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

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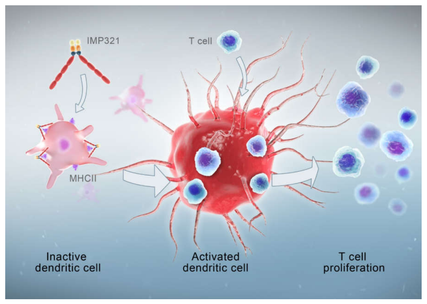
Background



IMP321 (eftilagimod alpha), a LAG-3Ig fusion protein, is a MHC class II agonist that activates antigen-presenting cell (APC) such as dendritic cells and monocytes (primary target cells) and then CD8 T-cells (secondary target cells). The activation of the dendritic cell network and the subsequent T cell recruitment at the tumor site with IMP321 may lead to stronger anti-tumor CD8 T cell responses than observed with pembrolizumab monotherapy. We hypothesize that the combination of an APC activator with an immune checkpoint inhibitor (ICI) will increase efficacy without additional toxicity.

We report here initial results of 3 cohorts of a dose escalation Phase 1 clinical trial investigating the use of pembrolizumab in combination with IMP321 at different dose levels (1, 6 and 30 mg) in patients with unresectable or metastatic melanoma (TACTI-mel clinical trial).

For more information, please visit:
http://www.immutep.com/technology/lag-3-technology.html

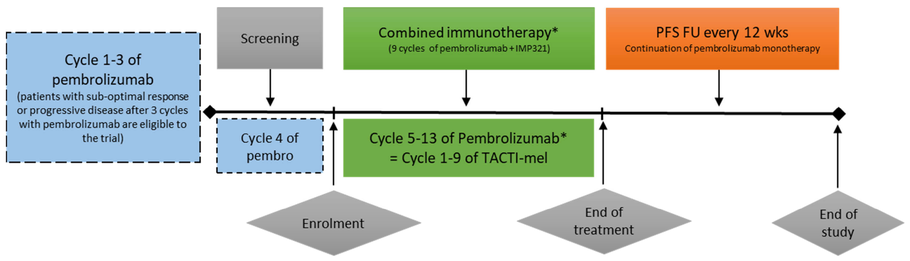
The trial identifiers are IMP321-P012 (sponsor code) and NCT02676869 (ClinicalTrials.gov). Corresponding author: Victoria Atkinson, Victoria.Atkinson@health.qld.gov.au

Trial Design

- Phase I, multi-center, open-label, dose escalation
- Recruitment of 24 patients in 7 sites in Australia
- The trial consists of 2 parts:
  - *Part A (n=18): IMP321 (eftilagimod alpha) at 1, 6 and 30 mg s.c. every 2 weeks starting with cycle 5 of pembrolizumab (2 mg/kg every 3 weeks)*
  - *Part B (n=6): IMP321 (eftilagimod alpha) at 30 mg s.c. every 2 weeks starting with cycle 1 of pembrolizumab (2 mg/kg every 3 weeks)*

Design Part A:

- Patients are on pembrolizumab monotherapy. After 3 cycles patients response to pembrolizumab is investigated. In the case of suboptimal response (irPR, irSD, irPD) and measurable disease patients are eligible for the study
- Beginning with cycle 5 of pembrolizumab, IMP321 injections are administered every 2 weeks for a duration of 6 months (maximum of 13 injections)
- In each cohort (1, 6, or 30 mg IMP321), the first 3 patients will start treatment one week apart.



*Tumor assessment acc to irRC

- Decision for dose escalation is done by the Data Safety Monitoring Board (DSMB). If more than 2 patients per cohort experience a dose-limiting toxicity (DLT), this dose will be considered at maximum tolerated dose
- DLTs are defined as follows:
  - *Clinically relevant changes of plasma cytokines/chemokines defined as an increase of more than 50 times over baseline of at least two cytokines (TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-8)*
  - *Grade ≥ 3 immune-related abnormalities*
  - *Grade ≥ 4 AEs of any aetiology*
- Imaging and decision on treatment continuation done accoring to irRC.

