

ASX/Media Release (Code: ASX: IMM; NASDAQ: IMMP)

Immutep Reports Positive Final Efficacy Data from TACTI-mel Trial in Melanoma

Key Trial Findings

- Favourable safety profile of eftilagimod alpha in combination with pembrolizumab
- Deep and durable responses have been observed with tumour shrinkage in 56% and 66% of patients in part A and B respectively
- Disease Control Rate of 66% of patients in each Part A and B (24 patients in total)

SYDNEY, AUSTRALIA – October 15, 2019 – <u>Immutep Limited</u> (ASX: IMM; NASDAQ: IMMP) ("Immutep" or "the Company"), a biotechnology company developing novel immunotherapy treatments for cancer and autoimmune diseases, today announces mature positive efficacy data from its TACTI-mel Phase I clinical study combining its lead product candidate, eftilagimod alpha ("efti" or "IMP321") with KEYTRUDA[®] (pembrolizumab) in metastatic melanoma.

The data will be presented by Dr. Frédéric Triebel, Chief Scientific Officer and Chief Medical Officer of Immutep at the World Immunotherapy Congress as part of the Festival of Biologics 2019 being held in Basel, Switzerland on 15th October 2019.

Commenting on the positive results, Dr. Triebel said, "The combination therapy with efti shows very encouraging efficacy signals of synergy with KEYTRUDA along with a favourable safety profile so far in this high-risk patient population. Patients are responding well to the combination treatment, their tumours are shrinking and not growing back over a long follow up period. In addition, we have seen the complete disappearance of all target tumour lesions for six patients plus one patient with a metabolic complete response on the PET-scan. The efficacy data is now final with a long follow up, the safety assessment is ongoing."

Overview of Trial

TACTI-mel evaluated the combination of efti with anti-PD-1 therapy KEYTRUDA[®] (pembrolizumab) in 24 patients with unresectable or metastatic melanoma. Patients participating in the trial had a very late stage of disease: 75% classified as M1c (associated with lowest probability of survival), 67% had lung metastasis, 50% had liver metastasis, 50% had elevated LDH (poor prognosis marker) and many had either a suboptimal response or disease progression with pembrolizumab treatment as a monotherapy. All patients received subcutaneous injections of efti every two weeks, with a treatment duration of up to either six or 12 months.

TACTI-mel is a multi-centre, open label clinical trial involving four cohorts of six patients per cohort:

• **Part A** includes the first three cohorts testing different dosages of efti (1mg, 6mg and 30mg) in combination with pembrolizumab, with efti treatment given for six months only and commencing at cycle five of pembrolizumab treatment.



• **Part B** includes the remaining cohort testing a 30mg dosage of efti given for 12 months in combination with pembrolizumab, starting at cycle 1, day 1 of pembrolizumab treatment.

The primary endpoint of the trial is safety and tolerability, with the outcome to determine the recommended dose for a Phase II trial. The trial also evaluated efficacy through Overall Response Rate (ORR), tumour shrinkage and Disease Control Rate (DCR).

Key Findings

- Efti has a favourable safety profile in combination with pembrolizumab with no dose-limiting toxicities.
- The recommended dosage level for a Phase II trial is 30mg of efti, which is the dosage level currently used in the ongoing TACTI-002 Phase II trial.
- Deep (with 12 patients (50%) having a decrease of ≥ 75% in the target lesions) and durable (9 patients (38%) being treated for ≥ 12 months with pembrolizumab ± efti) responses have been observed.

The key efficacy findings from the trial are:

| Measured according to irRC | Part A* N=18 | Part B** N=6 | Part A + B C1D1 analysis*** N=24 |
|--------------------------------|-----------------|-----------------|--|
| Overall Response Rate (ORR) | 6 (33%) | 3 (50%) | 14 (58%) |
| Patients with tumour shrinkage | 10 (56%) | 4 (66%) | 17 (71%) |
| Disease Control Rate (DCR) | 12 (66%) | 4 (66%) | Not reported |
| Progression free at 6 months | Not reported | 4 (66 %) | 14 (58%) |

* Part A: Combination treatment began at cycle 5 of pembrolizumab treatment with patients having suboptimal response to pembrolizumab monotherapy and included a dose escalation of efti.

