Systemic Management of Malignant Pleural Mesothelioma

Mir Alireza Hoda, MD PhD

Associate Professor for Surgery
Clinical Director Surgical Thoracic Oncology Program
& Translational Thoracic Oncology Laboratory

Division of Thoracic Surgery
Department of Surgery
Comprehensive Cancer Center
Medical University of Vienna
Systemic Management of Malignant Pleural Mesothelioma

Dragana Jovanovic
University Hospital of Pulmonology
Clinical Center of Serbia
Belgrade, Serbia
- Highly aggressive tumor linked to asbestosis
- Median survival 6 - 8 months for patients treated with best supportive care and 12 - 16 months with pemetrexed-platinum therapy.
- Therapy is generally palliative, improving symptoms and modestly increasing survival.
Diagnosis delay! Advanced disease in most cases

CT scan - diffuse or nodular pleural thickening suggestive of the disease.
Diagnosis of Mesothelioma

• Fine needle biopsies - low sensitivity (~30%)
• Surgical-type samples preferred for diagnosis
• Image-guided (US) needle core biopsies or

(Video)Thoracoscopy
Diagnosis in >90% of cases
Complete visual examination and multiple large biopsies.
WHO Classification of Tumors of the Pleura 2015

Mesothelial tumors
Diffuse malignant mesothelioma
  - Epithelioid mesothelioma
  - Sarcomatoid mesothelioma
  - Desmoplastic mesothelioma
  - Biphasic mesothelioma

Different treatment approach!

Epithelioid  50-70%
Sarcomatoid  10-20%
Biphasic     20-35%

IHC: CK 5/6 (+), calretinin (+), EMA (+), Mesotheline-1 (+), WT-1 (+), TTF-1 (-)

TNM Staging: Pretreatment Chest/Abdominal CT mandatory
Markers in MPM can be both prognostic and predictive

- **Nuclear grading, BAP1, mesothelin and PD-L1 expression** in malignant pleural mesothelioma: prognostic implications. (using a ≥5% cutoff, showed an acceptable safety profile and clinical activity in PD-L1+ and PD-L1− patients)

  *Forest F et al. Pathology. 2018, epub*

- 117 patients
- For epithelioid MPM, BAP1 loss, low grade = improved survival
- For epithelioid MPM, BAP1 retained/mesothelin + or -/PD-L1 > 1% is associated with shorter overall survival.
- In non-epithelioid MPM, BAP1 loss/mesothelin -ve/PD-L1 > 1% is associated with shorter overall survival.
Natural course of MPM

Survival 6-12-18 months from Diagnosis

Death is usually due to:

- Progressive dyspnea - respiratory insufficiency with extensive weight loss & muscle wasting
- Acute abdomen
- Cardiac tamponade/“constriction”
Prognostic factors

- **Stage and histology - the strongest prognostic factors**: sarcomatoid and biphasic histologic subtypes having worse outcomes compared with epithelioid mesothelioma.

- The pure epithelioid variant - the best prognosis especially if can be completely resected.

- Poor prognostic features include:
  - poor PS,
  - age >75 years,
  - elevated LDH,
  - hematologic abnormalities...
Pleural mesothelioma survival based upon histology

- At diagnosis, only a minority of MPM patients, those in early stage of disease, are candidates for definitive surgery.
- These patients have significantly better outcomes when managed with a multimodal approach.
- It is only feasible in patients without significant comorbidities.
- Upfront multidisciplinary evaluation is essential.

Rush et al JTO 2012
The Impact of Malignant Pleural Mesothelioma Histology on the Use of Surgery and Survival in a Population-Based Analysis

Overall survival for all (a) and surgical (b) patients with MPM stratified by histologic subtype

data from the National Cancer Data Base

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**Overall survival for all patients with MPM stratified by histologic subtype**

- **Sarcomatoid**: 5.3 months median survival
- **Epithelioid**: 16.2 months median survival
- **Biphasic**: 10.9 months median survival

**Surgical patients with MPM stratified by histologic subtype**

- **Sarcomatoid**: 7.7 months median survival
- **Epithelioid**: 22.6 months median survival
- **Biphasic**: 14.7 months median survival

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**Number at risk**

- **Sarcomatoid**: 538
- **Epithelioid**: 2325
- **Biphasic**: 481

**Number at risk (surgical patients)**

- **Sarcomatoid**: 91
- **Epithelioid**: 718
- **Biphasic**: 181
Volume/bulk is important

Total tumour thickness - prognostic

PET-derived volume also prognostic

Thickness at diaphragm may be most prognostic

FIGURE 3 a) Overall survival and b) disease-free survival according to total tumour thickness (TT) smaller or greater than 7 cm.

