Therapy of Mesothelioma in 2019

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The Netherlands Cancer Institute
Preceptorship course, March 9, 2019
Manchester, UK
Disclosures

• Grants from BMS, Pfizer and Roche
• Advisor for MSD, BMS, Aduro and Verastem

Some slides with courtesy of Dr A Tsao
British Humour
The treatment options 2018

• Chemotherapy provides symptom relief and increased OS

• The combination of cisplatin and anti-folate is standard
  • 80% of tumors recur after 2 years
  • Median OS is 16 – 18.8 months

• Multimodality studies use:
  • neoadjuvant chemotherapy
  • extrapleural pneumonectomy or pleurectomy/decortication
  • with or without RT
Comparative evolution of targeted therapy for mesothelioma vs lung cancer
New targets

- Mesothelin

- Arginine deprivation

- Bevacizumab +...

- BAP1
  - Somatic mutations in 20-60 %
  - Germline mutations in 1-2 %

- Immunotherapy
Stratifying by *cell surface* target expression

Genetic and Epigenetic stratification

Discovering *new* drug-gene interactions

IO therapy
Mesothelin is a selective marker for targeting mesothelioma
Anetumab Raptansine in patients in the relapsed setting
Initial phase

Mode of action:
- ADC targeting tumor-associated antigen mesothelin, and delivering toxophore DM4, which acts on proliferating cells (tubulin inhibitor)

Potential spectrum of indications determined by mesothelin expression pattern:
- mesothelioma (~90-100%)
- pancreatic cancer (~65%) and
- ovarian cancer (~65%)

Clinical program:
- Phase I with promising results including duration of treatment of >1,000 days
- Registrational phase II in metastatic pleural mesothelioma ongoing

<table>
<thead>
<tr>
<th>MTD (n=38)</th>
<th>Mesothelioma MTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=16)</td>
<td>1 prior line of systemic treatment (n=10)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Best overall response, RECIST, n (%)</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (18.4)</td>
<td>5 (31.3)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>18 (47.4)</td>
<td>7 (43.8)</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>10 (26.3)</td>
<td>4 (25.0)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Overall response (complete or partial response)</td>
<td>7 (18.4)</td>
<td>5 (31.3)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Disease control rate (complete or partial response or stable disease)</td>
<td>25 (85.8)</td>
<td>12 (75.0)</td>
<td>9 (90.0)</td>
</tr>
</tbody>
</table>
Phase II Anetumab Ravtansine as 2nd Line Treatment for Malignant Pleural Mesothelioma (MPM) - NCT02610140

ANETUMAB RAVTANSINE DOES NOT MEET PRIMARY ENDPOINT IN SECOND-LINE MESOTHELIOMA

Published on 21st July

A Phase II clinical trial evaluating its anetumab ravtansine, also known as BAY 949343, as a monotherapy in patients with recurrent malignant pleural mesothelioma or MPM who were previously treated, did not meet its primary endpoint of progression-free survival.

PI: Dr R Hassan, NCI
Stratifying by cell surface target expression

Genetic and Epigenetic stratification

Discovering new drug-gene interactions

IO therapy
Arginine Deprivation With Pegylated Arginine Deiminase in Patients With Argininosuccinate Synthetase 1-Deficient Malignant Pleural Mesothelioma: A Randomized Clinical Trial

Szlosarek et al,
JAMA Oncology 2016
Background:
Tumor cells require Arginine for cell division.
Sarcomatoid tumors lack ASS1
With ADI-PEG20 the blood is depleted from Arginine and tumor cells will die.
ADAM randomised trial design

Sarcomatoid and biphasic MPM

Co-Primary objective: PFS and ORR
Secondary objectives: disease-control rate (DCR), OS, duration of response, and safety
Plan: two stages Phase II for 140 pts; Phase III for 232 pts
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IO therapy
BAP1

Tumor suppressor regulating target genes in:

- Transcription
- DNA damage repair
- Cell cycle control
- Cellular differentiation
BAP1 mutation exposes a vulnerability to EZH2 inhibition in mesothelioma

La Fave et al, Nat Med 2015
EZH2 inhibitors

LaFave, Nature Medicine, 2015

Modern Medicine

BAP1 mutant

H2A expression

H2A expression

ASXL1

↑ubiquitination

↓HDAC2

expression

expression

HCF1/YY1

impaired

activation

E2F

BRCA/BARD

DNA damage

Traditional Chinese Medicine

Kageyama et al. Biomedicine & Pharmacotherapy 105, 2018; 690-696

Anti-tumor and anti-metastasis activities of honey bee larvae powder by suppressing the expression of EZH2

Masakatsu Kageyama[a,c], Kejuan Li[b], Shuang Sun*, Guoping Xing*, Ran Gao*, Zhongfeng Lei*, Zhenya Zhang**

LaFave, Nature Medicine, 2015

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Study of the EZH2 Inhibitor Tazemetostat in Malignant Mesothelioma

