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

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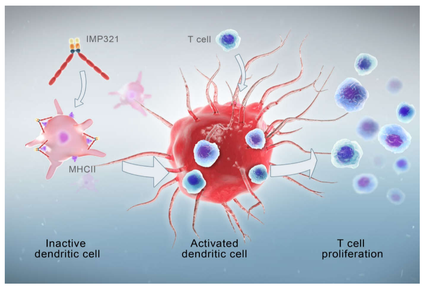
Background



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

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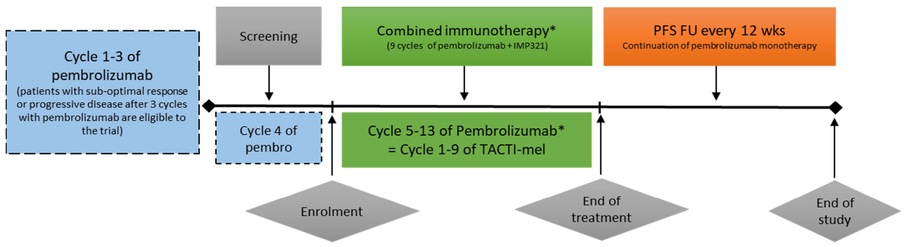
LAG-3 IMMUNOTHERAPY

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 according 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:

- Data-cut off 15th Oct 2018
- Pts 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 the end of combination treatment continued on pembrolizumab monotherapy
- No dose reductions were applied for any study drug

Table 1: Adverse events ≥ grade 3 and at least related to either IMP321 or pembrolizumab

Preferred term	Grade 3 N (%)	Grade 4 N (%)	Rel to efti / pembro
Maculo-papular rash	1 (6 %)	-	No / Yes
Decreased renal function	1 (6 %)	-	Yes / No
Colitis	1 (6 %)	-	No / Yes
Altered liver functions	1 (6 %)	-	No / Yes

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

Summary - Safety:

- Intracranial hemorrhage grade 4, not related to IMP321 or pembro, lead to death of 1 pt
- Anemia grade 3 (30 mg) – not related to pembro/IMP321, led to permanent discontinuation in 1 pt
- Three pts had a AE-induced treatment delay
- No dose limiting toxicities at 1, 6 or 30 mg IMP321

Table 2: Overview frequent TEAE (if ≥ 10 % of the pts)

Adverse Event*,	Any grade N (%)	Grade 3 or 4 N (%)	No of events
Arthralgia	3 (17)	-	3
Diarrhea	5 (28)	-	6
Fatigue	8 (44)	-	10
Hyperglycemia	3 (17)	3 (17)	3
Nausea	5 (28)	-	7
Rash	7 (39)	1 (6)	7

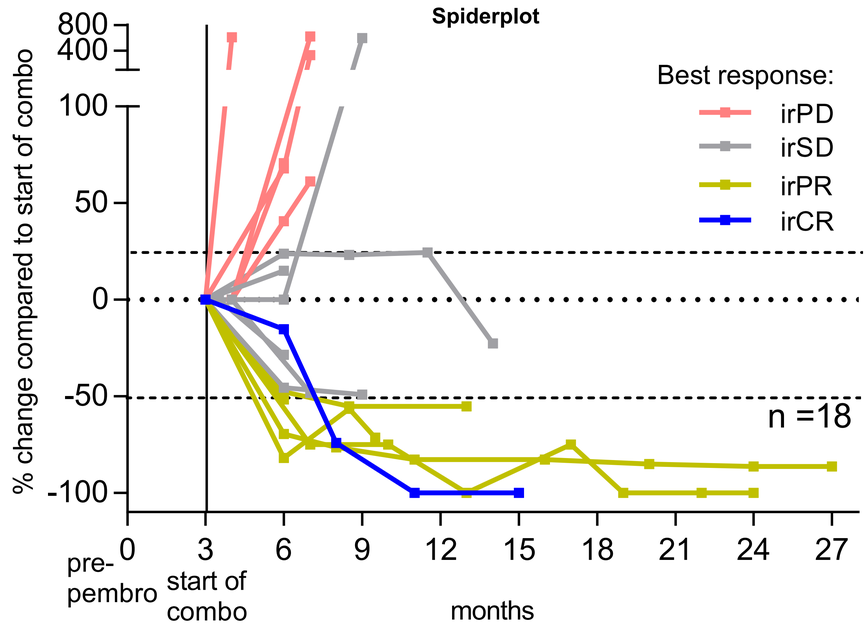
AE…adverse event
APC…Antigen-presenting cell
DCR…Disease Control Rate
DLT…dose-limiting toxicity
DSMB…Data Safety Monitoring Board
FU…follow up
ICI…immune checkpoint inhibitor
irPD…progressive disease
irPR…immune-related partial response
irRC…immune related Response Criteria
irSD…immune-related stabile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

