Systemic management of advanced MPM

GL Ceresoli, MD

8TH ESO ARAB AND SOUTHERN EUROPEAN COUNTRIES MASTERCLASS IN CLINICAL ONCOLOGY

23-27 January 2020, Limassol, Cyprus
Disclosure information

The speaker reports personal fees for advisory roles, speaker engagements, and travel and accommodation expenses from Boehringer-Ingelheim, Merck Sharp & Dohme, Astellas, Pfizer, and Novocure.
State of the art and unmet needs in MPM therapy

1. MPM incidence still increasing in several countries;
2. Controversial role of surgery and radiotherapy;
3. Pemetrexed/platinum standard first-line treatment;
4. No standard treatment in the second line setting.

JM Basquiat
The “g-old standard” chemotherapy for MPM

N=1704, evaluable: Cis 745, Carbo 752

Chemotherapy - maintenance: CALGB 30901

Randomized Phase II: PEM vs OBS after PR/SD following 4-6 cycles of plat/pem. Closed early due to slow accrual.

Dudek AZ et al., ASCO 2019
Chemotherapy - maintenance: NVALT 19

Randomized phase II trial
18 Dutch hospitals

Mar 2014 - Feb 2019

Primary endpoint
• Progression Free Survival

Secondary endpoints*
• Response Rate
• Overall survival
• Toxicity
• Biomarkers

*In 2016 funding became available that allowed PFS by independent review

130 pts with PR/SD after 4-6 cycles of plat/pem randomized 1:1 to receive maintenance gemcitabine (n = 65) or BSC (n = 65); 88% with epithelioid histology.

12 months PFS rate was 24% for gemcitabine vs 3% for BSC; G3-4 tox 57% vs 13%, mainly neutropenia in gemcitabine arm.

No data on OS and QoL.

Burgers SA et al. , ESMO 2019
Second-line chemotherapy in MPM

<table>
<thead>
<tr>
<th>Drug</th>
<th>PD</th>
<th>SD</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>59%</td>
<td>37%</td>
<td>4%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>47%</td>
<td>50%</td>
<td>-</td>
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</tbody>
</table>

FL-PFS > 12 months: median PFS after retreatment of 5.5 months

FL-PFS ≤ 12 months: median PFS after retreatment of 2.5 months; no patients in this group was progression-free at 1 year.

Zauderer et al., Lung Cancer 2014; Ceresoli et al., Lung Cancer 2011
An insurmountable challenge to date...

1. Absence of common targetable driver mutations;
2. Inter-patient heterogeneity;

1. Unique tumor microenvironment (angiogenesis, immunosuppression);
2. Many patients are not eligible in clinical trial (elderly).
Angiogenesis is a relevant phenomenon in MPM, as shown by preclinical models\(^1\) and by the established negative prognostic value of high serum VEGF levels in MPM patients.\(^2\)

Vascular endothelial growth factor (VEGF) and its receptors (VEGFR-1, VEGFR-2, and VEGFR-3) are highly expressed in MPM and may be potential therapeutic targets in this disease.\(^3\)


Scherpereel A, in Mesothelioma: From research to clinical practice, Eds. Ceresoli et al., Springer 2019
Bevacizumab: the MAPS trial

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

- MPM proved by pleural biopsies (thoracoscopy...)
- Written informed consent
- Age ≥18 - <75 years
- PS 0 - 2
- Chemonaive patients
- not candidate to curative intent surgery according to Multidisciplinary Board
- At least 1 evaluable or measurable lesion by CT
- Weight loss <10% within 3 months prior to enrolment
- No significant cardiovascular comorbidity and/or other usual chemo or bevac contra-indications (HTA, GI perforation...)
- Prophylactic radiotherapy (3 x 7 Gy) before chemo

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

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

Surveillance
PD: No cross-over allowed

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

Maintenance Bevacizumab 15 mg/kg D1, Q21D until PD

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

→ Phase 3 primary goal = OS; Secondary goals: PFS, QoL, ancillary studies

Stratification: center, histology (epithelioid vs sarcomatoid/mixed), PS (0-1 vs 2), smoking status