FIGURE 4 a, b) Total tumour thickness (TT), c, d) diaphragmatic TT and e, f) mediastinal TT correlated with time to recurrence and time to death. g, h) There was no correlation with time to recurrence and time to death in chest wall TT. Patients without recurrence were excluded from this analysis.
Blood Biomarkers?

• Only SMRP remains as a biomarker that has proven diagnostic, prognostic and monitoring capabilities at this time for mesothelioma.

• Other biomarkers, although promising, either have not had sufficient blinded validations or problems with secondary validations have failed due to differences in cohorts, sample preparation, or platform use.

• Nevertheless, as multiplexing platforms for genomics and proteomics evolve, investigators should exploit them since the chance for a single biomarker with sufficient sensitivity and specificity has not advanced since the discovery of SMRP.
Treatment options depend on Stage and Histology!

NCCN Guidelines Version 1.2019
Malignant Pleural Mesothelioma

PATHOLOGIC DIAGNOSIS

PRETREATMENT EVALUATION

CLINICAL ASSESSMENT

Malignant pleural mesothelioma

- Chest/abdominal CT with contrast
- Chest MRI with contrast (optional)\(^b\)

If suggested by imaging studies, consider VATS and/or laparoscopy if suspicion of contralateral or peritoneal disease

Clinical stage I-III\(^b\) and Epithelial histology
or Sarcomatoid or Mixed histology\(^c,d\)

Clinical stage IV or IIIB
or Medically inoperable
Treatment principles

Treatment decisions by multidisciplinary team with experience in MPM!

- **Multimodality treatment** for pts with stages I-III MPM who are medically operable.

- **Chemotherapy alone** for not operable patients, or clinical stage IV.

- **Radiotherapy** for palliation, preventive, and as a part of multimodality treatment
Pleurodesis

• Active control of pleural effusion is the mainstay of treatment in most patients with MPM.

• Early and successful pleurodesis - symptom control and a ‘trapped lung’ less likely to occur (before effusions have become loculated and/or the lung has become fixed and unable to expand fully).

• Pleurodesis should be performed at first relapse of effusion.
  ➢ Symptom control (pain, dyspnea...)

• Every patient should receive at least BSC
Systemic Treatment

Chemotherapy

Anti-angiogenic therapy

Targeted therapy

Immunotherapy
Cisplatin with pemetrexed – standard of care

- Carboplatin is an acceptable alternative to cisplatin (elderly)
- Should be stopped in case of progressive disease, grade 3–4 toxicities or cumulative toxic doses or following up to six cycles in patients who respond or who are stable.

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<th>EMPHACIS Trial</th>
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<td>TTP, months</td>
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HR: hazard ratio; OS: overall survival; RR: response rate; TTP: time to progression.

The History of advanced MPM treatment

Before 2000
- Chemo RR < 15%
- Palliative care

2000
Phase III
EMPHACIS trial
Cisplatin-Pemetrexed
- OS: 12.1mo
- RR: 41.3%
- TTP: 5.7mo

2003
Phase III
LUME trial
Cis-Pemetrexed + Nintedanib

2010
Phase III
MAPS trial
Cis-Pemetrexed + Bevacizumab

2015
Phase II
Immune checkpoint inhibitors

2016
2017
Anti-angiogenic treatment in combination with cisplatin-pemetrexed 1st line treatment for MPM

Bevacizumab 15mg/kg plus cisplatin-pemetrexed (CP) triplet versus CP doublet in Malignant Pleural Mesothelioma (MPM): Results of the IFCT-GFPC 0701 ‘MAPS’ randomized phase 3 trial

Positive for both PFS (primary endpoint) & OS

OS was significantly longer 18.8 mos vs 16.1 mos HR 0.77; p=0.0167, at the cost of expected manageable toxic effects.

Not recommended for PS 2, substantial CardioVasc. comorbidity, uncontrolled HTA, age over 75, bleeding or clotting risk, or other contraindication.

Zalcman et al, Lancet 2016
Other chemotherapy options?