**Part B: Combination treatment started from cycle 1 day 1 of pembrolizumab.

*** Part A+B C1D1 analysis: Performed exploratory analysis starting from cycle 1 day 1 of pembrolizumab, including the 4 cycles pembrolizumab monotherapy ("C1/D1 Analysis") and includes patients from part B.

The full presentation is attached below to this announcement and will be available on the Company's website at http://www.immutep.com/investors-media/presentations.html

About the TACTI-mel clinical trial

The TACTI-mel (Two ACTive Immunotherapies in melanoma) Phase I clinical trial is a multicentre, open-label study evaluating the combination of eftilagimod alpha ("efti") with pembrolizumab, in unresectable or metastatic melanoma patients that have had either a suboptimal response or had disease progression with pembrolizumab monotherapy (clinicaltrials.gov identifier NCT 02676869).



About Immutep

Immutep is a globally active biotechnology company that is a leader in the development of immunotherapeutic products for the treatment of cancer and autoimmune disease. Immutep is dedicated to leveraging its technology and expertise to bring innovative treatment options to market for patients and to maximize value to shareholders. Immutep is listed on the Australian Securities Exchange (IMM), and on the NASDAQ (IMMP) in the United States.

Immutep's current lead product candidate is eftilagimod alpha ("efti" or "IMP321"), a soluble LAG-3Ig fusion protein based on the LAG-3 immune control mechanism, is a best-and-first-in-class MHC II agonist. This mechanism plays a vital role in the regulation of the T cell immune response. Efti is currently in a Phase IIb clinical trial as a chemoimmunotherapy for metastatic breast cancer termed AIPAC; a Phase II clinical trial being conducted in collaboration with Merck & Co., Inc., Kenilworth, NJ, USA (known as "MSD" outside the United States and Canada) referred to as TACTI-002 (Two ACTive Immunotherapies) to evaluate a combination of efti with KEYTRUDA® (or pembrolizumab, an anti-PD-1 therapy) in several different solid tumours (clinicaltrials.gov identifier NCT03625323); a Phase I clinical trial being conducted in collaboration with Merck KGaA, Darmstadt, Germany and Pfizer Inc. referred to as INSIGHT-004 to evaluate a combination of efti with avelumab (clinical trials.gov identifier NCT03252938); and a Phase I combination therapy trial in metastatic melanoma termed TACTI-mel (clinicaltrials.gov identifier NCT02676869). Immutep is also developing a LAG-3 agonist monoclonal antibody for autoimmune diseases (IMP761) that is currently in preclinical development.

Further information can be found on the Company's website <u>www.immutep.com</u> or by contacting:

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A soluble LAG-3 protein (eftilagimod alpha) with an anti-PD-1 antibody (pembrolizumab): a new combination in immuno-oncology.

> Frédéric Triebel MD, PhD World Immunotherapy Congress Basel, October 15, 2019

Notice: Forward Looking Statements



The purpose of the presentation is to provide an update of the business of Immutep Limited ACN 009 237 889 (ASX:IMM; NASDAQ:IMMP). These slides have been prepared as a presentation aid only and the information they contain may require further explanation and/or clarification. Accordingly, these slides and the information they contain should be read in conjunction with past and future announcements made by Immutep and should not be relied upon as an independent source of information. Please refer to the Company's website and/or the Company's filings to the ASX and SEC for further information.

