EDISON

Immutep

LAG-3 progress in-house and via partners

Partners proceed to Phase II

Pharma & biotech

Immutep has reported encouraging progress from its in-house and partnered programmes over the past few months. Interim data from the TACTI-mel combo study included a 61% response rate from the start of the Keytruda monotherapy screening period among subjects who went on to receive eftilagimod alpha (efti or IMP321) combo therapy. Partners GSK and Novartis are progressing their in-licensed LAG-3 programmes into Phase II or proof of concept studies, which increases the likelihood that these programmes will return significant value to Immutep. Our valuation has increased to A$510m or A$0.17/share (from A$439m or A$0.14/share).

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS* (c)	P/E (x)	Yield (%)
06/17	4.1	(8.4)	(0.4)	0.0	N/A	N/A
06/18	6.9	(10.9)	(0.5)	0.0	N/A	N/A
06/19e	10.9	(6.8)	(0.2)	0.0	N/A	N/A
06/20e	2.8	(14.9)	(0.5)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding, exceptionals and share-based payments.

Encouraging TACTI-mel data – update due November

Patients in the first three TACTI-mel cohorts showed a 33% response rate from the start of efti/Keytruda combo therapy and 61% from the start of the Keytruda monotherapy screening period. The six-patient additional cohort is fully recruited; treatment with efti started at the same time as Keytruda (vs 12 weeks after the start of Keytruda therapy in the first three cohorts). A data update is due in November.

IND clears the path to TACTI-002 combo study

The FDA approved an Investigational New Drug (IND) application for efti in July. This is an important step in preparation for theTACTI-002 study of efti/Keytruda combo therapy in up to 120 patients with head and neck or lung cancer, in collaboration with Merck. The trial will commence in Q418; first data due in 2019.

Out-licensed programmes progress to Phase II

Novartis has commenced a Phase II study of LAG525 in breast cancer and plans to start a trial in melanoma in September, taking the total to four Phase I/II or Phase II trials of LAG525 combined with a checkpoint inhibitor. GSK has nominated ulcerative colitis as the lead indication for GSK'781 and anticipates proof of concept data in 2020. Both drugs are based on programmes in-licensed from Immutep.

Steady progress with AIPAC recruitment

As of 7 August, 126 out of 226 (56%) subjects had been enrolled in the breast cancer Phase IIb study of efti plus chemo. Top-line PFS data are expected in 2019.

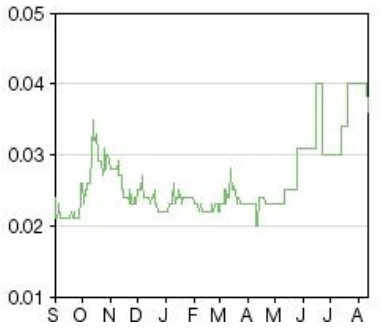
Valuation increased to A$510m, 17c per share

Our valuation increases to A$510m (from A$439m). We have increased the probability for the programmes partnered with Novartis and GSK, and have increased the forecast uptake of efti in lung cancer. Our valuation is equal to 17c per share on an undiluted basis (vs 14c) or 12c per share after accounting for dilution from options, warrants and convertible notes (vs 10c).

30 August 2018

Price	**A$0.034**
Market cap	**A$103m**
	US$0.76/A$
Gross cash (A$m) at 30 June 2018	23.5
Shares in issue	3,026.1m
Free float	87%
Code	IMM
Primary exchange	ASX
Secondary exchange	NASDAQ

Share price performance



%	1m	3m	12m
Abs	0.0	46.9	71.4
Rel (local)	(0.4)	43.5	56.5
52-week high/low	A$0.04	A$0.02	

Business description

Immutep is an ASX-listed biotechnology company focused on cancer immunotherapy. Its pipeline is based on four products using an LAG-3 immune control system: IMP321 for cancer chemo-immunotherapy, partnered products IMP731 (GSK) and IMP701 (Novartis), and IMP761 (preclinical).

Next events

TACTI-mel data update including additional cohort	November
Initiate TACTI-002 Phase II	Q418
Fully recruit AIPAC breast cancer Phase II	Q418/Q119

Analysts

Dr Dennis Hulme +61 (0)2 8249 8345

Maxim Jacobs +1 646 653 7027

healthcare@edisongroup.com

Edison profile page

Investment summary

Company description: LAG-3 immunotherapy programmes

Immutep is an ASX-listed immunotherapy company that is focused on developing products based on the lymphocyte activation gene 3 (LAG-3) pathway, following the acquisition of a private French immunotherapy company in December 2014. Its lead product, efti, is in Phase II in breast cancer and in Phase I in combination with the checkpoint inhibitor Keytruda, with a Phase II trial to start in Q418. Immutep retains all the product rights except for China (where it is partnered with Eddingpharm). IMP731 is progressing to a Phase II study with GSK for ulcerative colitis, while IMP701 is in Phase II studies for solid tumours and lymphoma in combination with a checkpoint inhibitor with Novartis. The company has facilities in Paris, France; Leipzig and Berlin, Germany; and its headquarters are in Sydney, Australia.