Other acceptable 1st line ChemoTh options

• Pemetrexed and Carboplatin
• Gemcitabine and Cisplatin
• Pemetrexed
• Vinorelbine
Currently no second-line standard

- A variety of agents have demonstrated some activity in previously treated patients:
  - Single-agent gemcitabine
  - Single-agent vinorelbine
  - Combination gemcitabine/vinorelbine
  - Combination epirubicin/gemcitabine

- Response rates are low (10-15%)
- No clear standard

Participation in Clinical trials recommended
Clinical Stage I-III Medically operable

A

Induction Chemotherapy
Cis/Pem
Resectable

Surgical exploration

Resectable

Pleurectomy/ decortication

or
Extrapleural pneumonectomy

Observation or RT

Unresectable

Chemotherapy

B

Resectable

Pleurectomy/ decortication

or
Extrapleural pneumonectomy

Chemotherapy followed by observation or Consider RT

Sequential chemotherapy + Hemithoracic RT

NCCN Guidelines v1. 2019
Radiotherapy in mesothelioma

- Palliation
- Preventive treatment
- Part of a multimodality treatment

- Palliative RT effective in temporarily relieving chest pain, bronchial or esophageal obstruction, infiltration of the chest wall or permeation nodules or other symptomatic sites.
- Debate whether a scar after thoracoscopy and/or drainage procedures should be irradiated prophylactically.

Palliative Radiotherapy

- **SYSTEMS phase II trial** – 40 adv. MPM, 20Gy/5fr – good results in pain control
  
  MacLeod et al. JTO 2015

- **SYSTEMS 2** – RT dose escalation, 20Gy/5fr vs 36Gy/6fr
  

- **Hemithoracic RT after Neoadjuvant ChT and EPP** –
  
  RCT phase II SAKK 17/04
  
  151 pts, 3 ChT cycles with RR 34%, 113 pts EPP – macroscopic R0 in 96 pts

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**Hemithoracic radiotherapy after neoadjuvant CT and EPP**

- **Study design**: randomized phase II SAKK 17/04 trial
  
- **Patient selection**: 151 pts, 3 ChT cycles, EPP
  
- **RT dose**: 36Gy/6fr
  
- **Primary outcomes**: 5-year OS, DFS, PFS, toxicity, overall survival
  
- **Secondary outcomes**: time to failure, local recurrence, salvage surgery, EPP

**Results**

- **5-year OS**: 55.4% (95%CI 40.5-70.4)
- **5-year PFS**: 43.5% (95%CI 33.0-54.7)
- **5-year DFS**: 43.5% (95%CI 33.0-54.7)
- **Toxicity**: grade 3 or higher nausea/vomiting in 11% of pts, oesophagitis in 7%

**Conclusion of the authors**

Our findings do not support routine use of hemithoracic RT for MPM after neoadjuvant CT and EPP.

Radiotherapy part of multimodality treatment
Trimodality treatment – EORTC phase II trial

- RT – timing, fields, doses, toxicity?
- Induction ChemoTh followed by EPP and PostOP RT in cT3N1M0 or less, 58pts

- 93% received ChemoTh, 74% EPP, 65% RT
- Median PFS 13.0 months, median OS 18.4months
- Only 42% success of treatment
- Toxicity ¾ long lasting, after 90 days in 5.5%

Trimodality treatment not completed within timelines, adjustments...

Van Schil et al. Eur Respir J 2010
IMRT (Intensity Modulated RT) in MPM

- After pneumonectomy, the dose to contralateral lung must be minimized, preferably with volume of lung receiving 20Gy to less than 5%, and a mean lung dose of app. 10Gy (if intact both lungs -20Gy)

  Kenneth R, Semin Thorac CAVS Surg 2013

- High dose IMRT after EPP and Neoadj. Cht –
  3-yr OS 53%, 5-yr OS 59% in ypN0 after 3 modalities
  De Perot et al. JCO 2009

- IMRT after PD – IMPRINT Study, primary endpoint - incidence of grade 3 or greater RT Pneumonitis
  All recovered, median OS 23,7 months, med PFS 12,4 months
  Rimner et al. JCO 2016.

- PreOP IMRT before EPP – SMART (Surgery for Mesothelioma after RT) - I/II phase
  Cho et al. JTO 2014.
Malignant Pleural Mesothelioma: 2019

• Majority of patients present with advanced disease and are not candidates for surgery

• 1\textsuperscript{st} line approved regimen is pemetrexed plus cisplatin with/without Bev (Bev addition in selected cases!)

• New Anti-angiogenic treatment options?