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LAG-3 as a Therapeutic Target



LAG-3 is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells \rightarrow **Prime target for an immune checkpoint blocker**



→ Positive regulation of antigen presenting cells (APC) → increase in antigen presentation to cytotoxic CD8⁺ T cells

→ Negative regulation of LAG-3⁺ T Cells

* APC: antigen presenting cell

Targeting LAG-3/MHC II May Lead to Multiple Therapeutics in Numerous Indications





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Lead Program Eftilagimod Alpha (IMP321)



Efti Mechanism of Action (MOA)

Efti's unique agonistic MOA leads to T cell expansion and proliferation => pushing the gas on the immune response



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Opportunity for Eftilagimod Alpha



Efti has multiple shots on goal in different indications and in different combinations

- · Best-and-First-In-Class MHCII agonist
- · Good safety profile and encouraging efficacy data thus far
- Estimated favorable (low) cost of goods, current flat dosing and manufacturing process
- Potential for use in various combination settings potential pipeline in a product







AIPAC: Active Immunotherapy PAC litaxel in HER2-/ HR+ MBC



Key features: double blinded, potentially pivotal trial in metastatic breast cancer patients

R2PD – recommended phase 2 dose, ORR – overall response rate, PFS – progression free survival, OS – overall survival, PK – pharmacokinetics



Efti Pharmacodynamic Effect AIPAC Immunomonitoring: Primary Target Cells





Primary target cells: Sustained increase of circulating Antigen-Presenting Cells (APCs) like monocytes (A) and dendritic cells (B). Rapid activation of monocytes (CD16 (C) and CD40 (D)).



Efti Pharmacodynamic Effect AIPAC Immunomonitoring: Secondary Target Cells





Secondary target cells: Sustainable increase in absolute numbers of effector cells like i.e. CD8 T cells (A) and Natural Killer cells (B). IMP321 induces early and sustainable increase of Th1 biomarkers like IFN- γ (C) and IP-10 (CXCL10, D).



TACTI trials: Two ACTive Immunotherapies

"Pushing the gas on the APC while releasing the brake on the T cell"





TACTI-mel: Two ACTive Immunotherapeutics in Melanoma

24 patients, 4 cohorts of 6 patients



7 sites in Australia

Phase I, multicenter, open label, dose escalation Recommended Phase II dose, safety and tolerability

| Other objectives | PK and PD of efti, response rate, PFS |
|-----------------------|---------------------------------------|
| Patient Population | Metastatic melanoma |

Australia

• <u>Part A:</u> 1, 6 and 30 mg efti s.c. every 2 weeks **starting with cycle 5** of pembrolizumab

 <u>Part B:</u> efti at 30 mg s.c. every 2 weeks starting with cycle 1 of pembrolizumab

→ Status: recruitment completed; interim results on following slides

 Pembrolizumab (Keytruda®) 2 mg/kg every 3 weeks i.v. part A and B





Efti has a favorable safety profile in combination with pembrolizumab -No DLTs or MTDs and no new safety signals observed

Frequent TEAE (selected if \geq 15 % of pts)

| Adverse Event* | Any grade N (%) | ≥ Grade 3 N (%) | |
|--------------------------------|--------------------|--------------------|---------|
| Abdominal pain (various terms) | 5 (21) | - | , at a |
| Arthralgia | 5 (21) | 1 (4) | 2 |
| Cough | 4 (17) | - | 1 |
| Diarrhea / Colitis | 6 (25) | 1 (4) | 2022 |
| Fatigue | 12 (50) | - | 000 |
| Headache | 4 (17) | - | |
| Injection site reaction | 6 (25) | - | |
| Nausea | 7 (29) | - | -7 < |
| Rash## | 12 (50) | 1 (4) | |

- 10 SAEs in 9 pts; one related to pembrolizumab, none to efti
- 6 pts (25 %) with \geq 1 AE \geq grade 3 (no grade 5)

Grade 3 / 4 TEAEs and rel. to study treatment

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

- 2 pts died due to AE (grade 4 intracranial hemorrhage, not related to treatment; grade 4 Sepsis, not related to treatment)
- 1 pt disc. due to an AE (anaemia; not related to treatment)
- 6 pts experienced treatment delays due to AEs