Objectives Part A

Primary:

- To evaluate the safety, tolerability and recommended phase 2 dose (RP2D) of IMP321 when combined with anti-PD-1 treatment starting with the 5th cycle (part A) of pembrolizumab (Keytruda®) in patients with unresectable or metastatic melanoma

Secondary:

- To assess the pharmacokinetic and immunogenicity properties of IMP321 when combined with anti-PD-1 treatment pembrolizumab
- To evaluate the antitumor activity of IMP321 when combined with anti-PD-1 treatment

Exposure and Safety

Summary - Exposure:

- Patients received median 10.0 (range 3-13) IMP321 injections and median of 7 (range 2-9) pembrolizumab infusions within the combination treatment period
- Pts with benefit at end of combination treatment continued on pembrolizumab monotherapy
- No dose reductions for pembrolizumab or IMP321 were applied

List of all SAEs	Severity
Influenza A	Grade 3
Sepsis	Grade 3
Hyperglycemia	Grade 3
Anaemia of chronic disease	Grade 3
Anaemia of chronic disease	Grade 3
Intracranial Hemorrhage	Grade 4
Pulmonary embolism	Grade 3

Note: none of the SAEs was related to IMP321 or pembrolizumab

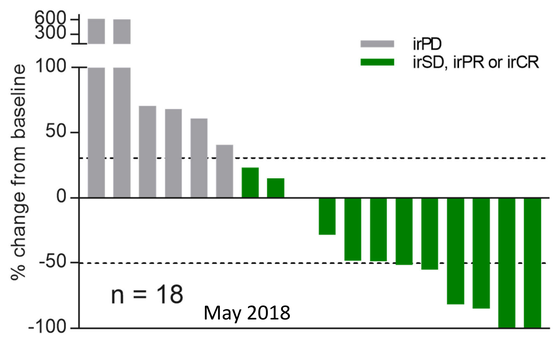
Safety Parameter	N (%)
Pts with any AE	18 (100)
Pts with any SAE	6 (33)
thereof rel. to IMP321	0 (0)
thereof rel. to Pembrolizumab	0 (0)
Pts with any grade 3/4 AE	8 (44)
thereof rel. to IMP321	1 (6)
thereof rel. to Pembrolizumab	2 (11)

Summary - Safety:

- In total 134 AEs in 18 patients; thereof 18 AEs ≥G3 in 8 pts (see table on the left)
- Intercranial hemorrhage, not related to IMP321 or pembro lead to death of 1 pt
- Anemia of chronic disease grade 3 (30 mg) – not related to pembro/IMP321 led to permanent discontinuation
- 6 AEs in 3 pts led to a treatment delay
- No dose limiting toxicities in both cohorts
- No noteworthy differences between IMP321 dose groups

AE…adverse event
APC…Antigen-presenting cell
DCR…Disease Control Rate
DLT…dose-limiting toxicity
DSMB…Data Safety Monitoring Board
FU…follow up
ICI…immune checkpoint inhibitor
irPD…progressive disease
irPR…immune-related partial response
irRC…immune related Response Criteria
irSD…immune-related stabile disease
PFS…progression-free survival
Pt…patient
RECIST…Response Evaluation Criteria In Solid Tumors
RR…Response Rate
SAE…Serious adverse event

Baseline Demographics and Efficacy Results



Baseline Parameter	Total (n=18) n (%)
Median (range) age, year	61 (48-88)
Men, n (%)	17 (94)
Caucasian, n (%)	18 (100)
ECOG 1/0 (%)	22% / 78%
Metastatis stage M1c	15 (83)
Elevated LDH, n (%)	7 (39)
Prior BRAF/MEK/IPI treatment	4 (22)

Summary - Baseline Characteristics:

- Patients very late stage of disease (M1c, elevated LDH)
- Majority not responding to pembrolizumab monotherapy (12 out of 1, 67 %)