• Several ongoing studies using different immune based therapies to treat mesothelioma – promising for 2\textsuperscript{nd} line treatment especially
Clinical studies Non-Immunotherapy - related

<table>
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<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>RR, %</th>
<th>Stable disease, %</th>
<th>PFS (OS), mo</th>
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LUME-Meso (NCT01907100): Phase II design and results

- Unresectable MPM
- Epithelioid and biphasic histology
- Measurable disease
- ECOG PS 0–1
- No prior chemotherapy

Randomise

- Nintedanib 200 mg bid + pemetrexed/cisplatin* (n=44) Non-PD patients
  - Nintedanib maintenance
  - PD
- Placebo 200 mg bid + pemetrexed/cisplatin* (n=43) Non-PD patients
  - Placebo maintenance
  - PD

Primary endpoint: PFS

Blood sampling: ↑ Baseline

- Clinically meaningful 3.7-month improvement in median PFS (HR=0.54; 95% CI: 0.33–0.87; p=0.010†)
- Trend for longer OS (HR=0.77; 95% CI: 0.46–1.29; p=0.319†)
- Efficacy most pronounced in patients with epithelioid tumours

Primary PFS favoured nintedanib, hazard ratio (HR) 0.56
A trend toward improved OS with nintedanib (HR, 0.77; P=0.319) especially epithelioid MPM subtype where median OS gain was 5.4 months (nintedanib 20.6 months vs. placebo 15.2 months; HR, 0.70; P=0.197) and median PFS gain was 4.0 months (nintedanib 9.7 months vs. placebo 5.7 months; HR, 0.49; P=0.006).
The effect of nintedanib on PFS and OS was consistent across all subgroups expect those with biphasic MPM where more than half (nintedanib 64% vs. placebo 70%) received subsequent therapy.
Tumor response was objectively superior with nintedanib than placebo.

Nowak, JCO 2017.
Nintedanib Is Active in Malignant Pleural Mesothelioma Cell Models and Inhibits Angiogenesis and Tumor Growth \textit{In Vivo}

Viktoria Laszlo, Zsuzsanna Valko, Ildiko Kovacs, Judit Oszvar, Mir Alireza Hoda, Thomas Klikovits, Dora Lakatos, Andras Czirok, Tamas Garay, Alexander Stiglbauer, Thomas H. Helbich, Marion Gröger, Jozsef Tovari, Walter Klepetko, Christine Pirker, Michael Grusch, Walter Berger, Frank Hilberg, Balazs Hegedus, and Balazs Dome

\textbf{DOI:} 10.1158/1078-0432.CCR-17-1507 Published August 2018
LUME-MESO Phase III study.

PFS by investigator assessment

Independent central review confirmed findings:
HR (95% CI) 0.99 (0.77–1.28), p=0.963

OS (interim analysis)

Scagliotti G et al. WCLC 2018
Clinical Studies on MPM Immunotherapy

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<th>Study</th>
<th>Patients</th>
<th>Drug</th>
<th>RR, %</th>
<th>Stable disease, %</th>
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Note: These studies were included in this table because they are immunotherapy clinical trials on human patients with some published results in 2017. This is a complete list as of November 2017.

*Information not available.

*International study not listed at ClinicalTrials.gov.

MPM, malignant pleural mesothelioma; RR, response rate; DCR, durable controlled response; PFS, progression-free survival; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein 1; NR, not reported; A, active, not recruiting; C, completed; R, recruiting.
Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028)

Response (RECIST 1.1)
- PD-L1 ≥ 1%
- Partial response 20%
- Duration 12 (3.7-NR)
- Stable disease 52%
- Duration 5.6 (3.6-12.0)

Progression-free survival (investigator assessed)
- Median 5.4 (3.4-7.5)
- 6 month 45.8%
- 12 months 20.8%

Overall Survival
- Median 18 (9.4-NR)
- 6 month 83.5%
- 12 months 62.6%
MAPS-2 trial
Mesothelioma Anti-PD-1 Study 2 - IFCT 1501
Randomized, non-comparative phase 2 trial - One-step Fleming design (each arm independently)

- Validated histological diagnosis of Malignant Pleural Mesothelioma
- Unresectable cancer with documented progression after maximum 1 or 2 previous lines of chemotherapy including a pemetrexed/platinum doublet
- Measurable disease
- ECOG PS 0-1
- Weight loss <10%
- Age > 18 years (M or F)
- Available tumor tissue...

