Immunotherapy- What is in the Future?

Dr. Quincy Chu MD FRCPC
Medical Oncologist/Associate Professor
Cross Cancer Institute/University of Alberta
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Disclosure

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Agenda

• Review of novel immunotherapy targets in mesothelioma
  • Mesothelin
  • Tumour associated macrophages, myeloid derived suppressor cells and Treg
  • Immune checkpoint including PD(L)1.
Mesothelin

- Mesothelin is 40 KDa glycoprotein expressed in
  - Mesothelioma
  - Adenocarcinoma of the lung
  - Pancreatic cancer
  - Ovarian cancer
  - Gastric cancer.
    - Limited expression in normal cells, including pleura, peritoneum and pericardium
    - Of unknown biological function
    - A 32KDa cleavage NH2-terminal of unknown function.

Mesothelin

- Soluble mesothelin is a 41-45 KDa with NH2-terminal amino acid sequence identical to that of the membrane-bound portion of mesothelin.
**Mesothelin-antibody drug conjugate**

**Anetumab raptansine (BAY 94-9343): an anti-mesothelin antibody-drug conjugate**

- Mesothelin is a membrane-associated differentiation antigen that is overexpressed in a number of solid tumors, including the vast majority of mesotheliomas\(^1,^2\).

- Anetumab raptansine (BAY 94-9343) is a novel, fully humanized anti-mesothelin immunoglobulin G1 antibody conjugated to a raptansine, a maytansine-derivative DM4 anti-tubulin cytotoxic agent.

**Mode of action:**

- Targeted delivery of the potent anti-proliferative toxophore DM4 (tubulin inhibitor) to cancer cells expressing the tumor-associated antigen mesothelin.

Here we report results from a Phase I open-label study of anetumab raptansine in patients with advanced solid tumors, with a particular focus on patients with mesothelioma.

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Randomized Phase II Study of Anetumab Ravtansine or Vinorelbine in Patients with Malignant Pleural Mesothelioma


1University of Chicago, Chicago, IL, USA; 2University of Turin, San Luigi Hospital, Orbassano, Italy; 3University of Leicester and Leicester University Hospitals, Leicester, UK; 4The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 5IRCCS Centro di Riferimento Oncologico – CRO, Pordenone, Italy; 6Cliniche Humanitas Gavazzeni, Bergamo, Italy; 7Erasmus Medisch Centrum, Rotterdam, Netherlands; 8King’s College London, Guy’s Hospital, London, UK; 9University Hospital of South Manchester, Manchester, UK; 10Freeman Hospital, Newcastle Upon Tyne, UK; 11KU Leuven, University Hospitals, Leuven, Belgium; 12University Hospital of Siena, Siena, Italy; 13Nederlands Kanker Instituut, Amsterdam, Netherlands; 14Epworth Healthcare, Richmond, Victoria, Australia; 15Bayer, Milan, Italy; 16Bayer AG, Berlin, Germany; 17Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA; 18National Cancer Institute, Bethesda, MD, USA.
Trial Design

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

Anetumab ravidansine
6.5 mg/kg Q3W (n=166)

Stratification factors:
- Geographical region
- TTP on 1L therapy

Vinorelbine
30 mg/m² QW (n=82)

1L, first line; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PROs, patient-reported outcomes; Q3W, once every 3 weeks; QW, once weekly; TTP, time to progression.
Primary Endpoint: PFS

Anetumab ravtansine (n=166) | Vinorelbine (n=82)
--- | ---
mPFS, months | 4.3 | 4.5 (95% CI) | (4.1–5.2) | (4.1–5.8)
HR (95% CI) | 1.215 (0.850–1.738) | One-sided $P$-value | 0.859
Probability of PFS

Number of patients at risk
AR | 166 | 152 | 114 | 89 | 83 | 49 | 28 | 25 | 16 | 14 | 7 | 6 | 2 | 0
V | 82 | 65 | 56 | 47 | 37 | 22 | 13 | 11 | 9 | 7 | 3 | 3 | 0 | 0