Zalcman et al., Lancet 2016
The MAPS trial: OS

Efficacy: ITT median Overall Survival (OS)

median follow-up= 39.4 months [11.0-83.05]

Arm A (PC): 16.07 mo, 95%CI: [14.00-17.93]

Arm B (PCB): 18.82 mo, 95%CI: [15.90-22.62]

Stratified HR=0.76; 95%CI [0.61-0.94]

p=0.015

IFCT 0 01 ‘MAPS’ randomized phase 3 trial

Zalcman et al., Lancet 2016
LUME-Meso Phase III

Patients with histologically confirmed, unresected epithelioid MPM
- Life expectancy of ≥3 months
- No previous systemic chemotherapy for MPM

Randomised 1:1

 Patients with histologically confirmed, unresected epithelioid MPM
- Life expectancy of ≥3 months
- No previous systemic chemotherapy for MPM

N = 458 Randomised 1:1

Selected endpoints
- Primary endpoint: PFS
- Key secondary endpoint: OS

Non-PD patients

ARM A

Nintedanib 200 mg bid* + pemetrexed/cisplatin §

Nintedanib maintenance

Non-PD patients

ARM B

Placebo 200 mg bid* + pemetrexed/cisplatin §

Placebo maintenance

*On Days 2–21; §500 mg/m² /75 mg/m² iv, every 21 days. Maximum treatment duration: 6 cycles; ¶By investigator assessment according mRECIST.

Clinical trial identifier: NCT01907100

Scagliotti et al., Lancet Resp Med 2019
LUME-Meso Phase III: PFS & OS

Scagliotti et al., Lancet Resp Med 2019
RAMES study: ramucirumab

Double-blind, placebo-controlled Multicenter Randomized Phase II Study

MPM pts with PD after Platinum/ Pemetrexed first-line chemotherapy

ARM1 (21-day-cycle)
Gemcitabine 1000mg/m² iv D1, D8 + Placebo iv D1

ARM2 (21-day-cycle)
Gemcitabine 1000mg/m² iv D1, D8 + Ramucirumab 10mg/Kg iv D1

Stratification factors
- ECOG/PS 0-1 vs 2
- Age < 70 vs > 70
- Histological subtype
- TTP < vs ≥ 6 mo

Primary objective
- OS
Secondary objective
- PFS
- ORR
- Safety
- QoL
- Predictive markers

RAMUCIRUMAB
Fully human monoclonal antibody targeting VEGF-R2.

December 2016 - July 2018: 164 pts randomized in 26 Italian Centers.
August 2019: 82 pts died (number of events for OS analysis not reached yet), 24 pts in treatment.

Ceresoli et al., AIOM 2019; Pagano et al., ESMO 2019
Mesothelin as a target in MPM

- Is a cell surface tumor differentiation antigen
- Normal expression limited to mesothelial cells of pleura, peritoneum and pericardium
- Highly expressed in many solid tumors including:
  - Mesothelioma and Pancreatic Cancer ~ 100%
  - Ovarian Cancer ~ 70%
  - Lung adenocarcinoma ~ 40%

<table>
<thead>
<tr>
<th>Mesothelioma</th>
<th>Ovarian Cancer</th>
<th>Pancreatic Cancer</th>
<th>Lung Cancer</th>
</tr>
</thead>
</table>

Hassan et al., Clin. Cancer Res., 2004

Fig 1. Approaches used to target MSLN in clinical trials. APC, antigen-presenting cell; CAR, chimeric antigen receptor; DM4, ravtansine; mAb, monoclonal antibody; PE, pseudomonas exotoxin.
Anetumab study: PFS & OS

**Patient selection criteria**
- Unresectable/metastatic MPM
- One prior line of chemotherapy
- Mesothelin-overexpression (≥30% of cells medium and strong) by central lab
- ECOG PS 0–1
- Age ≥18 years
- No/mild corneal epitheliopathy

**Endpoints**
- **Primary**
  - PFS (central review; HR 0.50, 90% power)
- **Secondary**
  - OS
  - Response (ORR, DCR, DOR)
  - PROs
  - Safety and tolerability
- **Other**
  - Pharmacokinetics
  - Immunogenicity
  - Biomarkers