Nivolumab
3 mg/kg IV / 2 weeks

Nivolumab
mg/kg IV / 2 weeks + Ipilimumab
1mg/kg IV / 6 weeks

57 patients

until progression or unacceptable toxicity (or 2 years max)

CT-scan every 12 weeks

57 patients

until progression or unacceptable toxicity (or 2 years max)

Presented By Arnaud Scherpereel at 2017 ASCO Annual Meeting
Second or Third Line Nivolumab vs Nivolumab plus Ipilimumab in MPM Patients MAPS-2

**Efficacy: ITT median Progression-free Survival (PFS)**

- Median follow-up: 10.4 mo [10.0-11.1]
- Data cut-off: March 31th, 2017
- Database export: May 2nd, 2017

- Median PFS, IC95%: 4.0 [2.8-5.7], events = 50, censored = 13
- Median PFS, IC95%: 5.65 [3.25-10.4], events = 39, censored = 23

- **4.0 months** (NIVO arm n=63)
- **5.6 months** (NIVO+IPI arm n=62)

**Efficacy: ITT preliminary Overall Survival (OS)**

- Median follow-up: 10.4 mo [10.0-11.1]
- Data cut-off: March 31th, 2017
- Database export: May 2nd, 2017

- Median OS, IC95%: 10.4 [6.7-NR], events = 30, censored = 33
- Median OS, IC95%: NR, events = 20, censored = 42

- **10.4 months** (NIVO arm n=63)
- **Not Reached (NR)** (NIVO+IPI arm n=62)

- Investigators concluded that nivolumab ± ipilimumab potentially a new option as second-/third-line treatment for relapsing MPM
Avelumab in patients with advanced unresectable mesothelioma from the JAVELIN solid tumor phase Ib Trial: Safety Clinical activity and PD-L1 expression

Pleural, peritoneal mesothelioma
Prior platinum/pemetrexed
PS 0-1

Avelumab 10mg/Kg Until PD
N=53

Best Overall Response (RECIST 1.1); safety, tolerability, PD-L1 analyses

Hassan R et al. J Clin Oncol 34, 2016 (suppl; abstr 8503); J Clin Oncol 36, 2018 (suppl; abstr 8563)
Avelumab in patients with advanced unresectable mesothelioma from the JAVELIN solid tumor phase I b Trial: Safety Clinical activity and PD-L1 expression

**Progression Free Survival**

<table>
<thead>
<tr>
<th>Response</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Overall response RECIST 1.1</td>
<td><strong>9.4%</strong> (3.1-20.7)</td>
</tr>
<tr>
<td>Complete Response</td>
<td><strong>1.9%</strong></td>
</tr>
<tr>
<td>Partial response</td>
<td><strong>7.7%</strong></td>
</tr>
<tr>
<td>Stable disease</td>
<td><strong>49.1%</strong></td>
</tr>
<tr>
<td>Progressive disease</td>
<td><strong>34%</strong></td>
</tr>
<tr>
<td>Median PFS</td>
<td><strong>4.1</strong> (1.4-6.2)</td>
</tr>
<tr>
<td>Median OS</td>
<td><strong>10.9</strong> (7.5-21.0)</td>
</tr>
</tbody>
</table>

Based on ≥5% threshold for tumor cell staining; 39/53 patients were evaluable for PD-L1 expression status

Hassan R et al. J Clin Oncol 34, 2016 (suppl; abstr 8503); J Clin Oncol 36, 2018 (suppl; abstr 8563)
DREAM
A phase 2 trial of Durvalumab with first line chemotherapy in Mesothelioma with a safety run in

Single-arm, multicentre phase II trial, N=54 (31 in this Stage 1 analysis)

Population
1st line MPM
Non-surgical
ECOG PS 0-1
No PD-L1 selection

Exclusions
AID, steroids, prior IO agent

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

Maintenance
Durvalumab 1125mg q3w x 52 w
(Until PD or toxicity)

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

DREAM

- Objective tumour RR 58%
- Adverse events comparable to Chemoth and Immunoth alone
- Corresponds with recent results from Keynote-189

Progression free survival 6 months = 65% (n=31)

Median PFS: 7.3 months (95% CI: 5.8-11.0)

Response Rate confirmed mRECIST 55%

Presented By Anna Nowak at 2018 ASCO Annual Meeting; J Clin Oncol 36, 2018 (suppl; abstr 8503)
Facts on PD-1 and PD-L1 inhibitors:

