Treatment of unresectable malignant pleural mesothelioma: current armamentarium and future prospects

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Disclosures

Advisory boards
AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Clovis, Eli Lilly, Lab21, Oncos, Polaris

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Speaker bureau
Boehringer Ingelheim, Roche, BMS, MSD
Nintedanib

In the European Union and other countries worldwide, nintedanib is approved in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy.

Nintedanib is not approved in any oncology indication in Switzerland.
Mesothelioma: at a therapeutic plateau since circa 2003

**Rapid development**

**Therapeutic plateau**

MS, median survival; OS, overall survival; Pem/cis, pemetrexed/cisplatin.


Please see slide notes for copyright acknowledgements
Targeting angiogenesis

Immunotherapy

Molecularly stratified therapy
MAPS: an open-label, randomised Phase II/III trial

**Patients**
- MPM
- No CV comorbidity
- ECOG PS 0–2
- No previous chemotherapy
- Eligible for bevacizumab therapy

**RANDOMISE**

1:1

N=448

- **Bevacizumab 15 mg/kg (Day 1) + pemetrexed + cisplatin** (n=223)
- **Bevacizumab 15 mg/kg until progression**
- **Pemetrexed + cisplatin** (n=225)
- **Surveillance**

**Endpoints:**
- **Primary:** DCR at 6 months (Phase II)/OS (Phase III)
- **Secondary:** PFS, quality of life and safety

- **Stratification factors:** ECOG PS (0/1 vs 2); centre; histology (epithelioid vs sarcomatoid or mixed); smoking status

*500 mg/m² pemetrexed plus 75 mg/m² cisplatin in 21-day cycles for up to 6 cycles. CV, cardiovascular; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; MPM, malignant pleural mesothelioma; PFS, progression-free survival. Zalcman et al. Lancet 2016;387:1405–14.
MAPS: efficacy of bevacizumab in combination with pemetrexed/cisplatin

**PFS**

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab + chemotherapy</th>
<th>Placebo + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI); months</td>
<td>9.2 (8.5–10.5)</td>
<td>7.3 (6.7–8.0)</td>
</tr>
<tr>
<td>HR (95% CI); p value</td>
<td>0.61 (0.5–0.75); p=0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab + chemotherapy</th>
<th>Placebo + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI); months</td>
<td>18.8 (15.9–22.6)</td>
<td>16.1 (14.0–19.9)</td>
</tr>
<tr>
<td>HR (95% CI); p value</td>
<td>0.77 (0.62–0.95); p=0.0167</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.
Nintedanib as therapy for MPM

- Nintedanib is an oral, multikinase inhibitor targeting VEGFRs 1–3, PDGFRs α/β, FGFRs 1–3, as well as Src and Abl kinase signalling\(^1,2\)

- Nintedanib has a manageable safety profile in combination with commonly used chemotherapy agents\(^3–7\)

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LUME-Meso: Phase II study design

- Patients with unresectable MPM
- Epithelioid and biphasic histology
- Measurable disease according to modified RECIST criteria
- ECOG PS 0–1
- No prior chemotherapy

**RANDOMISE**

Nintedanib: 200 mg bid + pemetrexed/cisplatin*  
Non-PD patients  
Nintedanib maintenance  
Arm A

Placebo: 200 mg bid + pemetrexed/cisplatin*  
Non-PD patients  
Placebo maintenance  
Arm B

Primary endpoint: PFS: Arm A vs Arm B  
Secondary endpoints: OS, ORR  
Further endpoint: FVC

Stratification by histology (epithelioid vs biphasic)

LUME-Meso Phase II: PFS

**ITT population**

<table>
<thead>
<tr>
<th></th>
<th>Nintedanib + chemotherapy</th>
<th>Placebo + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI); months</td>
<td>9.4 (6.7–11.2)</td>
<td>5.7 (5.5–7.0)</td>
</tr>
<tr>
<td>HR (95% CI); p value</td>
<td>0.54 (0.33–0.87); p=0.010</td>
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</tbody>
</table>