**Randomization**
2:1

N=248

**Primary Endpoint: PFS**

<table>
<thead>
<tr>
<th></th>
<th>Anetumab raptansine (n=166)</th>
<th>Vinorelbine (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, months (95% CI)</td>
<td>4.3 (4.1–5.2)</td>
<td>4.5 (4.1–5.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.235 (0.850–1.738)</td>
<td>1.099 (0.720–1.667)</td>
</tr>
<tr>
<td>One-sided P-value</td>
<td>0.259</td>
<td>0.599</td>
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</tbody>
</table>

**OS – Interim Analysis**

<table>
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<tr>
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<th>Anetumab raptansine (n=166)</th>
<th>Vinorelbine (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months (95% CI)</td>
<td>10.1 (7.6–NE)</td>
<td>11.6 (7.7–12.5)</td>
</tr>
<tr>
<td>One-sided P-value</td>
<td>0.721</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*OS analysis had occurred at the time of primary PFS analysis.

Kindler et al., WCLC 2017
Genetic alterations in MPM and potential therapeutic targets

No specific mutation in a single driver gene; accumulation of several non-driver mutations (long latency phase);

Frequent alterations in BAP1, NF2, CDKN2A (oncosuppressor genes).

EZH2: enhancer of zeste homolog2: hystone methylation: transcriptional repression

Guo et al., Cancer Res 2015
Bueno et al., Nat Genet 2016
McCcambridge et al., JTO 2018
Effect of arginine deprivation on MPM tumor cells

ASS-1: argininosuccinate synthetase; ADI-PEG20: pegylated arginine deiminase

Slozarek et al., JAMA Oncol 2017; Beddowes et al., JCO 2017; McCambridge et al., JTO 2018
Stratified therapy in MPM: rare genomic events as therapeutic opportunity

**MiST Trial** (PhII)
Mesothelioma Stratified Therapy
British Lung Foundation
Chemotherapy: Trabectedin/Lurbinectedin

Direct effects on TUMOR CELLS
- DNA binding
- Cell cycle block
- DNA repair
- Inhibition TF

Effects on the tumor MICRO-ENVIRONMENT
- Mono-TAM apoptosis
- Inhibition of CCL2, CXCL8, IL-6
- Inhibition of angiogenesis

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Germano et al., Cancer Cell 2013; D’Incalci et al., Oncotarget 2013; Belgiovine et al., Br J Cancer 2017
<table>
<thead>
<tr>
<th>Agent</th>
<th>Study design and patients</th>
<th>PFS 12 wks (primary endpoint)</th>
<th>ORR</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
</table>
| **Trabectedin (ATREUS)** | **145 pts (E 78, B/S 67)**  
Non R Phase II, 2 cohorts  
Epithelioid MPM (E): 2-nd line;  
Biphasic/sarcomatoid (B/S): :1-st or 2-nd line | E: 43.5%  
B/S: 30.8% | E: PR 7%, SD 57%  
B/S: PR 2%, SD 64% | E: 2.4 mos  
B/S: 1.7 mos | E: 9.0 mos  
B/S: 5.4 mos |
| **Lurbinectedin (SAKK/1716)** | **42 pts (E 33, S 5, B 4)**  
Single arm Phase II  
2-nd line, 3-rd line if also previous line of immunotherapy | 52.4% | CR 2.4%  
PR 2.4%  
SD 47.6% | 4.1 mos* | 11.1 mos* |

* No difference according to histology, previous immunotherapy, response to first-line, except for longer OS in long responders to platinum/pemetrexed.

Cortinovis et al., IASLC Mesothelioma 2019; Metaxas et al., ESMO 2019
### Trabectedin/Lurbinectedin: G3-4 toxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Hepatotoxicity</th>
<th>Neutropenia</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trabectedin</strong> (ATREUS)</td>
<td>All pts: 59% 70% at full dose* 40% at reduced dose*</td>
<td>All pts: 20% 24% at full dose 15% at reduced dose</td>
<td>All pts: 8% Similar at the two dose levels</td>
</tr>
<tr>
<td><strong>Lurbinectedin</strong> (SAKK/1716)</td>
<td>0%</td>
<td>23.8% (9.5% febrile neutropenia)</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

* Due to the high rate of hepatotoxicity the initial dose was amended from 1.3 mg/m2 to 1.1 mg/m2.