Response rate
- Single agents 9-20%; 55% for chemo- durvalumab
- Durable responses
- PFS 4-7, OS 10-18 months

What is not known
- Efficacy versus SOC in first and second line
- Single agent or in combination
- Histologic subtypes
- Markers of response
Malignant Pleural Mesothelioma
Stage III or IV
ECOG PS ≤2
Progression following platinum based chemotherapy

Simon’s optimal two-stage design:
Stage 1: 1 objective response in 11 patients the total number of participants was to be increased to 29.
Target response rate of 17% was considered active, with a type 1 error probability of 5% and a type 2 error probability of 30%, four objective responses in 29 treated patients required

Tremelimumab
15 mg/kg once every 90 days (until PD or excessive toxicity)

Luana Calabrò et al. Lancet Oncol 2013; 14: 1104–11
Mesot-TREM-2008 (NCT01649024)

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Patients N=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>2 6.9% (0.0–16.1)</td>
</tr>
<tr>
<td>SD</td>
<td>7 24.1% (8.6–39.7)</td>
</tr>
<tr>
<td>PD</td>
<td>20 69.0% (52.1–85.8)</td>
</tr>
<tr>
<td>DCR</td>
<td>9 31.0% (14.2–47.9)</td>
</tr>
<tr>
<td>PFS</td>
<td>6.2 months</td>
</tr>
<tr>
<td>OS</td>
<td>10.7 months</td>
</tr>
</tbody>
</table>

1 patient had initial disease progression followed by long-lasting partial response (18 months at the end of follow-up).

Luana Calabrò et al. Lancet Oncol 2013; 14: 1104–11
**Determine:** Phase IIb Randomized Double Blind, Placebo Controlled Trial of Tremelimumab as 2$^{nd}$ or 3$^{rd}$ line treatment of unresectable malignant mesothelioma

- **Pleural or peritoneal mesothelioma**
  - PS≤1
  - 1-2 prior regimens including platinum
  - Measurable disease

**Tremelimumab i.v.**
- 10mg/Kg q4weeks for 7 doses then q 12 weeks

- Placebo i.v.

**Stratification factors**
- Pleural vs. peritoneal
- 2$^{nd}$ vs. 3$^{rd}$ line
- EORTC low vs. high risk

**Primary endpoint:** Overall survival
**Secondary endpoints:** 18 month OS; Progression Free Survival; ORR; Safety

Maio M et al. Lancet Oncol. 2017;18(9):1261
Determine: Phase IIb Randomized Double Blind, Placebo Controlled Trial of Tremelimumab as 2nd or 3rd line treatment of unresectable malignant mesothelioma

H.L. Kindler, J Clin Oncol 34, 2016 (suppl; abstr 8502)
**Determine:** Phase IIb Randomized Double Blind, Placebo Controlled Trial of Tremelimumab as 2\textsuperscript{nd} or 3\textsuperscript{rd} line treatment of unresectable malignant mesothelioma

<table>
<thead>
<tr>
<th>Response</th>
<th>Tremelimumab %</th>
<th>Placebo %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>4.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>27.2</td>
<td>21.7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>45.8</td>
<td>58.7</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>22.5</td>
<td>18.5</td>
</tr>
<tr>
<td><strong>Objective response rate</strong></td>
<td>4.5</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Disease control rate/ 6mo</strong></td>
<td>31.7/ 16.8</td>
<td>22.8/ 11.6</td>
</tr>
</tbody>
</table>

Pembrolizumab Immunotherapy Versus Standard Chemotherapy for Advanced pre-treated Malignant Pleural Mesothelioma (PROMISE-meso) NCT02991482
European Thoracic Oncology Platform

MPM
Inoperable
ECOG 0-1
Prior platinum based chemoth.
Measurable disease

Pembrolizumab 200mg q 3 weekly for two years or PD

Gemcitabine 1000mg/m2 or vinorelbine 30mg/m² D1 and 8 q 3 weekly

Primary endpoint: PFS
Secondary endpoints: Overall response rate; time to treatment failure; toxicity; investigator assessed PFS
What we know for PD-1 and PD-L1 inhibitors:
Response rate
- Single agents 9-20%; 55% for chemo- durvalumab
- Durable responses
- PFS 4-7, OS 10-18 months