**Patients with epithelioid histology**

<table>
<thead>
<tr>
<th></th>
<th>Nintedanib + chemotherapy</th>
<th>Placebo + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI); months</td>
<td>9.7 (6.7–11.2)</td>
<td>5.7 (5.5–7.0)</td>
</tr>
<tr>
<td>HR (95% CI); p value</td>
<td>0.49 (0.30–0.82); p=0.006</td>
<td></td>
</tr>
</tbody>
</table>

ITT, intention to treat.  
**LUME-Meso Phase II: overall frequency of Grade ≥3 AEs**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nintedanib + chemotherapy</th>
<th>Placebo + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia*</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Liver-related investigations</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Increased GGT</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Anaemia</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

**AEs leading to study discontinuation were reported in 6.8% of patients in the nintedanib arm and 17.1% of patients in the placebo arm**

AEs by user-defined group terms and worst CTCAE grade. *Two patients in the nintedanib arm were reported to have febrile neutropenia. Fatal serious AEs: one nintedanib-treated patient (PD unrelated to treatment); three placebo-treated patients (PD unrelated to treatment, n=2; PD and treatment-related nephrotic syndrome, n=1). AE, adverse event; ALT, alanine aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma-glutamyltransferase. Grosso et al. J Clin Oncol 2017:35:3591–600.
**LUME-Meso Phase III study design**

- Patients with unresectable MPM
- Epithelioid histology
- Measurable disease according to modified RECIST criteria
- ECOG PS 0–1
- No prior chemotherapy

**RANDOMISE**

- Non-PD patients
- Nintedanib maintenance
- PD**

- Non-PD patients
- Placebo maintenance
- PD**

**Endpoints:**
- **Primary endpoint:** PFS
- **Key secondary endpoint:** OS

Results expected later in 2018

*On Days 2–21; §Pemetrexed 500 mg/m² iv over 10 minutes on Day 1 of each 21-day cycle (maximum 6 cycles); ¶Cisplatin 75 mg/m² iv over 2 hours on Day 1 of each 21-day cycle (maximum 6 cycles); **Treatment beyond progression is allowed if clinical benefit is perceived.
Targeting angiogenesis

Immunotherapy

Molecularly stratified therapy
## Anti-PD-1 checkpoint inhibition in unresectable pretreated MPM

<table>
<thead>
<tr>
<th>Study</th>
<th>Keynote 28&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Chicago cohort&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NivoMes&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Study design</td>
<td>Non-randomised, open-label, single arm Phase Ib</td>
<td>Non-randomised, open-label, single arm Phase II</td>
<td>Non-randomised, open-label, single arm Phase II</td>
</tr>
<tr>
<td>Treatment</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>21%</td>
<td>15%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>52%</td>
<td>59%</td>
<td>36%</td>
</tr>
<tr>
<td>DCR</td>
<td>72%</td>
<td>80%</td>
<td>51%</td>
</tr>
<tr>
<td>PFS</td>
<td>5.4 months (95% CI: 3.4–7.5)</td>
<td>6.2 months (95% CI: 3.2–8.2)</td>
<td>–</td>
</tr>
<tr>
<td>OS</td>
<td>18 months (95% CI: 9.4–NR)</td>
<td>11.9 months (95% CI: 6.4–NR)</td>
<td>–</td>
</tr>
<tr>
<td>Durable response</td>
<td>12 months</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

NR, not reached; PD-1, programmed death-1; PR, partial response.

# Recruiting studies: IO Phase III

<table>
<thead>
<tr>
<th>Study</th>
<th>PROMISE-Meso</th>
<th>CONFIRM</th>
<th>Checkmate 743</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>142</td>
<td>336</td>
<td>600 (estimated)</td>
</tr>
<tr>
<td>Treatments</td>
<td>Pembrolizumab vs standard chemotherapy</td>
<td>Nivolumab vs placebo</td>
<td>Nivolumab + ipilimumab vs pemetrexed with cisplatin or carboplatin</td>
</tr>
<tr>
<td>Setting</td>
<td>Second-line</td>
<td>≥Third-line</td>
<td>First-line</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td>PFS</td>
<td>OS</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Clinical trial identifier</td>
<td>NCT02991482</td>
<td>NCT03063450</td>
<td>NCT02899299</td>
</tr>
</tbody>
</table>

IO, immuno-oncology; PD-L1, programmed death-ligand 1.
PD-L1: predictive of anti-PD-1 checkpoint inhibition in MPM?