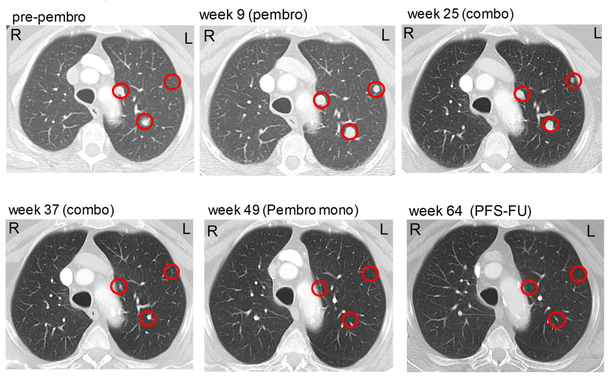
Summary – Results:

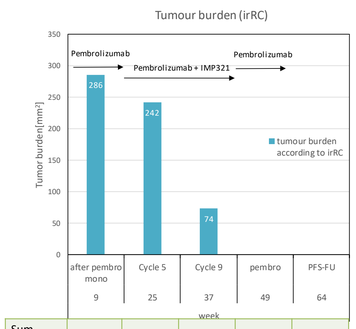
- Two pts with complete disappearance of all target lesions incl. 1 confirmed complete response (see case below) after 11 and 18 months
- Response are generally durable
- Follow-up of 4 patients still ongoing

Response Parameter (irRC)	Total (n=18) n (%)
irCR	1 (6)
irPR	5 (28)
irSD	6 (33)
irPD	6 (33)
Overall Response Rate (ORR)	6 (33)
Disease Control Rate (DCR)	12 (66)
Patients with tumor shrinkage	9 (50)

Patient Case #1 (Pembrolizumab + 1 mg IMP321)

- Male, Caucasian, 84 years
- stage IV visceral disease (lung and thorax metastases), best response pembrolizumab monotherapy irPD
- Patient completed study, PFS-FU (incl. Pembrolizumab monotherapy) was stopped due to patient wish after week 64 → PFS censored week 64
- **Best Response: confirmed irCR**

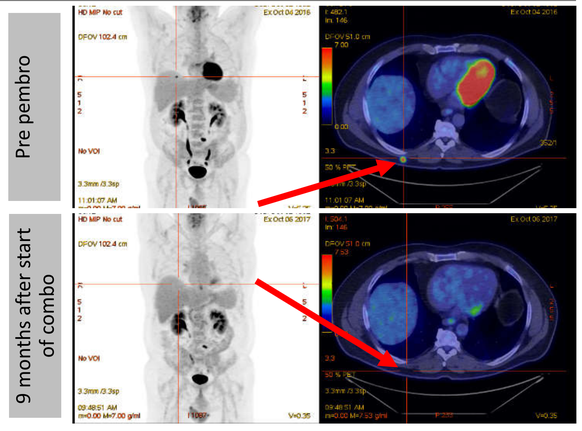




Sum Target Lesions	286 mm²	242 mm²	74 mm²	0 mm²	0 mm²
In %	100%	85%	26%	0%	0%
irRC	N/A	irSD	irPR	irCR	irCR

Patient Case #2 (Pembrolizumab + 6 mg IMP321)

- Male, Caucasian, 54 years
- Stage IV skin/superficial disease → best response pembrolizumab monotherapy was irSD
- Target lesion: chest wall; Non-target lesion: Left common iliac LN
- Patient has completed the study treatment, PFS-FU (incl. Pembrolizumab monotherapy) ongoing → PFS 22+ months
- Complete disappearance of target lesions, lymph node normalized
- **Best Response: confirmed irPR**



Conclusion & Outlook:

- **Combination of IMP321 (1, 6 and 30 mg) and pembrolizumab in advanced metastatic melanoma patients is safe and well tolerated**
- **Anti-tumor activity (tumor reduction) was observed in 9/18 patients (50 %) in this study, including 2 patients with complete disappearance of all target lesions**
- **The results support the hypothesis that combining an APC activator (IMP321, eftilagimod alpha) with a checkpoint inhibitor (pembrolizumab) results in a therapeutic synergy and a potential clinical benefit over checkpoint inhibitor monotherapy**
- **Part B of the study is ongoing with 6/6 enrolled patients treated with Pembro and 30 mg IMP321 starting from D1 as combination treatment**
- **Further investigation of IMP321 in combination with PD-1/ PD-L1 checkpoint inhibitors is ongoing in NSCLC and HNSCC (NCT NCT03625323)**