Baseline Demographics and Efficacy Results

Summary - Baseline Characteristics:

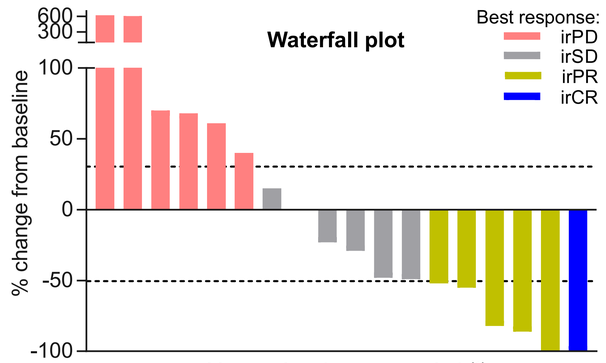
- Patients very late stage of disease (M1c, elevated LDH)
- Majority not responding to pembrolizumab monotherapy (11 out of 18 patients, 61 %)
- 5 patients (28 %) pre-treated before starting pembrolizumab

Baseline Parameters	Total (n=18) n (%)
Median (range) age, year	65 (48-85)
Female, n (%)	17 (94)
Caucasian, n (%)	18 (100)
ECOG 1/0 (%)	22% / 78%
Metastatic stage M1c	14 (78)
Elevated LDH, n (%)	7 (39)
Prior BRAF/MEK/IPI treatment	5 (28)



Summary – Results:

- Two pts with complete disappearance of all target lesions after 11 and 18 months
- Tumor shrinkage in 56 % of these pts → ORR of 33 % incl. 1 confirmed irCR
- 28 % (n=5) of pts with long term (>12 mts) benefit
- 4 pts still on therapy



Response Table – Standard (Start of combo)

Response Parameter (irRC), (cut off 15th Oct 2018)	Total (N=18) N (%)
irCR	1 (6)
irPR#	5 (28)
irSD	6 (33)
irPD	6 (33)
Overall Response Rate (ORR)	6 (33)
Patients with tumor shrinkage	10 (56)
Disease Control Rate (DCR)	12 (66)

Response Table – Explorative C1D1 analysis(1)

Best Overall Response acc. to irRC (C1/D1 analysis)(1)	Total (N=18) N (%)
irCR	1 (6)(1)
irPR#	10 (56)(1)
irSD	5 (28)(1)
irPD	2 (11)(1)
Overall Response Rate (ORR)	11 (61)(1)
Patients with tumor shrinkage	13 (72)
Progression free at 6 months	12 (66)(1)

(1) Performed analysis starting from cycle 1 day 1 of pembrolizumab, including the 4 cycles of pembrolizumab monotherapy

Conclusion & Outlook:

- **Combination of IMP321 (1, 6 and 30 mg) and pembrolizumab in advanced metastatic melanoma patients is safe and well tolerated without any DLTs**
- **Anti-tumor activity (tumor size reduction) was observed in 10/18 patients (54 %) in this study, including 2 patients with complete disappearance of all target lesions**
- **5 pts (28 %) have long lasting (≥12 months) disease control/remission**
- **The results support the hypothesis that combining an APC activator (IMP321, eftilagimod alpha) with a checkpoint inhibitor (pembrolizumab) results in a therapeutic synergy**
- **Part B of the study is ongoing with patients treated addition of 30 mg IMP321 starting from cycle 1 day 1 of pembrolizumab. No DLTs have been observed.**
- **Based on these results investigation of IMP321 in combination with pembrolizumab is ongoing in NSCLC and HNSCC (NCT03625323) and also in combination with avelumab (NCT03252938)**