Results from a Phase I dose escalation trial (TACTI-mel) with the soluble LAG-3 protein (IMP321, eftilagimod alpha) together with pembrolizumab in unresectable or metastatic melanoma

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Presenter Disclosure Information

The following relationships exist related to this presentation:

*Travel Sponsorship & Speaker Honorarium: Immutep*
eftilagimod alpha (IMP321): APC activator (i.e. not an ICI)

“PUSHING THE ACCELERATOR ON IMMUNE RESPONSES”

eftilagimod alpha:  
- MHC II agonist  
- LAG-3 fusion protein

eftilagimod alpha (efti, IMP321):

**APC activator**
- Boost and sustain the CD8+ T cell responses
- Activate multiple immune cell subsets

“RELEASING THE BRAKE ON THE T CELL”

LAG-3 antagonist antibodies:

**Immune checkpoint inhibitor (ICI)**
- increase cytotoxicity of the pre-existing CD8 T cell response
Primary target cells: Sustained increase of circulating Antigen-Presenting Cells (APCs) such as monocytes (A) and dendritic cells (not shown). Rapid activation of monocytes (CD16 (B) and CD40 (not shown)).

Secondary target cells: Sustainable increase in absolute numbers of effector cells such as i.e. CD8 T cells (C) and Natural Killer cells (not shown). IMP321 induces early and sustainable increase of Th1 biomarkers like IFN-γ (D) and IP-10 (not shown).
Pharmacokinetics efiltigamod alpha (IMP321)

Soluble LAG-3 (efti) blood concentration after 1st dose

- Dose proportional increase in PK parameters
- Variability between patients receiving the same dose
- Efti is an MHC II agonist: a few ng/ml in the blood is enough to see sustained APC activation

* Theoretical time points, actual measurement might differ
New Rationale for Combining eftilagimod alpha (IMP321) with PD-1 Antagonists (pembrolizumab)

- Baseline innate immunity status seems to be important for the response and survival to pembrolizumab
- Data suggests that low monocyte numbers at baseline are associated with poor efficacy of anti-PD-1 therapy in melanoma patients
- Data shows that the APC activator eftilagimod alpha boosts innate immunity

Study Scheme Part A:

Cycle 1-3 of pembrolizumab (patients with sub-optimal response or progressive disease after 3 cycles with pembrolizumab are eligible to the trial)

Screening

Combined immunotherapy* (9 cycles of pembrolizumab + IMP321)

PFS FU every 12 wks
Continuation of pembrolizumab monotherapy

Cycle 4 of pembrol

Cycle 5-13 of Pembrolizumab* = Cycle 1-9 of TACTI-mel

Enrolment

End of treatment

End of study

- 18 pts in total → 6 pts per efti dose group
- Patients received:
  - 2 mg/kg pembrolizumab i.v. every 3 weeks
  - 1, 6, 30 mg efti s.c. every 2 weeks for up to 6 months
- Imaging was done every 12 weeks
**TACTI-mel: Safety Summary**

*Overview grade 3 / 4 TEAEs and rel. to study treatment*

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Grade 3 N (%)</th>
<th>Grade 4 N (%)</th>
<th>Rel to efti / pembro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculo-papular rash</td>
<td>1 (6 %)</td>
<td>-</td>
<td>No / Yes</td>
</tr>
<tr>
<td>Decreased renal function</td>
<td>1 (6 %)</td>
<td>-</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (6 %)</td>
<td>-</td>
<td>No / Yes</td>
</tr>
<tr>
<td>Altered liver functions</td>
<td>1 (6 %)</td>
<td>-</td>
<td>No / Yes</td>
</tr>
</tbody>
</table>

- No new safety signals
- 1 pt died due to an AE (grade 4 Intercranial hemorrhage, not rel.)
- 1 pt discontinued due to an AE (not rel.)
- 3 pts experienced treatment delay due to an AE

*Overview frequent TEAE (PT selected if ≥ 10 % of the pts)*

<table>
<thead>
<tr>
<th>Adverse Event*, Any grade N (%)</th>
<th>Grade 3 or 4 N (%)</th>
<th>No of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia 3 (17)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea 5 (28)</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue 8 (44)</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>Hyperglycemia 3 (17)</td>
<td>3 (17)</td>
<td>3</td>
</tr>
<tr>
<td>Nausea 5 (28)</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Rash## 7 (39)</td>
<td>1 (6)</td>
<td>7</td>
</tr>
</tbody>
</table>

