (7.6, NE)</td>
<td>68.5% (56.5, 77.8)</td>
</tr>
</tbody>
</table>

NE: Not estimable

Adjusting for Cross-over

<table>
<thead>
<tr>
<th>Analysis</th>
<th>HR* (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censored</td>
<td>1.44 (0.77, 2.67)</td>
<td>0.25</td>
</tr>
<tr>
<td>Inverse probability weighting (IPW)</td>
<td>1.07 (0.67, 1.71)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

HR*: Stratified by histological subtype

No at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>+ Censored</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stratified by histological subtype
### PFS (BICR) by PD-L1 status

**ETOP 9-15 PROMISE-meso | 2019 ESMO Congress, Barcelona**

#### Events/N Table

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95%CI)</th>
<th>6m PFS (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemo.</strong></td>
<td>4.4 m (1.4, 7.4)</td>
<td>46.3% (20.2, 69.1)</td>
</tr>
<tr>
<td><strong>Pembro.</strong></td>
<td>4.2 m (2.1, 7.6)</td>
<td>34.0% (14.0, 55.3)</td>
</tr>
</tbody>
</table>

**HR* (95%CI):**

- **TPS <1%**
  - 1.26 (0.56, 2.83)  
  - p* = 0.57

- **TPS ≥1%**
  - 1.06 (0.63, 1.80)  
  - p* = 0.82

*Stratified by histological subtype

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**OS (ITT) by PD-L1 status**

<table>
<thead>
<tr>
<th></th>
<th>Deaths/N</th>
<th>Median OS (95%CI)</th>
<th>6m OS (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemo.</strong></td>
<td>9/17</td>
<td>9.9 m (4.0, NE)</td>
<td>70.6% (43.1, 86.6)</td>
</tr>
<tr>
<td><strong>Pembro</strong></td>
<td>7/19</td>
<td>11.7 m (7.6, NE)</td>
<td>78.9% (53.2, 91.5)</td>
</tr>
</tbody>
</table>

**TPS <1%**

- **Chemotherapy**: 12/34
  - Median OS: NR (7.3, NE)
  - 6m OS: 76.5% (58.4, 87.5)

- **Pembro**: 16/32
  - Median OS: 10.7 m (6.8, NE)
  - 6m OS: 71.9% (52.9, 84.3)

**HR* (95%CI): 1.47 (0.69, 3.11)**

**p* = 0.32**

---

**TPS ≥1%**

- **Chemotherapy**: 9/17
  - Median OS: 9.9 (4.0, NE)
  - 6m OS: 70.6% (43.1, 86.6)

- **Pembro**: 7/19
  - Median OS: 11.7 m (7.6, NE)
  - 6m OS: 78.9% (53.2, 91.5)

**HR* (95%CI): 0.72 (0.26, 2.00)**

**p* = 0.53**

---

*Stratified by histological subtype*
Safety summary (N=142 patients, safety cohort)

<table>
<thead>
<tr>
<th>Safety cohort</th>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety cohort</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>Patients experiencing:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Adverse Event (AE)</td>
<td>70 (97.2)</td>
<td>65 (92.9)</td>
</tr>
<tr>
<td>Any Treatment-related AE (TrAE)</td>
<td>50 (69.4)</td>
<td>51 (72.9)</td>
</tr>
<tr>
<td>TrAEs of grade 3-5</td>
<td>14 (19.4)</td>
<td>17 (24.3)</td>
</tr>
<tr>
<td>TrAEs leading to treatment discontinuation</td>
<td>6 (8.3)</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>TrAEs leading to death</td>
<td>1* (1.4)</td>
<td>1** (1.4)</td>
</tr>
</tbody>
</table>

* Confusion
**Dyspnea, with disease progression being the primary cause of death

Most frequent treatment-related AEs (≥10%)

- Fatigue
- Diarrhea
- Nausea
- Anorexia
- Constipation
- Pruritus
- Mucositis oral
- Dry skin
- Vomiting
- Rash maculo-papular
- Neutrophil count decreased

- Pembrolizumab
- Chemotherapy

p<5%
CA209-743: A phase III, randomized, open label trial of nivolumab in combination with Ipiilimumab 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 m-RECIST 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