*Cortinovis et al., IASLC Mesothelioma 2019; Metaxas et al., ESMO 2019*
TTFIELDS (Tumor Treatment Fields): a new treatment modality

TTFIELDS (Tumor Treatment Fields) are a loco-regional treatment\(^1\), comprising low intensity alternating electric fields delivered through a portable medical device.

TTFIELDS are delivered to the patient by transducer arrays (ceramic electrodes embedded in adhesive patches) connected to the field generator and applied to the patient skin surrounding the tumor.

TTFIELDS act with an anti-mitotic mechanism; they disrupt spindle formation during metaphase and interfere with localization of intracellular organelles during telophase\(^2\).

TTFIELDS had been already approved by FDA in association with temozolomide for newly-diagnosed glioblastoma\(^3\),

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STELLAR trial: TTFIELDS in unresectable MPM

Unresectable* malignant pleural mesothelioma
- Any histological subtype
- ECOG PS 0-1
- No significant co-morbidities
- No implanted electronic medical devices

N=80

* Pts not candidate for curative surgery according to the local multidisciplinary board of each site, including a thoracic surgeon.

TTFIELDS (150kHz, ≥ 18 h/day) + Pemetrexed/Cisplatin or Pemetrexed/Carboplatin x 6

TTFIELDS alone until Disease Progression

Follow-up for survival

- Follow-up q3w
- CT scan q6w: modified RECIST

Primary Endpoint: OS
Secondary Endpoints: PFS, ORR, Safety

Sample size provides 80% power (α, 0.05) to detect an increase in median OS of 5.5 months vs historical data (i.e. mOS of 17.6 mo, HR of 0.67)

The STELLAR study was sponsored by Novocure Ltd, Haifa, Israel

Cesoli GL et al., Lancet Oncol 2019
Median OS was longer in patients with epithelioid histology (21.2 months) than in those with non-epithelioid histology (12.1 months).

44 pts (56%) received post-study therapy (mainly single-agent chemo); most had PD.

Ceresoli GL et al., Lancet Oncol 2019
There was no increase in systemic toxicity with TTFields.

- Fifty-three patients (66%) had grade 1-2 TTFields-related skin toxicity (dermatitis beneath the transducer arrays).
- Four patients (5%) had grade 3 skin toxicity.
- Most skin toxicities resolved after treatment with topical corticosteroids or a short treatment break.
- No serious adverse event was related to TTFields.

Approved on MAY 23, 2019 under the Humanitarian Device Exemption (HDE) pathway.

Ceresoli GL et al., Lancet Oncol 2019
Immunotherapy for MPM

The cancer immunity cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Anti-CTLA4

Anti-PD1/PDL1

Chen & Mellman, Cell 2013

Pardoll, Nat Rev Cancer 2012; Ribas, NEJM 2012
Tremelimumab in MPM

Confirmed RR: 2% TROME, 1% PLACEBO; DCR 29% vs 23%

Maio et al., Lancet Oncol 2017
<table>
<thead>
<tr>
<th>Agent</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
</tr>
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<tbody>
<tr>
<td>Study</td>
<td>Keynote 028</td>
<td>NivoMes</td>
</tr>
<tr>
<td></td>
<td>Chicago</td>
<td>Japan (MERIT)</td>
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<tr>
<td>Design</td>
<td>Phase I basket</td>
<td>Phase II</td>
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<tr>
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<td>Phase II R</td>
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<tr>
<td>Author</td>
<td>Alley et al.</td>
<td>Desai et al.</td>
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<td></td>
<td>Lancet Oncol 2017</td>
<td>WCLC 2018</td>
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<td>Quispel-Janssen et al.</td>
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<td>Okada et al.</td>
<td>Scherpereel et al.,</td>
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<td>Clin Cancer Res</td>
<td>Lancet Oncol 2019</td>
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<tr>
<td>PD-L1</td>
<td>PD-L1 +</td>
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<td>24%</td>
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<tr>
<td></td>
<td>29%</td>
<td>19%</td>
</tr>
<tr>
<td>DCR</td>
<td>72%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
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<td>47%</td>
</tr>
<tr>
<td></td>
<td>68%</td>
<td>40%</td>
</tr>
<tr>
<td>mPFS</td>
<td>5.4 mos</td>
<td>4.1 mos</td>
</tr>
<tr>
<td></td>
<td>3.6 mos</td>
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<td></td>
<td>6.1 mos</td>
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<tr>
<td>mOS</td>
<td>18 mos</td>
<td>11.5 mos</td>
</tr>
<tr>
<td></td>
<td>7.2 mos</td>
<td>11.8 mos</td>
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<tr>
<td></td>
<td>17.3 mos</td>
<td>11.9 mos</td>
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</table>
### COMBO IO TRIALS IN PRETREATED MESOTHELIOMA