Valuation: DCF valuation of A$510m, 17c/share

Our DCF valuation is A$510m or 17c/share (12c/share fully diluted). The fully diluted value per share is based on potential dilution from the 1.3bn options, warrants and convertible notes that would be in the money at the undiluted valuation of 17c/share, including an assumption that the A$13.75m Ridgeback Capital convertible note is converted to 688m shares at 2c/share. There would be further upside if the LAG-3 products progress and if studies indicate broader potential in new indications. The next catalysts include efficacy data from the additional cohort of six patients in TACTI-mel, the initiation of the TACTI-002 Phase II study in collaboration with Merck, and top-line data from AIPAC in 2019. We also anticipate newsflow from the ongoing clinical trials of IMP701 with Novartis and IMP731 with GSK.

Financials: Cash position of A$23.5m

Immutep reported a net loss of A$12.7m in FY18, 36% higher than the A$9.4m loss reported in FY17. Expenses associated with R&D projects rose by 33% to A$10.0m, corporate and administrative expenses rose by 67% to A$7.2m. While the expenses were broadly in line with our expectations, we have modestly increased our forecast expenditure for FY19. Immutep's gross cash position at the end of June 2018 was A$23.5m. Our forecasts assume that Immutep receives a risk-adjusted US$6m (A$8m) milestone payment from GSK in FY19 under the IMP731/GSK2831781 licence agreement, which would extend its cash reach to the end of FY20. If no milestone payments are received in the period, we estimate that an extra A$7m will be needed to fund operations until end-FY20.

Sensitivities: Relying on LAG-3

Immutep is exposed to the same clinical, regulatory and commercialisation risks as all biotech companies. The key sensitivity is clinical progress of its pipeline of LAG-3 candidates, primarily the internally funded efti. While Immutep has funds to complete the efti Phase II study in metastatic breast cancer (mBC), it would require a partnership or alternative forms of funding to advance this indication further. Existing partnerships with big pharma reduce the financial and execution risk for IMP701 and IMP731; in addition, if the proof of concept study of IMP731 in ulcerative colitis reveals evidence of efficacy, it could lead GSK to extend the study to additional indications including rheumatoid arthritis, psoriasis and multiple sclerosis, which could increase the potential peak sales and therefore the value of the product.

Focused on LAG-3 immunotherapies

Immutep acquired its core LAG-3 technology through the acquisition of a French private immunotherapy company in December 2014. Immutep has a pipeline of four products, two of which are partnered, based on pathways in the LAG-3 immune control mechanism.

The acquisition brought established relationships with GSK, Novartis and Eddingpharm, together with potential milestones of over US$100m plus royalties. The founder of the private immunotherapy company, Professor Frédéric Triebel, a leading expert on LAG-3, joined Immutep as CMO/CSO.

Exhibit 1: Immutep pipeline

Product /Partner	Indication	Status	Notes
efti/**Eddingpharm**, (China)/ **Merck** clinical trial collaboration	Metastatic breast cancer + chemotherapy; melanoma + Keytruda; lung cancer and head and neck cancer + Keytruda	Phase IIb/ Phase I Phase II in preparation	Clinical trials underway as an antigen-presenting cell activator combined with chemotherapy or immune checkpoint inhibitor. Efti/Keytruda combo studies in lung cancer and head and neck cancer are being conducted in collaboration with Merck. WuXi AppTec China produces efti under terms of partnership with Eddingpharm, to US European and Chinese GMP standards.
GSK2831781/IMP731/**GSK** (worldwide)	Autoimmune disease/ulcerative colitis	Phase I	Depleting anti-LAG-3 antibody, depletes activated T-cells. Phase I trial in healthy subjects and patients with plaque psoriasis completed. Proof of concept Phase II in ulcerative colitis announced, proof of concept data due 2020. Potential milestone payments of up to US$100m + royalties.
LAG525/IMP701/**Novartis** (worldwide)	Cancer and chronic infectious disease	Phase II	Antagonist anti-LAG-3 antibody, activates T-cell proliferation, immune checkpoint blocker. Three Phase I/II or Phase II trials are underway in solid tumours including breast cancer as well as lymphoma; a fourth Phase II to start in September.
IMP761	Autoimmune disease	Preclinical	First in class LAG-3 agonist antibody. Preclinical studies to investigate potential applications to help treat autoimmune disease by temporarily switching off activated LAG-3^{+} T cells.

Source: Immutep, Edison Investment Research

Efti uses soluble LAG-3 to activate APCs

Immutep's lead product, eftilagimod alpha (efti or IMP321), is a LAG-3 Ig fusion protein that is based on the soluble form of LAG-3 and can activate antigen presenting cells (APCs). These activated APCs process tumour antigens, including those released from cells killed by chemotherapy, transport the antigens to lymph nodes and present the tumour antigens to T lymphocytes, thus activating and amplifying the immune response.

Immutep is currently collaborating with Merck to investigate efti in combination with Keytruda in lung cancer and head and neck cancer.