AR, anetumab ravtansine; CI, confidence interval; mPFS, median progression-free survival; V, vinorelbine.
OS – Interim Analysis*

<table>
<thead>
<tr>
<th>Months</th>
<th>Survival probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Anetumab ravtansine (n=166)

- mOS, months: 10.1 (95% CI: 7.6–NE)
- One-sided P-value: 0.721

Vinorelbine (n=82)

- mOS, months: 11.6 (95% CI: 7.7–12.5)

Number of subjects at risk:

<table>
<thead>
<tr>
<th>AR</th>
<th>166</th>
<th>160</th>
<th>147</th>
<th>132</th>
<th>124</th>
<th>95</th>
<th>74</th>
<th>61</th>
<th>44</th>
<th>33</th>
<th>23</th>
<th>17</th>
<th>11</th>
<th>6</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>82</td>
<td>71</td>
<td>67</td>
<td>64</td>
<td>55</td>
<td>45</td>
<td>38</td>
<td>31</td>
<td>24</td>
<td>20</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

mOS, median overall survival; NE, not estimable.

*87 of 159 target events for OS analysis had occurred at the time of primary PFS analysis.
### Response

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>Anetumab ravtansine (n=166)</th>
<th>Vinorelbine (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>14 (8)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>108 (65)</td>
<td>51 (62)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>24 (14)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Not available</td>
<td>20 (12)</td>
<td>17 (21)</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>14 (8)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>122 (73)</td>
<td>56 (68)</td>
</tr>
</tbody>
</table>

ORR = CR + PR; DCR = CR + PR + SD.
CR, complete response; PR, partial response; SD, stable disease.
## Most Frequent Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>TEAE, %</th>
<th>Anetumab ravtansine (n=163)</th>
<th>Vinorelbine (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Nausea</td>
<td>41.1</td>
<td>0</td>
</tr>
<tr>
<td>Corneal epitheliopathy</td>
<td>39.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20.9</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>17.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>16.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>15.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Fever</td>
<td>14.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>9.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

≥15% in either cohort. Three patients in the anetumab ravtansine group and 10 patients in the vinorelbine group did not receive study drug and were not included in the safety population.
BMS-986148, an Anti-Mesothelin Antibody-Drug Conjugate (ADC), Alone or in Combination with Nivolumab Demonstrates Clinical Activity in Patients with Select Advanced Solid Tumors

Lolkema et al. ACR-NCI-EORTC meeting 2019:B057.
Background

- Traditional cancer chemotherapy is often accompanied by systemic toxicity to the patient
  - Antibody–drug conjugates (ADCs) use antibodies to deliver a potent cytotoxic compound selective to tumor cells, thus improving the therapeutic index of chemotherapeutic agents\(^5\)
- BMS-986148 is a fully human IgG1 anti-mesothelin monoclonal ab conjugated to tubulysin to promote selective cytotoxic delivery to tumor cells
  - Tubulysins disrupt microtubule assembly, leading to impaired cell division and subsequent apoptosis\(^6\)
  - In preclinical models, combination of anti–mesothelin-tubulysin with anti–PD-1 promoted a synergistic antitumor response and influx of tumor-infiltrating lymphocytes\(^7\)
- Here, we present initial data for BMS-986148 ± nivolumab (NIVO; anti–PD-1) from a phase 1/2a trial in a biomarker-defined population of patients (pts) with select advanced solid tumors (NCT02341625)\(^8\)

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**Study Design**

**Dose Escalation**

- **BMS-986148 Q3W Monotherapy**
  - Mesothelin-unselected tumors
  - 0.1 mg/kg
  - 0.2 mg/kg
  - 0.4 mg/kg
  - 0.8 mg/kg
  - 1.2 mg/kg
  - 1.6 mg/kg