<table>
<thead>
<tr>
<th>Study</th>
<th>INITIATE</th>
<th>NIBIT-MESO1</th>
<th>MAPS2</th>
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<tbody>
<tr>
<td>Drugs</td>
<td>Nivolumab+Ipilimumab</td>
<td>Durvalumab+Tremelimumab</td>
<td>Nivolumab+Ipilimumab</td>
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<tr>
<td>Phase</td>
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<td>II</td>
<td>II R</td>
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<td>40</td>
<td>62</td>
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<tr>
<td>Line</td>
<td>≥2</td>
<td>1-2</td>
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<tr>
<td>RR</td>
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<tr>
<td>DCR</td>
<td>67%</td>
<td>65%</td>
<td>52%</td>
</tr>
<tr>
<td>mPFS</td>
<td>6.2 mos</td>
<td>5.7 mos</td>
<td>5.6 mos</td>
</tr>
<tr>
<td>mOS</td>
<td>NR</td>
<td>16.6 mos</td>
<td>11.9 mos</td>
</tr>
<tr>
<td>G3-4 TOX</td>
<td>34%</td>
<td>18%</td>
<td>26% (3 toxic deaths, 5%)</td>
</tr>
</tbody>
</table>
ETOP 9-15 PROMISE-meso trial (Phase III, R 1:1)

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

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

Institutional choice Chemotherapy
- Gemcitabine 1000 mg/m² d1/8 q3w i.v. or
- Vinorelbine 30 mg/m² d1/8 q3w i.v. or
- Vinorelbine 60/80 mg/m² d1/8 q3w p.o.

Cross-over to pembrolizumab allowed at progression

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

SEP 2017 - AGO 2018; UK, Switzerland, Spain. 144 randomized pts

Popat S et al., ESMO 2019
No difference in PFS and OS when analyzed according to PDL1 status

Popat S et al., ESMO 2019
PROMISE-meso trial: ORR

- **ORR (95% CI)**
  - Pembrolizumab: 22% (13%, 33%)
  - Chemotherapy: 6% (2%, 14%)

- **Median DOR* (95% CI)**
  - Pembrolizumab: 4.6 months (2.2, 10.3)
  - Chemotherapy: 11.2 months (6.2, 15.3)

- **Updated as of August 2019**

- **16 responders**
  - Pembrolizumab: 7 PD and 4 deaths
  - Chemotherapy: 3 PD

N=66, excluding 7 NE patients.

* Stratified p=0.004

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Popat S et al., ESMO 2019
Hyper-progression (HPD) in MAPS2 trial

5-9% (according to different definitions) of patients in MAPS2 study had HPD

Scherpereel A et al., Lancet Oncol 2019; Zalcman G et al., ESMO 2019
MPM has a low mutational burden

Is mesothelioma immunogenic?

- Relatively low mutational burden
- Neoepitope formation limited

Bueno et al. Nat Genetics 2016
**Microenvironment in MPM**

Tumor micro-environment in MPM is highly heterogeneous.