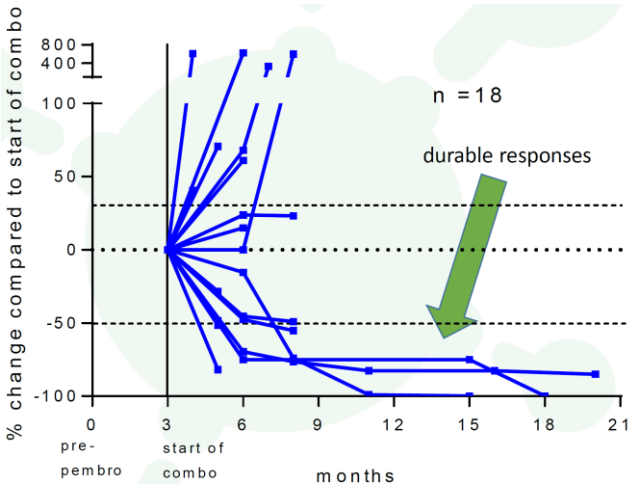
Encouraging TACTI-mel response rate

Immutep's chief medical and scientific officer, Dr Frédéric Triebel, reported updated response data from the Phase I TACTI-mel trial at the Third Annual Advances in Immuno-oncology Congress in London on 25 May. This study tested three doses of efti (1, 6 and 30mg) in combination with the anti-PD-1 immune checkpoint inhibitor (ICI) Keytruda (pembrolizumab, Merck) in 18 patients with advanced melanoma who have had a suboptimal response to initial treatment with Keytruda.

The spider plot in Exhibit 2 shows that 6/18 (33%) of the patients who were treated with efti/Keytruda combo therapy in the three dose-finding cohorts experienced at least a 50% reduction in tumour burden, including five partial responses and one complete response. Furthermore, 9/18 (50%) of patients had at least some tumour shrinkage after efti/Keytruda combination therapy.

The 33% overall response rate (ORR) from the start of efti combo treatment in the 18 subjects in the three dose-finding cohorts, was consistent with the ORR (33%) reported for the first two cohorts last November.

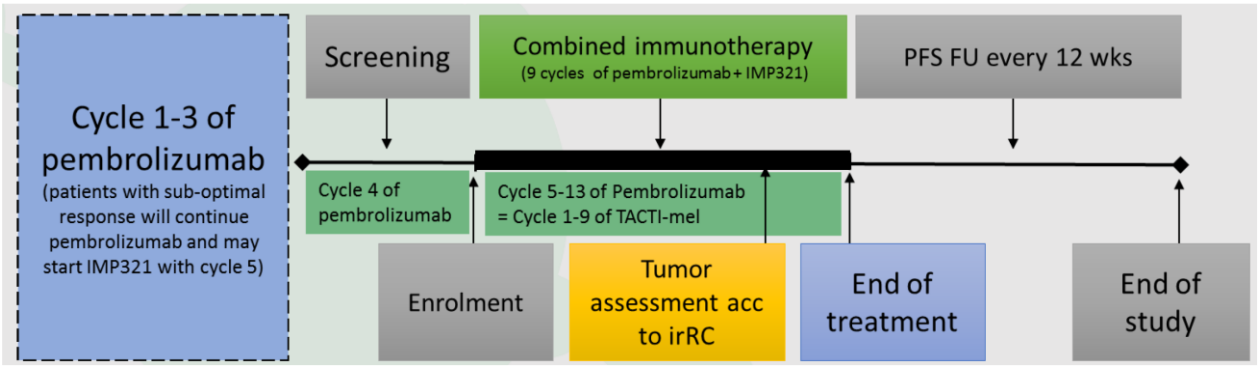
Exhibit 2: Spider plots of tumour responses from TACTI-mel cohorts 1 to 3



Source: Immutep presentation. Note: pembro= pembrolizumab (Keytruda)

Exhibit 3 shows that the subjects were assessed after they had undergone a pre-screening period of three cycles (nine weeks) of treatment with Keytruda. Patients with a suboptimal response (partial response, stable disease or progressive disease not requiring urgent intervention) were eligible to enrol in the trial and receive efti combo therapy, starting with the fifth Keytruda cycle at week 13.

Exhibit 3: TACTI-mel Phase I status and preliminary results



Source: Immutep presentation. Note: irRC= immune-related response criteria; PFS= progression free survival; FU= follow-up

The design of the TACTI-mel study is unique, as far as we are aware. Although starting the treatment with efti 12 weeks after commencing Keytruda allowed the impact of efti on patient safety and tolerability to be closely examined, it means that we are unable to directly compare the efficacy results of this study to any previous study. Immutep has gone some way towards addressing this by disclosing that the response rate from the start of Keytruda monotherapy for the 18 patients in the three dose-finding cohorts in the study was 61%, and that 66% of subjects were progression-free six months after starting Keytruda.