- **BMS-986148 QW Monotherapy**
  - Mesothelin-unselected tumors
  - 0.4 mg/kg
  - 0.6 mg/kg

- **BMS-986148 Q3W + NIVO 360 mg Q3W**
  - Mesothelin-unselected MAD
  - 0.8 mg/kg BMS-986148

**Dose Expansion**

- **Monotherapy (Q3W)**
  - Mesothelin-selected tumors
  - Mesothelioma
  - Ovarian
  - NSCLC

- **BMS-986148 Q3W + NIVO 360 mg Q3W**
  - Mesothelin-selected tumors
  - Mesothelioma
  - Pancreatic

MTD = 1.2mg/kg Q3W with DLT Liver toxicity

*Intermediate dose; *QW for 3 weeks followed by 1 week off; *Cohorts clinically evaluated.
## Best Overall Response

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Escalation (n = 45)</td>
<td>All Expansion (n = 51)</td>
</tr>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (2)^c</td>
<td>3 (6)^d</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>SD</td>
<td>12 (27)</td>
<td>24 (47)</td>
</tr>
<tr>
<td>PD</td>
<td>27 (60)</td>
<td>16 (31)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not reported</td>
<td>5 (11)</td>
<td>8 (16)</td>
</tr>
<tr>
<td><strong>DCR, n (%)</strong></td>
<td>13 (29)</td>
<td>27 (53)</td>
</tr>
<tr>
<td><strong>PFS, median, mo</strong></td>
<td>NA</td>
<td>3 [2, 4]</td>
</tr>
</tbody>
</table>

CR, complete response; DCR, disease control rate; NA, not available; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

^aIncludes patients from dose escalation and expansion groups. ^bIncludes only patients from expansion group. An additional n=3 mesothelioma patients were treated in escalation, with n=2 reporting a confirmed partial response lasting 9.69 and 10.41 months, respectively. ^cN=1 with mesothelioma assigned to 0.8 mg/kg Q3W had a confirmed partial response lasting 10.22 months. ^dORR was 0% for NSCLC. ^eMean ORR was 31% with combo in escalation and expansion cohorts with mesothelioma (n= 16).
Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Mono Q3W&lt;sup&gt;a&lt;/sup&gt; (n = 84)</th>
<th>Mono QW&lt;sup&gt;a,b&lt;/sup&gt; (n = 12)</th>
<th>Combo Q3W (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TRAE, n (%)</td>
<td>Any Gr</td>
<td>Gr 3-4</td>
<td>Any Gr</td>
</tr>
<tr>
<td></td>
<td>72 (86)</td>
<td>42 (50)</td>
<td>11 (92)</td>
</tr>
<tr>
<td>TRAEs in ≥ 10% of all pts, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>41 (49)</td>
<td>20 (24)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>39 (46)</td>
<td>17 (20)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34 (40)</td>
<td>6 (7)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Nausea</td>
<td>27 (32)</td>
<td>0</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22 (26)</td>
<td>1 (1)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>20 (24)</td>
<td>5 (6)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (17)</td>
<td>2 (2)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (18)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (13)</td>
<td>1 (1)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td>9 (11)</td>
<td>2 (4)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 (12)</td>
<td>2 (2)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6 (7)</td>
<td>0</td>
<td>3 (25)</td>
</tr>
<tr>
<td>TRAEs leading to treatment discontinuation, n (%)</td>
<td>15 (18)</td>
<td>11 (13)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Serious TRAEs were reported in 15 patients (18%) in the mono Q3W group, 2 patients (17%) in the mono QW group, and 7 patients (23%) in the combination group.
- One treatment-related death occurred in the mono Q3W group (1.2 mg/kg Q3W; pneumonitis).
- The majority of ophthalmic AEs were mild and manageable with topical treatments when indicated:
  - One subject in the mono Q3W group (1.2 mg/kg Q3W) experienced Grade 3 keratopathy and Grade 3 reduced visual acuity
  - One subject in the mono Q3W group (1.2 mg/kg Q3W) experienced Grade 3 cataracts (left and right eyes)