Legend:
- PD-1
- PD-L1
- mAb
- Y anti-PD-1 mAb
- TAM
- T cell
- NK cell
- Immune Suppression
- Tumor Promotion

- Low tumour mutational burden
- Low T cell-inflamed gene signature

- Chemokine downregulation
- Immunosuppressive Cytokines
- MDSC
- TGFβ
- VEGF
- CAFs
- Mutations
- β-catenin
- TGFβ
- VEGF
- CAFs
- Mutations
- β-catenin
- Defective vascularization


Do not duplicate or distribute without permission from the author and ESO.
Chemotherapy has the potential to modify the TME

Different PD-L1 expression levels on tumor and immune cells and peritumoral and intratumoral CD8+ T lymphocytes in paired tumor samples from the same patients before and after chemotherapy.

Pasello G et al., Ann Oncol 2018
DREAM study: Results

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

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

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

**12 month OS estimate**
- 65% (95% CI 53-79%)

**Median survival**
- NR

**Median PFS, mo (95% CI)**
- Chemotherapy + Durvalumab: 6.2 (5.5-9.0)
- PFS6: 31/54 (57%)

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Nowak A et al., WCLC 2018
IND227 study

**Canadian CTG- IND227**

**Phase II Schema:**

- **ARM A N=42**
  - Cisplatin*/Pemetrexed

- **ARM B N=42**
  - Cisplatin*/Pemetrexed/Pembrolizumab → Pembrolizumab

- **ARM C N=42**
  - Pembrolizumab

**Phase II/III Schema:**

- **ARM A N=195**
  - Cisplatin*/Pemetrexed

- **ARM B N=195**
  - Cisplatin*/Pemetrexed/Pembrolizumab → Pembrolizumab

**Stratification:** histology, PDL1

* carboplatin is acceptable after CCTG approval

PFS, RR, QOL, SAFETY
Other ongoing randomized studies with IO in advanced MPM

<table>
<thead>
<tr>
<th>Study</th>
<th>Checkmate 743</th>
<th>Canadian CTG- IND227</th>
<th>Confirm</th>
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<tbody>
<tr>
<td>Phase</td>
<td>III R</td>
<td>II-III R</td>
<td>III R</td>
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<td>Agents</td>
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<td>IPI/NIVO vs PEMETREXED/CIS(CARBO)PLATIN</td>
<td>PEMBRO vs PEMETREXED/CIS(CARBO)PLATIN</td>
<td>NIVO vs PLACEBO</td>
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<td>N. pts</td>
<td>600</td>
<td>126 → 390</td>
<td>336</td>
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<td>PRIMARY ENDPOINT</td>
<td>OS</td>
<td>PFS → OS</td>
<td>OS</td>
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<tr>
<td>SECONDARY ENDPOINTS</td>
<td>RR, DCR</td>
<td>PFS, RR, QOL, SAFETY</td>
<td>RR, DCR</td>
</tr>
</tbody>
</table>
Angiogenesis-modulating factors have effects on the immune system

Khan & Kerbel, Nat Rev Clin Oncol 2018
BEAT-meso: BEvacizumab and ATezolizumab in MPM

Primary endpoint: Progression free survival & Overall survival
Secondary endpoints:
- Response rate
- Disease control rate
- Time to treatment failure
- Duration of response
- Safety and tolerability
- Patient reported outcome
- Quality of life

Target Sample Size: 320 Randomised Patients

ETOP network, PI E. Felip
Not only CTLA-4 & PD-1/PD-L1

VISTA (V-domain Ig suppressor of T-cell activation) is a member of negative checkpoint regulators, expressed on the surface of several immune cell types. It can function as both receptor and ligand.

Highly expressed in epithelioid mesothelioma

Comprehensive, multiplatform, genomic study of 74 MPM samples, as part of the Cancer Genome Atlas (TCGA)

Pardoll et al., Nat Rev Cancer 2012; Hmeljak et al., Cancer Discov 2018
MPM: Conclusions & take-home messages

1. First-line chemotherapy with platinum/pemetrexed remains the only approved treatment for unresectable MPM;

2. Angiogenesis inhibitors have shown conflicting results;

3. Targeted therapy: no results so far; rare genomic events as therapeutic opportunity;

4. TTFIELDS + chemo: a new promising treatment modality;

5. Immunotherapy with antiPD1/PDL1 +/- antiCTLA4: only a minority of pts are responders;

6. Hope: combination of ICI with chemo/antiangiogenics/other; targeting new checkpoints.