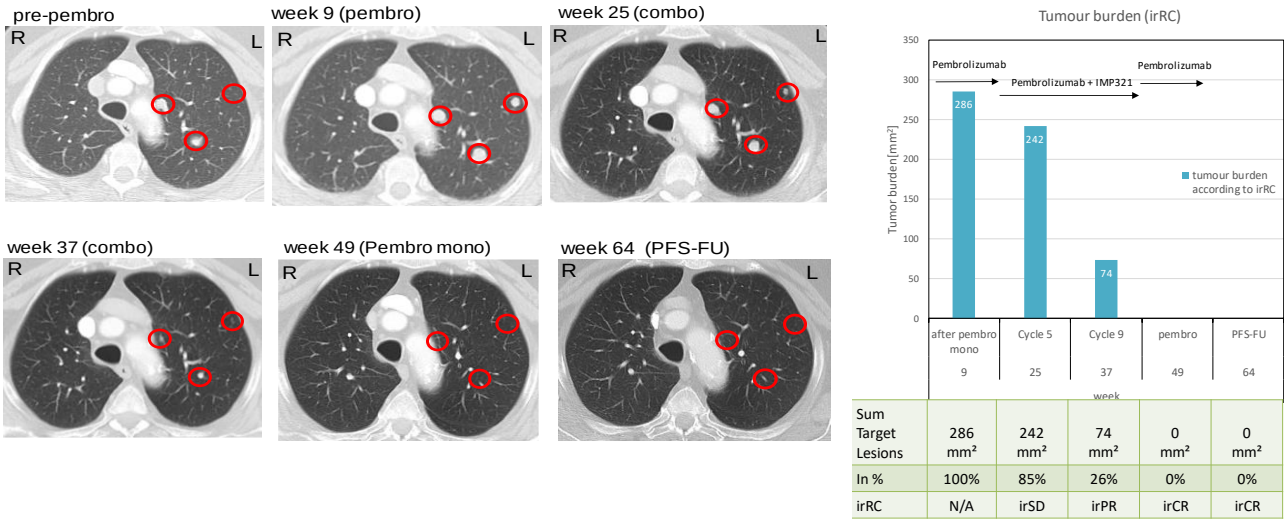
Complete response in a patient who progressed on Keytruda

One of the most impressive results in the TACTI-mel study was the patient with lung metastases who experienced a complete response (tumours disappeared altogether) after being treated with the lowest (1mg) dose of efti in combination with Keytruda, despite having experienced tumour

progression while receiving Keytruda monotherapy. Exhibit 4 shows the progressive shrinkage and then disappearance of the tumours, which was first reported in 2017.

While delayed responses are a well-recognised (though relatively uncommon) feature of ICI therapy, this complete response suggests that efti is having the desired effect of boosting immune responses and providing a clinical benefit over ICI monotherapy.

Exhibit 4: TACTI-mel first cohort (1mg/kg efti) complete responder



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

Source: Immutep presentation at SITC 2017 Annual Meeting, National Harbor, Maryland.

No serious adverse events related to efti or the combination of efti with Keytruda have been reported; the combination was considered to be safe and well tolerated in advanced metastatic melanoma patients.

Additional TACTI-mel cohort fully recruited

Immutep has completed recruitment of an additional cohort of six melanoma patients in the TACTI-mel study who are being treated at the highest dose (30mg) of efti in combination with Keytruda, with administration of efti starting at the same time as the first dose of Keytruda. Although the number of patients is quite small, the efficacy data for this cohort will, for the first time, be directly comparable to previous Keytruda monotherapy and combination therapy studies.

Immutep expects to report updated data from TACTI-mel in November.

IND approval clears the way for TACTI-002 trial in Q418

The company is making good progress as it prepares to initiate its TACTI-002 Phase II study in collaboration with Merck in Q418. TACTI-002 will evaluate efti plus Keytruda in two different cancers: squamous cell carcinoma of the head and neck (second-line therapy in PD-1/L1 naïve patients) and non-small cell lung cancer (NSCLC, first- and second-line therapy). The trial will recruit up to 110 patients in up to 15 study centres in the US, Europe and Australia. Treatment with efti (30mg by subcutaneous injection) will commence on the same day as Keytruda treatment in this study, just as in the additional cohort in the TACTI-mel study.

The focus of TACTI-002 has changed somewhat since the collaboration with Merck was originally announced in March, and it is no longer planned to include a third indication of ovarian cancer. Instead, it now includes separate cohorts for first-line PD-1/L1 naïve and for second-line PD-1/L1 refractory NSCLC patients. The primary end point will be ORR (as per irRECIST). First data from the study are expected in mid-2019.

Increase in monocytes further supports ICI combos

A recent study by Kreig et al[1] reported that high levels of a type of white blood cell known as classical monocytes in blood samples were a strong predictor of response to treatment with anti-PD-1 antibodies in melanoma patients. Patients for whom classical monocytes made up at least 19.4% of peripheral blood mononuclear cells were more likely to respond to anti-PD-1 therapy and had higher overall survival (Exhibit 5).

Immutep has shown that classical monocytes increased in the 15 breast cancer patients in stage one of AIPAC following treatment with efti plus paclitaxel, with the majority above the 19.4% threshold identified by Krieg et al at both the three-month and six-month time points after the start of treatment. Based on the Krieg study, the increase in classical monocytes suggests that the combination treatment in the AIPAC study may increase the likelihood that the patients would respond to subsequent (or concurrent) anti-PD-1 therapy.

The biopsy data from AIPAC stage 1 further support the rationale of combining efti with ICI therapy, either as an efti/ICI combo as in TACT-002, or potentially as part of an efti/ICI/chemo triple combo.