Phase II A open label/single arm US, France, UK
Oral Tazemetostat 800mg BID

Stage 1
All/PK

Stage 2
BAP1 negative

Endpoint. Response rate

ASCO 2018:
DCR 50% at 12 weeks
DCR 26% at 24 weeks

(NCT02860286)
A platform for accelerating stratified therapy

Mesothe llioma Stratified Therapy (MiST)

Open label / single arm / 2 stage

Multi-Arm Study

- Arm 1
- Arm 2
- Arm 3
- Arm 4

Selection

Efficacy

- Exceptional Response
- Drug resistance

Molecular pre-screening Panel
(Biomarker 1-4)
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IO therapy
Why would IO work in MPM

- PD-L1 expression
- Mutational Load
- Chromothripsis
For Subsequent Systemic Therapy, the following are added as treatment options:

- Nivolumab-ipilimumab
- Pembrolizumab
BEAT meso (ETOP 13-18)

A flowchart showing the treatment plan for advanced malignant pleural mesothelioma. The treatment includes chemotherapy (4–6 cycles) with Carboplatin AUC5 + Pemetrexed 500mg/m² Q3W, followed by Bevacizumab 15mg/kg Q3W, and then Atezolizumab 1200mg Q3W. The chart also indicates weekly evaluations for CT, QoL, Blood, and FFPE samples. The diagram notes that 320 pts are involved.
# Summary of PD-1/PD-L1 + CTLA4 in MPM

<table>
<thead>
<tr>
<th>Agents</th>
<th>NCT</th>
<th>Population</th>
<th>N</th>
<th>ORR</th>
<th>DCR</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>PD-L1 IHC status</th>
<th>TMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIBIT-Meso-1 Tremelimumab + Durvalumab</td>
<td>02588131</td>
<td>1st or 2nd line</td>
<td>40</td>
<td>27.5%</td>
<td>65%</td>
<td>14.1 median duration DC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>INITIATE Iplimumab + Nivolumab</td>
<td>03048474</td>
<td>At least 1 prior therapy</td>
<td>33</td>
<td>28%</td>
<td>50%</td>
<td>4.7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>IFCT MAPS 2 Iplimumab + Nivolumab vs Nivolumab</td>
<td>02716272</td>
<td>2nd or 3rd line</td>
<td>125</td>
<td>Nivo-Ipi 24.2% Nivo 17.5%</td>
<td>Nivo-Ipi 50% Nivo 44.4%</td>
<td>Nivo-Ipi 5.6 vs Nivo 4</td>
<td>Nivo-Ipi not reached vs Nivo 10.4</td>
<td>Correlates with response</td>
<td>NR</td>
</tr>
</tbody>
</table>

## Safety

<table>
<thead>
<tr>
<th></th>
<th>&gt; Grade 3 toxicity</th>
<th>Grade 5</th>
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</thead>
<tbody>
<tr>
<td>NIBIT-Meso-1</td>
<td>17.5%</td>
<td>-</td>
</tr>
<tr>
<td>INITIATE</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>MAPS2</td>
<td>16%</td>
<td>3*</td>
</tr>
</tbody>
</table>

NR – not reported

Correlates with response

Safety > Grade 3 toxicity

Grade 5

* treatment-related deaths 1 fulminant hepatitis, 1 encephalitis, 1 acute RF
## Selected Ongoing I/O Frontline Unresectable Studies

<table>
<thead>
<tr>
<th>Agents</th>
<th>Phase</th>
<th>NCT</th>
<th>Target</th>
<th>Population</th>
<th>Planned N</th>
<th>Primary endpoint</th>
</tr>
</thead>
</table>
| CheckMate 743
Ipilimumab-nivolumab vs platinum-pemetrexed                       | III   | 02899299 | PD-1+CTLA4 inhibitors vs chemo              | Frontline  | 600        | OS               |
| Durvalumab + cisplatin-pemetrexed (PrE0505)                           | II    | 02899195 | PD-L1 inhibitor + chemo                     | Frontline  | 55         | OS               |
| Durvalumab + cisplatin-pemetrexed (DREAM – Australia ALTG)           | II    | -      | PD-L1 inhibitor + chemo                     | Frontline  | 54         | 6 month PFS      |
| Pembrolizumab + cisplatin-pemetrexed vs cisplatin-pemetrexed alone (Canadian Cancer Trials Group) | II    | 02784171 | PD-1 inhibitor + chemo                     | Frontline  | 126        | PFS              |
| ONCOS-102 + cisplatin-pemetrexed (Spain)                              | Ib/II | 02879669 | Immune-priming GM-CSF coding oncolytic adenovirus + chemo | Frontline  | 30         | Safety Toxicity  |
Conclusions new therapeutic options in MPM

• Mesothelin directed studies so far not successful

• Treatment option for sarcomatoid type emerging

• BAP1 as possible new target

• Combination of IO or IO + chemotherapy will probably become standard
SUPER BREXIT FRAGILISE EUROPE -CASUS BELLUS TOTALUM GLOBAL BRITANNICUS...