MAPS-2 - accrual duration 5 months
DREAM- accrual 8 months ahead of schedule

DETERMINE STUDY: n=658
accrual 22nd May 2013- Dec 2014
**Primary Endpoint:** Overall Survival

**Secondary Endpoints:** Progression Free Survival; Response Rate; Quality of Life; Incremental Cost Effectiveness; Tolerability; Predictive/prognostic value of PD-L1
Study of Nivolumab Combined With Ipilimumab Versus Pemetrexed and Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma Patients (CheckMate743) NCT02899299

Malignant pleural mesothelioma
Inoperable
ECOG 0-1
No prior chemotherapy
Measurable disease

N=600

Nivolumab; Ipilimumab

Pemetrexed; platin

Primary endpoints: OS and PFS; secondary endpoints: objective response rate; disease control rate; PD-L1 expression and efficacy
Clinical Studies on MPM Immunotherapy

• Promising *preliminary* signal of activity
• Preliminary results of efficacy are not always maintained when tested in larger randomized trials
• Insufficient data to recommend checkpoint inhibitors outside of clinical trial
• Enrol patients on randomized trials to determine the role of checkpoint inhibitors in mesothelioma

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Drug</th>
<th>Stable RR, %</th>
<th>Stable disease, %</th>
<th>DCR, %</th>
<th>PFS, mo Target</th>
<th>Phase</th>
<th>Status</th>
<th>Clinical Trial Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CTLA-4</td>
<td>8374</td>
<td>DETT</td>
<td>2004</td>
<td>7508</td>
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<tr>
<td>Anti-PDL1</td>
<td>4806</td>
<td>JAVR</td>
<td>9371</td>
<td>6272</td>
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<tr>
<td>Nivolumab</td>
<td>18131</td>
<td>MERE</td>
<td>8474</td>
<td>6272</td>
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<td>KEYNOTE-042</td>
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<td>Keyt</td>
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<td>Chidanevari</td>
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<td>INITIATION</td>
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<td>MAPS-201</td>
<td>18131</td>
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</tbody>
</table>

Note: These studies were included in this table because they are immunotherapy clinical trials on human patients with some published results in 2017. This is a complete list as of November 2017.

a) Information not available.

b) International study not listed at ClinicalTrials.gov.

MPM, malignant pleural mesothelioma; RR, response rate; DCR, durable controlled response; PFS, progression-free survival; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein 1; NR, not reported; A, active, not recruiting; C, completed; R, recruiting.
**Something very new!**

**Electric Field as Anti-Cancer Agent**

**STELLAR: Study design & Patient characteristics (NCT02397928)**

Unresectable malignant pleural mesothelioma, N=80

The sample size provides 80% power ($\alpha$, 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).

Key Inclusion Criteria:
- Pathological evidence of Stage IV MPM
- At least one measurable lesion (mRECIST)
- ECOG PS score 0-1

Key Exclusion Criteria:
- Candidate for curative treatment
- Significant comorbidities
- Implanted electronic medical devices

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

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
<th>Epithelioid histology</th>
<th>Sarcomatoid/Biphasic</th>
<th>Unspecified histology</th>
<th>Locally advanced Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>67 (27-78)</td>
<td>53 (66%)</td>
<td>21 (26%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>45 (56%)</td>
<td></td>
<td>6 (8%)</td>
<td>35 (44%)</td>
</tr>
<tr>
<td></td>
<td>35 (44%)</td>
<td></td>
<td></td>
<td>13 (16%)</td>
</tr>
</tbody>
</table>

- TTFIELDS cycles:
  - Median (range): 8.0 (2-41)
- Chemotherapy cycles:
  - Median (range): 6.0 (1-7)
- Carboplatin: 50 patients (63%)

1. Vogelzang et al., J Clin Oncol 2003
Summary of new systemic therapies

- Immune checkpoint inhibitors, used alone or in combination, showed activity in MPM with manageable toxicities.
- Inhibiting angiogenesis is promising (MAPS Phase III with Bev was positive, LUME-Meso Phase II with Nintedanib is positive, Phase III trial neg)

Predictive biomarkers – unmet need!
Conclusion

- Malignant pleural mesothelioma (MPM) is a highly aggressive tumor, almost always a fatal disease.

- Early diagnosis of crucial importance, made based on histological and IHH examination.

- Treatment decisions within MDT

- Active control of pleural effusion is the mainstay of treatment in most patients.

- Cisplatin with pemetrexed ± Bev as standard of care in 1st line systemic treatment