Exhibit 5: Low monocyte numbers associated with poor outcomes of anti-PD-1 therapy

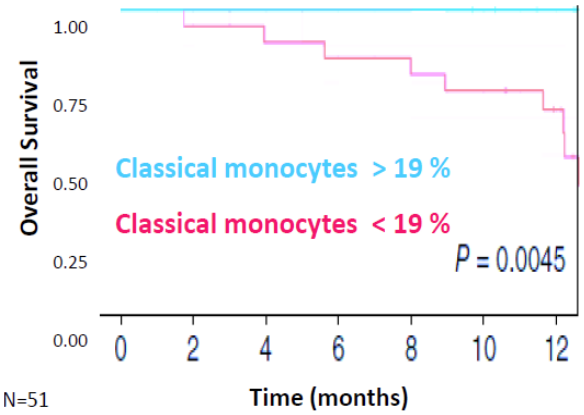
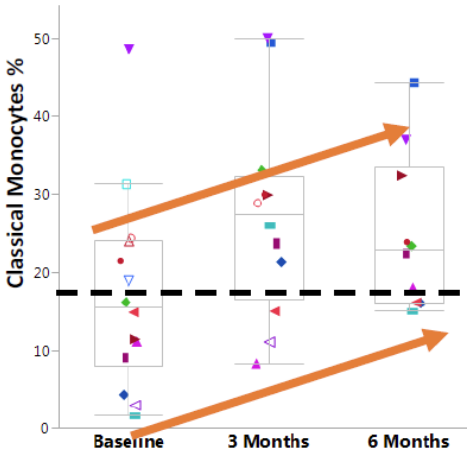


Exhibit 6: Efti increased monocyte numbers in AIPAC stage 1



Source: Immutep presentation

Further evidence that activating APCs can increase ICI response rates

Immutep's TACTI-mel study is investigating the use of efti (its LAG-3-based antigen presenting cell activator) to enhance efficacy in melanoma patients who have had a suboptimal initial response to the anti-PD-1 ICI Keytruda. Positive early data from other compounds with a similar mechanism of action presented at recent conferences provided additional support for the strategy of combining APC-activator and ICI drugs in melanoma patients.

Firstly, in a poster presented at ASCO in June 2018, Dynavax reported high response rates in melanoma patients who received intralesional injections of SD-101 in combination with Keytruda. SD-101 activates dendritic cells to mature into antigen presenting cells by engaging Toll-like receptor 9 (TLR9). In patients who received intralesional injections of up to 2mg of SD-101 every week for four weeks and then every three weeks after that, the ORR (excluding patients who had not yet reached first scan) was 70% (21/30). The six-month progression-free survival (PFS) was 76%. In the 8mg dose cohort the BORR was 38% (15/39). There was no evidence of an increase in the incidence or severity of adverse events over monotherapy.

1 Kreig et al Nat Med. 2018 Feb;24(2):144-153. doi: 10.1038/nm.4466

Secondly, Checkmate Pharmaceuticals reported positive results from intratumoural injection of its TLR9 agonist[2] drug CMP-001 combined with iv Keytruda therapy in melanoma patients who were resistant to prior ICI therapy, at AACR in April 2018. The ORR was 22% (15/69) versus the company's estimate of 7% expected for Keytruda monotherapy.

One big advantage that efti has over these TLR9 agonists is that it is administered by subcutaneous injection. This is far more convenient for the majority of cancers which, unlike melanoma, do not have tumours that are close to the surface of the skin and therefore readily accessible for intratumoural injection. Although intratumoural injection of deep tumours is technically feasible with image guidance (eg ultrasound) it would be much less convenient that subcutaneous injection for diseases such as lung cancer.

Incyte IDO1 Phase III failure underlines the importance of confirmatory studies

Incyte's IDO1 inhibitor, epacadostat, failed to show any benefit when combined with Keytruda in a Phase III study in first-line melanoma patients. There was no significant difference in PFS, overall survival (OS) or ORR between the combo and Keytruda monotherapy groups.[3] The ORR was 34.2% for combo vs 31.5% for Keytruda alone, while the OS was numerically slightly worse for the combo group (HR=1.13).

The Phase III failure came despite the fact that an earlier Phase I/II dose escalation study of epacadostat plus Keytruda had reported a very encouraging ORR of 55% (12/22) in advanced melanoma patients;[4] responses were also seen in 5/12 NSCLC and 3/11 kidney cancer patients.

It is important to note that epacadostat is not an APC activator and has quite a different mechanism of action to efti. It is an oral inhibitor of IDO1, an enzyme that induces immune tolerance by T-cell suppression.

The failure of the epacadostat Phase III study is a reminder that response rates and other efficacy estimates from small studies should be treated with caution, as the outcomes can be quite different when the drug is investigated in a larger number of patients.

Novartis: Four LAG525 combo studies in 2018

IMP701, which is partnered with Novartis, is an antagonist mAb, which blocks the LAG-3-mediated inhibitory signal given to tumour-infiltrating T-cells and thus activates T-cell proliferation and enhances the anti-tumour activity of anti-PD-1 ICI drugs. LAG525 is Novartis's humanised version of IMP701, which it has taken into clinical development.