<sup>a</sup>All dose-escalation levels combined; <sup>b</sup>QW for 3 weeks followed by 1 week off.
Mesothelin antibody drug conjugate

• Other agents in development:
  • LMB-100:
    • Mesothelin antibody with an immunotoxin.
Mesothelin CAR-T cell Therapy

Image of courtesy of the National Cancer Institute
Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

• T-regs, myeloid derived suppressor cells and tumour associated macrophages in the tumour stroma induce CD8 cells apoptosis and tolerance.

• TAMs can be divided into 2 groups:
  • M1 in the tumour islets:
    • Anti-tumour
    • Induces TH1 response.
  • M2 in the tumour stroma:
    • Promotes scavenging of debris
    • Promotes angiogenesis
    • Remodels and repairs.
    • High expression of
      • Cytokines: IL-10, CCL17, CCL22 and CCL2
      • MMP
      • CD206 (mannose receptor), CD163 (scavenger receptor), and galactose type receptor
    • Loss of antigen presentation function.

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- Ujiie et al. examined 8 infiltrating immune cells and 5 cytokines and receptors in tumours and stroma:
  - Univariate analysis found
    - High CD4 T cell and CD20 B-Cell are associated with good prognosis
    - High IL-17R on CD8 T cell is associated with poor prognosis.
  - Multivariate analysis found
    - CD20 (Mature B-cell) is associated with good prognosis
    - High CD163 (M2) is associated with poor prognosis.
  - TAMs lead to increase IL10 and B7-H3 expression on tumour cells which inhibit T-cell immune response.¹, ²

¹. Ujiie et al. Oncoimmunology 2015;19:e1009285
Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- In hypoxic environment, M1 is converted to M2, leading to angiogenesis and lymphogenesis via VEGF and MMP-9 overexpression.

- Mesothelioma cells secrete prostaglandin E2 which activates macrophages to M2 and, in turn, leads to differentiation of T-cell to T-reg and decrease in CD8 cells proliferation.1, 2, 3

1. Lievense et al. JTO 2016;11:1755-64
Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

• CD47 or SIRP-alpha:

  • Inhibition of CD47 or SIRP-alpha leads to activation of M1, and anti-tumour activity.¹

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- CSF-1:
  - Responsible for recruitment of TAMs and MDSC
  - Inhibition of CSF-1 leads to reprogramming of TAMs and thus anti-tumour inflammatory response and CD8 activation.¹

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- IL6/IL6-R and STAT3

- Responsible for MDSC proliferation, increase in Treg, decrease in CD8 cells and maturation of dendritic cell.¹
- Increase in PDL-1 expression on tumour cells and Treg
- Increase in IDO1 and thus kynurenine and other immunosuppressive secretory factors: Arginine and adenosine¹,²,³
- Associated with increase phosphoesterase 5 expression.⁴

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells-

• CCR5:
  • Increase in CCR5 expression on MDSC by upregulation of CCR5 ligands, IL6, GM-CSF and other inflammatory factors and increase infiltration of MDSC.\(^1\)
  • Important for Treg differentiation and its migration to inflammatory sites\(^2\)
  • Increase resistance to DNA damaging agents and thus increase in metastases and stemness of cancer cells.\(^2\)

Immune Checkpoints
PD1/PDL-1 and Chemotherapy

Chemotherapy can promote tumor immunity in two major ways

1. Inducing immunogenic cell death as part of its intended therapeutic effect

2. Disrupting strategies that tumors use to evade the immune response

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TL, CD8 cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cell; NK, natural killer; TAM, tumor-associated macrophage

Lorenzo Galluzzi et al, cancer Immuno Res 2016
The IND 227 Trial Schema is an academic open-label, multicentre, phase II randomized study in patients with malignant pleural mesothelioma (MPM) receiving first-line treatment for incurable advanced or metastatic disease.