* - Adverse events occurred in > 10 % of pts
## - Any kind of rash

- No Dose limiting toxicities observed
- 6 pts (33 %) with ≥ 1 SAE; none related to any study drug
- 8 pts (44 %) with ≥ 1 AE with ≥ grade 3 (no grade 5)

preliminary data, status Oct 15th 2018
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>N = 18 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>67 yrs</td>
</tr>
<tr>
<td>Sex (f/m)</td>
<td>1 (6 %) / 17 (94 %)</td>
</tr>
<tr>
<td><strong>Elevated LDH</strong></td>
<td>7 (39%)</td>
</tr>
<tr>
<td><strong>Metastasis stage M1c</strong></td>
<td>14 (78 %)</td>
</tr>
<tr>
<td>Pre-treated with BRAF/MEK/ipilimumab</td>
<td>5 (28 %)</td>
</tr>
<tr>
<td>irPD/irSD to pembro after 3 cycles</td>
<td>11 (61 %)</td>
</tr>
</tbody>
</table>

- Very late stage of disease (M1c, elevated LDH) and majority not responding to pembrolizumab monotherapy

<table>
<thead>
<tr>
<th>Best Overall Response acc. to irRC</th>
<th>N = 18 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>irCR</td>
<td>1 (6 %)</td>
</tr>
<tr>
<td>irPR#</td>
<td>5 (28 %)#</td>
</tr>
<tr>
<td>irSD</td>
<td>6 (33 %)</td>
</tr>
<tr>
<td>irPD</td>
<td>6 (33 %)</td>
</tr>
</tbody>
</table>

| Best overall response rate (ORR)       | 6 (33 %)   |
| Patients with tumor shrinkage          | 10 (56 %)  |
| Disease control rate                   | 12 (66 %)  |

# - incl. 1 pt with complete disappearance of all target lesions

- If response is calculated from pre-pembro timepoint → ORR is 61 % acc. to irRC
TACTI-mel: Response patterns

→ Tumor shrinkage in 10 (56%) of these patients incl. 2 pts with complete disappearance of all target lesions

→ 1 pt with confirmed CR + 4 pts still on Tx after 12 months

→ 5 (28%) pts with long term (>12 mths) treatment/benefit

Society for Immunotherapy of Cancer

#SITC2018
TACTI-mel: Single Case

- 84 year old male with multiple lung metastases from melanoma
- BRAF wild type

• Patient progressing on pembrolizumab monotherapy
• At 1 yr all lesions disappeared $\Rightarrow$ CR (confirmed)
• Patient without treatment and disease free $\Rightarrow$ now lost to FU

pre-pembro  week 9 (pembro)  week 25 (combo)  week 37 (combo)  week 49 (Pembro mono)

Tumor progression

week 64  (PFS-FU)

preliminary data, status Oct 15th 2018
Lessons and Take Home Messages

- Efti in combination with Pembrolizumab was well tolerated and no new safety concerns were observed
- The combination showed encouraging clinical activity in patients with sub-optimal response to pembrolizumab monotherapy
- TACTI-mel Part B is ongoing in Australia with no DLTs observed so far
- Results warrant further investigation of efti + pembrolizumab, potentially also in other indications (NSCLC and HNSCC) → TACTI-002 trial being initiated (NCT03625323; Poster for Abstract ID: 10328)
Acknowledgement and Thank You

We would like to thank to all patients and their families for participation

The sites and the study teams at:

- Royal Brisbane Womens Hospital, Brisbane, Queensland, Australia, 4029
- Princess Alexandra Hospital, Brisbane, Queensland, Australia, 4102
- Greenslopes Private Hospital, Brisbane, Queensland, Australia, 4120
- Fiona Stanley Hospital, Perth, Western Australia, Australia, 6150
- Ballarat Hospital, Ballarat, Victoria, Australia, 3353
- Alfred Hospital, Melbourne, Victoria, Australia, 3181
- Flinders Medical Centre, Adelaide, South Australia, Australia, 5042

The study was sponsored by **Immutep Australia PTY Ltd**