Novartis has three Phase I/II or Phase II studies of LAG525 underway, and plans to initiate a fourth study (in melanoma) in September. In each of these studies, LAG525 is combined with Novartis's in-development anti-PD-1 antibody spartalizumab (also known as PDR001).

The original Phase I/II study of LAG525 as a single agent and in combination with PDR001 that commenced in June 2015, is ongoing (Clinical trials.gov: NCT02460224; Novartis protocol LAG525X2101C). Preliminary data from the Phase I component of the study were presented at ASCO in June and are discussed below. The Phase II component of the study comprises cohorts with NSCLC, melanoma, renal cancer, mesothelioma and triple-negative breast cancer (TNBC) who

2 A TLR9 agonist activates TLR9 receptor signalling

3 http://abstracts.asco.org/214/AbstView_214_220309.html

4 Gangadhar et al Annals of Oncology 27 (Supplement 6): vi379–vi400, 2016

are being treated with LAG525 plus PDR001. In total, 515 patients are expected to be enrolled in the study, which is scheduled to complete in August 2019.

A second Phase II study of LAG525 plus PDR001 commenced in January 2018 (NCT03365791; Novartis protocol CPDR001XUS01). This adaptive, open label Phase II study will enrol up to 210 patients with solid or haematological cancers including small cell lung cancer, gastric/oesophageal, prostate, ovarian cancers or diffuse large B-cell lymphoma. The primary end point is clinical benefit rate at 24 weeks, with clinical benefit referring to patients achieving either a complete response, partial response or stable disease. Study completion is expected in January 2020.

Novartis has also initiated a randomised Phase II study in TNBC patients in which LAG525 will be combined with either PDR001 or carboplatin chemotherapy, or with both PDR001 and carboplatin (NCT03499899). The trial, which commenced on 2 July, will recruit 96 patients. Top-line ORR data are expected in December 2019.

Lastly, Novartis has disclosed that LAG525 will be one of three drugs randomly assigned for use in combination with PDR001 in 135 patients with advanced melanoma in the PLATforM Phase II study (NCT03484923). The study is scheduled to commence in September, with top-line data expected in early 2021.

Phase II supported by efficacy signals in combo Phase I/II

At ASCO in June, Novartis reported[5] encouraging signs of efficacy from the LAG525 in combination with PDR001 from the Phase I component of its ongoing Phase I/II study (NCT02460224). Among 121 patients with solid tumours treated with LAG525 plus PDR001 at a wide range of doses there were 13 durable responses, including 3/8[6] mesothelioma patients and 2/5 TNBC patients. In TNBC tumour biopsies, there was a trend to conversion from immune-cold to immune-activated biomarker profiles.

No responses were observed in 134 patients treated with LAG525 alone.

Encouraged by the preliminary anti-tumour activity observed with the LAG525 plus PDR001, Novartis has established a comprehensive Phase II programme to investigate the combination in a range of cancers, as described above.

BMS's LAG-3 success likely encouraging Novartis

Last year, BMS reported encouraging results from a Phase I study of its anti-LAG-3 antibody relatlimab (BMS-986016) in melanoma patients who had not responded to or had become resistant to ICI therapies. In that study, 18% of LAG-3-positive patients responded to combination therapy with relatlimab plus Opdivo, versus only a 5% response rate in patients with low tumour LAG-3 expression.[7]

BMS is currently undertaking a Phase III study of relatlimab plus Opdivo versus Opdivo alone in 700 patients with untreated advanced melanoma. Top-line results are expected in July 2020.

According to clinicaltrials.gov, there are a further 15 Phase I or Phase II trials of relatlimab combinations in a range of tumour types either underway or in preparation.

We expect Novartis to continue to aggressively pursue its LAG525 clinical trial programme as it seeks to ensure that it does not allow BMS to gain a dominant position in the anti-LAG-3 antibody space.

5 Hong et al 2018. http://novartis.medicalcongressposters.com/Default.aspx?doc=e07a1

6 3/8 includes an additional partial response after the data cut-off date for the conference abstract.

7 Ascierto et al 2017 https://academic.oup.com/annonc/article/28/suppl_5/mdx440.011/4109923

GSK progressing IMP731 to Phase II

GSK disclosed in a recent results presentation that it has selected ulcerative colitis as the lead indication for GSK'781 (IMP731). It expects a proof of concept study in ulcerative colitis to report data in 2020. There is currently no entry for the study on clinicaltrials.gov, so we presume that the study has not yet begun.

The GSK results presentation included data showing that LAG-3 levels increase as the severity of ulcerative colitis increases. It also showed that the number of LAG-3-positive cells reduces in responders but not in non-responders to established biologics. These results suggest that targeting LAG-3-positive cells using GSK'781 could be a way to reduce inflammation in ulcerative colitis patients.

GSK completed a Phase I study of GSK'781 in psoriasis patients in March 2018. To the best of our knowledge, it has not yet disclosed the results of the study. It seems likely to us that the Phase I study was conducted in psoriasis patients because it is easy to assess responses to treatment in psoriasis skin lesions, and because it would be convenient to collect tissue biopsy samples from the skin lesions in order to assess the impact of the treatment on inflammatory markers in the tissue.