Patients will be stratified by histological subtype (epithelioid vs. other histology). PD-L1 tumour status will be used retrospectively at the time of clinical outcome analysis.
Phase 3

**Primary Objective**
- To evaluate whether pembrolizumab improves overall survival when added to standard chemotherapy in malignant pleural mesothelioma compared to standard chemotherapy.

**Secondary Objectives**
- To evaluate the tolerability of pembrolizumab, alone and given to patients receiving standard chemotherapy.
- To assess antitumour activity of pembrolizumab given to patients receiving standard chemotherapy.
- To evaluate whether pembrolizumab improves progression-free survival when added to standard chemotherapy.
- To evaluate the quality of life impact of pembrolizumab given to patients receiving chemotherapy.
- To explore predictive and prognostic value of PDL-1 expression and presence of T-cells subsets within the tumour microenvironment.
- To explore health economics when adding pembrolizumab to standard chemotherapy.

**Exploratory Objective**
- To explore predictive and prognostic value of exploratory blood based biomarkers.
- To explore predictive and prognostic value of other immune cells in tumour microenvironment.
First IND International Phase 2/3 Trial

Marilina Piccirillo, Napoli

Quincy Chu

Laurent Greillier, Marseille

Dean Fennell, Leister
CD40


Activation and Class-switching of B-cells

1. APC presents antigen to T-helper cells
2. B7 is expressed and interacts with CD28, activating T-helper cells
3. Activated Th cells interact with B-cells via CD40 ligand, activating B-cells to proliferate, differentiate, and secrete antibodies
4. Th cells secrete cytokines that determine class switching

Nature Reviews | Immunology
Immune Checkpoints

• Salaroglio et al. demonstrated increase in
  • Treg and MDSC (granulocyte or macrophage derived) which is a negative predictor for PFS and OS
  • Increase in LAG3 and TIM3 expression on CD8 cells associated to negative OS.
  • MHC1 mutation in 59% of mesothelioma associated dendritic cells or antigen presenting cells.¹

• B7-H3:
  • A member of B7 family, which interacts with CD28 family molecules such as PD1, CD28, CTLA4 and ICOS, as a co-inhibitory signal leading to immune suppression.²
  • Expressed on antigen presenting cells and mesothelioma cell lines
  • High expression in 54% of epithelioid subtype of mesothelioma and uncommon in sarcomaotid subtypes.³

LAG525X2101C is an open-label, Phase I/II study of cohorts with single-agent LAG525 or the combination of LAG525 and spartalizumab (NCT02460224; Figure 2).

Figure 2. LAG525X2101C Study Design
3/8 mesothelioma patient responded.
Immune Checkpoints

• Salaroglio et al. demonstrated increase in
  • Treg and MDSC (granulocyte or macrophage derived) which is a negative predictor for PFS and OS
  • Increase in LAG3 and TIM3 expression on CD8 cells associated to negative OS.
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TGF-Beta

• Exposure to chrysotile leads to activation of the MAPK/ERK pathway and thus p38, which in turn leads to increase in TGF-B1 expression and Treg infiltration and immune suppression.¹

• Loss of NF2 or other component of the Hippo pathway is common in mesothelioma which leads to over-expression and activation of TGF-beta 1 receptor and thus mesothelioma formation.²,³

• In part leads to infiltration of CD8+, CD4+ and FOXP3+/CD4+/CD25+ Treg into the tumour and thus immune suppression.⁴

Conclusions

• With further understanding of the mutational and immune landscapes of mesothelioma:
  • Biology
  • Targets
  • Therapeutics.

• Mesothelioma may
  • A collection of different subtypes
  • Novel therapeutics should be moving forward based on biology and efficacy in preclinical models, particularly immune competent mouse models.
  • Novel clinical trial designs with international collaboration will be needed.
Thank you