**Australian cohort**
- N=46 (93% more than one prior line of therapy)
- PR=15% (Median duration NR), stable disease = 33% (DCR 48%)
- ORR 50% PD-L1^{HI}>50% vs 22% PD-L1^{low} <5%

**PFS**
- HR=0.17 (95% CI: 0.02–1.47, p=0.11)

**OS**
- HR=0.28 (95% CI: 0.04–2.2, p=0.2)

Immunotherapy combinations under investigation in mesothelioma

Conventional therapies
- Chemo
- Chemo/RT
- RT

Immune checkpoint inhibitors
- OX40
- CTLA4
- IDO

PD-1/PD-L1

Vaccine
- LADD

Targeted therapy
- ADC

IME modulators
- AXL
- FAK
- VEGF
- ASS1

ADC, antibody-drug conjugates; ASS1, argininosuccinate synthetase-1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; FAK, focal adhesion kinase; IDO, indoleamine-2,3-dioxygenase; LADD, live attenuated double-deleted (Listeria platform); RT, radiotherapy.
Re-programming dendritic cells to attack mesothelioma: the DENIM Phase III trial

Horizon 2020: The EU Framework Programme for Research and Innovation
Targeting angiogenesis

Immunotherapy

Molecularly stratified therapy
Arginine deprivation is synthetic lethal to ASS1 deficient mesothelioma

ASS negative mesothelioma

ADI monotherapy

ASS1 loss greater than 75%

HR=0.25
(95% CI: 0.09 – 0.70)
p=0.008

BSC
ADI-PEG20

ATOMIC (Phase III)

Biphasic/sarcomatoid MPM

ADI, arginine deiminase.

Mesothelioma subtypes exhibit distinct genomic landscapes

CNV, copy number variation; SNV, single nucleotide variant.
BAP1: a new, promising drug target

BAP1 mutation causes mesothelioma via EZH2

Loss of BAP1 function leads to EZH2-dependent transformation

BAP1, BRCA1 associated protein 1; EZH2, enhancer of zeste homolog 2; PRC2, polycomb repressive complex 2. LaFave et al. Nat Med 2015;21:1344–9.
The gene BAP1 when mutated, sensitises to inhibitors of EZH2

Identifying novel synthetic lethal interactions: BAP1

Cell lines

Xenografts

Explants


Please see slide notes for copyright acknowledgements
Countering miRNA loss: miR-16 targomiRs

PRMT5 inhibition for MTAP negative mesothelioma?

Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5

Molecular stratification: time for adaptable umbrella designs?

Stage 1: Molecular pre-screening

- Inoperable mesothelioma
- Pleural, peritoneal mesothelioma
- Histologically confirmed
- ECOG 0–1
- Post-first-line therapy
- Consent for tissue

Stage 2: Treatment stratification

- BAP1/BRCA1–: Rucaparaib
- p14INK4A–: Abemaciclib
- N/A: AXL/PD-1
- PD-1: VEGF/PD-L1

Stage 3: Genomic interrogation

- Primary endpoint response
- Secondary endpoint DCR
- Rebiopsy, responders

Warm post-mortem phylogenetics

Comprehensive genomic analysis

British Lung Cancer Foundation and Mesothelioma Research Programme, Leicester.
Treatment of unresectable MPM: current armamentarium and future prospects

• Therapy for mesothelioma has languished at a therapeutic plateau for over a decade

• Angiogenesis presents a new, clinically relevant therapeutic target

• Harnessing the immune system shows promise: personalisation may be essential

• Molecularly stratified therapy is feasible and could expand the repertoire of targets in the future
“The meaning of life is having a spectacular view.”