At this stage, we do not know whether the choice of ulcerative colitis as the lead indication for GSK'781 was driven by the size of the commercial opportunity, by a belief that the mechanism of action of GSK'781 was more likely to be effective in that condition, the pathway to regulatory approval, or by other factors.

Ulcerative colitis is a type of inflammatory bowel disease. Ulcerative colitis and Crohn's disease are the most common types of inflammatory bowel diseases. The US Centers for Disease Control and Prevention estimates that the prevalence of ulcerative colitis is 0.24% of the population, which is equivalent to 780,000 patients in the US.

The key drugs for ulcerative colitis are Humira (adalimumab), Entyvio (vedolizumab), Remicade (infliximab) and Simponi (golimumab). Allied Market Research estimated the global ulcerative colitis market at US$4.8bn in 2016 and forecast it to grow to US$7.5bn by 2023.

INSIGHT study of intratumoural efti

INSIGHT is an investigator-sponsored trial by IKF in Frankfurt, Germany that is investigating the safety and feasibility of intratumoural or intraperitoneal injection of efti in patients with accessible solid tumours or peritoneal carcinomatosis, respectively (clinicaltrials.gov: NCT03252938). As of July, 10 patients had been recruited. Immutep expects its partner to report interim data later in H218.

Given the high response rates seen with intratumoural injection of TLR9 agonists, in future studies it may be of interest to compare intratumoural or intraperitoneal injection of efti to the current preferred route of administration via subcutaneous injection.

AIPAC breast cancer Phase II study over 50% recruited

The AIPAC Phase IIb breast cancer study is over 50% recruited, with enrolment passing the halfway mark (113/226) in June and reaching 126 (56%) as of 7 August. The trial is testing the efti soluble LAG-3 fusion protein combined with paclitaxel in women with hormone receptor positive mBC who have not previously received chemotherapy for metastatic disease.

Immutep dosed the first patient in the randomised Phase IIb component of AIPAC in January 2017. The randomised double-blind phase will enrol 226 patients, with half receiving standard paclitaxel chemotherapy plus 30mg of efti, while the other half will receive paclitaxel plus placebo. Recruitment is ongoing at 32 clinical sites in Belgium, France, the Netherlands, the UK, Poland, Germany and Hungary.

AIPAC had originally been expected to be fully recruited in H118, but the company believes that the approval of the CDK4/6 inhibitor Ibrance (palbociclib) led to a temporary slowdown in recruitment in the study. Ibrance is taken alongside hormone therapy as first-line treatment to delay the progression of hormone receptor positive, HER2 negative mBC, prior to the initiation of chemotherapy with paclitaxel. In a pivotal clinical trial, adding Ibrance to hormone therapy increased median PFS from 10.2 months to 20.8 months.

The introduction of Ibrance to treatment protocols led to a temporary reduction in the number of women with progressive mBC who were candidates for paclitaxel therapy at the participating trial sites. Now that women who have been treated with Ibrance are experiencing disease progression and are being treated with paclitaxel, recruitment in the AIPAC study has increased.

The analysis of the PFS primary end point of AIPAC will be conducted after a pre-specified number of subjects have experienced disease progression (event-driven analysis). As a number of women have been on the study for a lengthy period, the number of PFS events could potentially be reached soon after patient recruitment is completed. The record for AIPAC on clinicaltrials.gov (NCT02614833) indicates that collection of data for the PFS primary end point is expected to be completed in June 2019.

The randomised stage of AIPAC was preceded by a safety run-in phase in which 15 women were treated with either 6mg or 30mg of efti in combination with weekly paclitaxel chemotherapy (80mg/m^2 in three weeks out of every four). Both doses of efti were found to be safe and well tolerated when used in combination with paclitaxel, with no dose-limiting toxicities reported. The ORR for the 15 patients was 47% and the disease control rate (tumour response or stable disease) was 87%. The 47% ORR compares favourably with response rates of 23–41% reported in historical studies[8,9].

IMP761 LAG-3 agonist in preclinical development

Immutep has completed a preclinical study of IMP761 in cynomolgus monkeys, with data expected to be reported later this year. IMP761 is a novel mAb that acts as an agonist to stimulate the activity of the LAG-3 receptor. One of the goals of the ongoing preclinical development programme is to better understand the potential applications of IMP761.

IMP761 is the first known therapeutic antibody with agonist properties that enable it to activate the LAG-3 receptor on the surface of activated T cells, and thereby down-regulate T cell activation and proliferation. In contrast, LAG525 and the other known anti-cancer LAG-3 antibodies are antagonist antibodies that block LAG-3 signalling and thereby prevent the down-regulation of T cell immune responses.

The mechanism of action of IMP731 is also different to the company's partnered IMP731/GSK2831781 cytotoxic mAb, which aims to treat autoimmune disease by killing LAG-3-positive T cells. IMP761 offers the opportunity to fine-tune immune responses, which could benefit sufferers of autoimmune diseases by temporarily switching off activated LAG-3-positive T cells that are damaging tissue or causing inflammation.