Patients in very late stage of disease (M1c, elevated LDH, liver metastasis)

| Baseline Characteristics | Part A N = 18 (%) | Part B N = 6 (%) | Overall N =24 (%) |
|---------------------------------------|----------------------|---------------------|----------------------|
| Median Age | 67 yrs | 61 yrs | 62 yrs |
| Sex (f/m) | 6 % / 94 % | 17 % / 83 % | 8 % / 92 % |
| ECOG 1/0 | 22 % / 78 % | 50 % / 50 % | 29 % / 71 % |
| Pre-treated with BRAF/MEK/ipilimumab | 5 (28 %) | 0 (0 %) | 5 (21 %) |
| Poor prognostic marker at study entry | | | |
| Elevated LDH (>ULN) | 7 (39%) | 5 (83%) | 12 (50 %) |
| Liver metastasis | 10 (56 %) | 2 (33 %) | 12 (50 %) |
| Lung metastasis | 11 (61 %) | 5 (83 %) | 16 (67 %) |
| Metastatic, stage M1c | 14 (78 %) | 4 (66 %) | 18 (75%) |





Majority not responding to pembrolizumab monotherapy → Tumor shrinkage in 56 % incl. 2 pts with disappearance of all baseline index lesions

| Best Overall Response acc. to irRC | N = 18 (%) | <u>Spider plot* (part A)</u> (starting with cycle 5 of pembrolizumab) | <u>Waterfall plot* (part A)</u> (starting with cycle 5 of pembrolizumab) |
|--|-------------------------|---|---|
| irCR | 1 (6 %) | 8007 | |
| irPR# | 5 (28 %)# | Best response: | |
| irSD | 6 (33 %) | | 100 Best irSD response: irPR |
| irPD | 6 (33 %) | | irCR |
| Best overall response rate (ORR) | 6 (33 %) | ompared of the second s | |
| Patients with tumor shrinkage | 10 (56 %) | n = 18 | -50 |
| Disease control rate | 12 (66 %) | 0 12 24 36 48 60 72 84 96 108 120 132 | n = 18 |
| # - incl. 1 pt with complete disapp target lesions; CR acc. to RECIST | earance of all Γ 1.1 | pembro start of combo weeks | |
| | | * - according to in | rRC |
| Exploratory an | alysis | | |
| (C1D1 pembroliz | umab): | | |
| ORR of 61 | % | | |
| | | | |





Confirmed deep partial responses in 3 (50%) of the pts

| Best Overall Response acc. to irRC | N = 6 (%) |
|---------------------------------------|-----------|
| irCR | 0 (0 %) |
| irPR# | 3 (50 %)# |
| irSD | 1 (17 %) |
| irPD | 2 (33 %) |
| Best overall response rate (ORR) | 3 (50 %) |
| Patients with tumor shrinkage | 4 (66 %) |
| Disease control rate | 4 (66 %) |

- incl. 1 pt with complete disappearance of all target lesions (red asterix, case 1) and incl 1 add. pt with no metabolic active disease as per PET-CT (blue asterix, case 2)



• 4 patients (all non-PD) continue on pembrolizumab monotherapy after completion of the trial



Efti in Melanoma TACTI-mel – Results Part B Single Case study (1)



- 61-year old male patient
- TxNxM1b at study entry in March 2018
- irPR reached by week 12 and maintained until end of study (week 72)



Baseline; lesion 17 mm



Week 72; lesion 0 mm

Single index (or target) lesion completely disappeared by week 12 Non-index lesions remained present



Efti in Melanoma TACTI-mel – Results Part B

Single Case study (2)



- 46-year old female patient
- TxNxM1c at study entry in August 2018
- irPR reached by week 12 and maintained until end of study
- PET-scans negative on two occasions at the time of end of treatment and after end of study

Deep irPR, residual tumor mass not metabolically active (complete metabolic response, CMR)



PET-scans

June 2018

May 2019

August 2019





TACTI-002: <u>Two ACT</u>ive <u>Immunotherapeutics</u> in different indications



Key features: PD-X refractory patients (part B), chemo-free option for NSCLC, first FDA IND

NSCLC – non-small-cell lung cancer, HNSCC – head and neck squamous cell cancer, ORR – overall response rate, PFS – progression free survival, OS – overall survival, PK – Preliminar

Preliminary data, cut-off September 2019



Thank you

Frédéric Triebel MD, PhD World Immunotherapy Congress Basel, October 15, 2019