- Primary Outcome Measures:
  - OS / PFS
- Secondary/exploratory Outcome Measures:
  - ORR, DCR, PRO, association between PD-L1 expression and efficacy measures, safety, PK/immunogenicity
<table>
<thead>
<tr>
<th>Phase</th>
<th>Line</th>
<th>Primary endpoint</th>
<th>Sample size</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II/III</td>
<td>1L</td>
<td>OS</td>
<td>320</td>
<td>A Multicentre Randomised Phase III Trial Comparing Atezolizumab Plus Bevacizumab and Standard Chemotherapy Versus Bevacizumab and Standard Chemotherapy as First-line Treatment for Advanced Malignant Pleural Mesothelioma (BEAT-meso) NCT03762018</td>
</tr>
<tr>
<td>Phase II/III</td>
<td>1L</td>
<td>PFS OS</td>
<td>126</td>
<td>A Phase II/III Randomized Study of Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma NCT02784171</td>
</tr>
<tr>
<td>Phase II/III</td>
<td>Maintenance</td>
<td>OS</td>
<td>230</td>
<td>A Randomized, Open-Label Phase II/III Study With Dendritic Cells Loaded With Allogeneic Tumour Cell Lysate in Subjects With Mesothelioma as Maintenance Treatment After Chemotherapy (DENIM) NCT03610360</td>
</tr>
<tr>
<td>Phase III</td>
<td>2L</td>
<td>RR QL</td>
<td>336</td>
<td>CheckpOiNt Blockade For Inhibition of Relapsed Mesothelioma (CONFIRM): A Phase III Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy of Nivolumab in Relapsed Mesothelioma NCT03063450</td>
</tr>
</tbody>
</table>
Study design:
- Randomised multicentre phase III
- ETOP sponsored

Co-primary endpoints:
- Progression-free survival
- Overall survival

Secondary endpoints:
- Overall response
- Disease control
- Time to treatment failure
- Duration of response
- Safety and tolerability
- Patient reported outcome / QoL

Sample size:
320 randomized patients

ClinicalTrials.gov Identifier: NCT03762018
Comparison of median PFS and OS

- Targeted median PFS for the atezolizumab combination is 13 months vs 9 months without atezolizumab.
- 298 PFS events expected during 67 months, to detect 4 months increase (power=80%, 1-sided $\alpha=1\%$, HR=0.692)
- Targeted median OS for the atezolizumab combination is 24 months vs to 17 months without atezolizumab.
- 253 OS events expected during 67 months, to detect 7 months increase (power=83.7%, 1-sided $\alpha=4\%$, HR=0.708).
### ETOP 13-18 BEAT-meso – Participating Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of participating centres</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planned</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>10</td>
</tr>
<tr>
<td>Switzerland</td>
<td>9</td>
</tr>
<tr>
<td>Spain</td>
<td>7</td>
</tr>
<tr>
<td>France</td>
<td>9</td>
</tr>
<tr>
<td>Italy</td>
<td>6</td>
</tr>
<tr>
<td>Belgium</td>
<td>2</td>
</tr>
<tr>
<td>Portugal</td>
<td>1</td>
</tr>
<tr>
<td>Slovenia</td>
<td>1</td>
</tr>
</tbody>
</table>

| Total | 45 | 24 |
ETOP 13-18 BEAT-meso – Accrual

**Total patients**

<table>
<thead>
<tr>
<th>Year</th>
<th>Actual accrual</th>
<th>Accrual forecast</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>53 pts randomised</td>
<td>as of 25.11.2019</td>
</tr>
<tr>
<td>2020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2021</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2022</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FPI**

- 30.04.2019

<table>
<thead>
<tr>
<th>Country</th>
<th>Accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>19</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>11</td>
</tr>
<tr>
<td>Switzerland</td>
<td>9</td>
</tr>
<tr>
<td>Belgium</td>
<td>-</td>
</tr>
<tr>
<td>France</td>
<td>-</td>
</tr>
<tr>
<td>Italy</td>
<td>-</td>
</tr>
<tr>
<td>Portugal</td>
<td>-</td>
</tr>
<tr>
<td>Slovenia</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>39</strong></td>
</tr>
</tbody>
</table>
CONFIRM: a double-blind, placebo-controlled phase III clinical trial investigating the effect of nivolumab in patients with relapsed mesothelioma: study protocol for randomised controlled trial

- Randomized phase III
- 336 patients
- Primary endpoint OS
Autologous Dendritic Cells Pulsed with Allogeneic Tumor Cell Lysate in Mesothelioma: From Mouse to Human
Scientific advances and new frontiers in mesothelioma therapeutics
Arginin deprivation with pegylated arginine deiminase in patients with argininosuccinate synthetase 1-deficient malignant pleural mesothelioma

- Patients registered: 201
  - ASS1 negative: 97
  - Randomized: 70
    - ASS1-negative patients not randomized: 27
    - ASS1 positive: 83
      - ASS1 status unknown: 21

- Randomized to ADI-PEG20 + BSC: 46
  - Randomized to BSC alone: 24
  - Ineligible: 2
    - ECOG 2
    - Nonmeasurable disease
  - Received ADI-PEG20 + BSC as randomized: 44
    - Received BSC as randomized: 22
      - Withdrew from study because they wanted chemotherapy
    - Analyzed for PFS and OS: 24
      - Analyzed for PFS and OS (intention-to-treat analysis): 25
    - ASS1-negative patients analyzed for OS: 44
    - ASS1-positive patients analyzed for OS: 25

- Median survival, mo:
  - ADI-PEG20 vs BSC:
    - Alive and progression-free:
      - Hazard ratio: 0.56 (95% CI: 0.33-0.96)
      - Log rank P = .03 (1-sided P = .02)
    - Median survival:
      - BSC: 2.0
      - ADI-PEG20 vs BSC: 3.2
  - Alive:
    - Hazard ratio: 0.68 (95% CI: 0.39-1.16)
    - Log rank P = .15 (1-sided P = .08)

- No. at risk:
  - BSC: 24
    - Time Since Randomization, mo:
      - 0 3 6 9 12 15 18 21
      - Alive and Progression-Free, %:
        - Median survival, mo: 2.0
        - Hazard ratio: 0.56 (95% CI: 0.33-0.96)
        - Log rank P = .03 (1-sided P = .02)
  - ADI-PEG20: 44
    - Time Since Randomization, mo:
      - 0 3 6 9 12 15 18 21
      - Alive and Progression-Free, %:
        - Median survival, mo: 3.2
        - Hazard ratio: 0.56 (95% CI: 0.33-0.96)
        - Log rank P = .03 (1-sided P = .02)

Szlosarek, JAMA Oncol 2016
Phase I study of lentiviral-transduced chimeric antigen receptor-modified T cells recognizing mesothelin in advanced solid cancers

CART-meso cells were well tolerated and expanded in the blood of all patients but showed limited clinical activity.
SAKK 17/16: Lurbinectedin as second or third line palliative chemotherapy in malignant pleural mesothelioma: a multi-center, single-arm phase II trial

**RESULTS: PFS**

<table>
<thead>
<tr>
<th>PFS12wks</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon’s First-stage</td>
<td>11/21</td>
</tr>
<tr>
<td>All patients</td>
<td>22/42 (52.4%) (90% CI: 38.7%-63.5%)</td>
</tr>
</tbody>
</table>

RR 5%

Median PFS 4.1 months

95% CI 2.6 - 5.5 months
Conclusions on immune checkpoint inhibition in mesothelioma

- Mesothelioma have a low TMB but are associated with an inflammatory T cell signature
- Immune checkpoint inhibition in second line results in an objective response rates ranging from from 9 to 29% and progression-free survival ranging from 2.6 to 6.1 months
- PROMISE-meso, the only randomized trial of second line pembrolizumab as compared to single agent chemotherapy failed to show an improvement in progression free-survival or overall survival
- Nevertheless, pembrolizumab was associated with a significantly improved objective response rate as determined by independent radiological review
Conclusions on immune checkpoint inhibition in mesothelioma

• Further exploratory translational work is ongoing to identify subgroups that could benefit from pembrolizumab
• Ongoing randomized phase III trials include CONFIRM in second line and CheckMate-743 and BEAT-meso in first line