8 Gray et al, J Clin Oncol. 2009 Oct 20;27(30):4966-72.

9 Martin et al, Lancet Oncol 2011; 12: 369–76

Intellectual property portfolio continues to build

Immutep has further strengthened its intellectual property portfolio over the past year, adding four new patents across major geographical markets. The four new patents were a Japanese patent and a European patent relating to efti, a Japanese patent for IMP731 and a US patent for LAG525 (IMP701).

Valuation

Our valuation of Immutep has increased to A$510m (previously A$439m) or 17c per share (undiluted) (vs 14c per share). On a fully diluted basis, our valuation is 12c per share (vs 10c per share previously), after taking into account the options, warrants and convertible notes on issue. Exhibit 7 summarises the constituent parts of our valuation, which is based on a discount rate of 12.5%.

We have rolled our risk-adjusted NPV model forward in time and have updated our financial forecast to account for the FY18 financial results and the share purchase plan in April raising A$6.3m (before costs), rather than the maximum of A$10m that we had previously modelled. The total number of shares on issue is now 3,026m.

We have increased assumed market penetration for efti in combination with Keytruda in NSCLC from 10% to 12.5%, due to the inclusion of both first-line and second-line indications for this disease in the upcoming TACTI-002 study. We retain the ovarian cancer indication in our model, despite the fact that this indication will no longer be included in TACTI-002, as a modest recognition of the potential for efti to be used in a wide range of cancers, if it is safe and effective in pivotal studies. We do, however, delay forecast launch in ovarian cancer by two years to 2027.

We have increased the likelihood of success for both IMP701/LAG525 and IMP731/GSK'781 to 20% (from 15%), as they are both now in Phase II studies. The choice of ulcerative colitis as the lead indication does not affect our peak sales estimate for this product, which is based on the broader autoimmune disease market.

The gross cash balance at end FY18 was A$23.5m. For valuation purposes we deduct the A$13.75m face value of the Ridgeback Capital convertible note in calculating end-FY18 net debt of A$9.7m as shown in Exhibit 7. We note that this is different to the accounting treatment of the convertible note, which includes only the A$6.6m estimated fair value of the convertible note as a non-current liability with the remainder treated as equity, resulting in a balance sheet net cash figure of A$16.8m as shown in Exhibit 9.

Our other model assumptions are unchanged, including the launch of efti for breast cancer in Europe in the second half of 2021.

Exhibit 7: DCF valuation of Immutep

Value driver	Launch date	Likelihood of success	Peak sales (US$m)	Royalty	Value (A$m)	Value per share (A$)
efti-mBC*	2021 (EU), 2024 (US)	35%	971	17.5%	215.3	0.07
efti+anti-PD1 ICI-melanoma	2025	15%	480	17.5%	33.3	0.01
efti+Keytruda NSCLC	2025	15%	2,300	17.5%	202.0	0.07
efti+Keytruda ovarian	2027	15%	500	17.5%	24.0	0.01
efti+head and neck	2025	15%	470	17.5%	32.6	0.01
efti milestones - assume partnered post PII in MBC	US$225m estimated risk-adjusted milestones from out-licensing North American and European rights.				55.60	0.02
IMP731-autoimmune disease	2023	20%	1,079	8%	64.8	0.02
Potential IMP731 milestones from GSK	US$90m of total US$100m in risk-adjusted milestones from GSK				23.9	0.01
IMP701-solid tumours (lung cancer)	2025	20%	2,440	5%	67.1	0.02
Potential IMP701 milestones from Novartis	US$20m in risk-adjusted milestones from Novartis				3.4	0.00
Grants					2.8	0.00
R&D expenses					(22.1)	(0.01)
Admin expenses					(17.0)	(0.01)
Capex					(0.0)	(0.00)
Tax					(185.7)	(0.06)
Net cash	End FY18 net cash (including A$13.75m convertible note at face value)				9.7	0.00
Total					**509.7**	**0.17**

Source: Edison Investment Research. *mBC = metastatic breast cancer

Exhibit 8 shows that in addition to the 3,026m Immutep shares on issue, there are a further 1,546m potential shares that could be issued on the exercise of options, warrants, performance rights and convertible notes, all of which would be in the money at our 17c per share undiluted valuation. Exhibit 8 shows that after taking into account these potential shares, our diluted valuation is 12c per share. Depending on trial progress and the timing of milestone payments from partners, Immutep may require additional funding to complete the efti clinical trials; our diluted valuation of 12c per share does not take into account potential dilution from any future capital raising.

Exhibit 8: Potential further dilution and value per share

	Average exercise price (A$)	m
Current number of shares		3,026
Ridgeback convertible note potential shares	0.020	688
Ridgeback warrants	0.024	380
Unlisted warrants#	0.033	197
Unlisted options	0.050	151
Performance rights*	0.000	130
Total in-the-money potential shares		1,546
Total potential diluted number of shares		4,572
Net cash raised from options and CN exercise		A$37
Valuation (above plus additional cash)		A$547
Diluted value per share		**A$0.12**

Source: Edison Investment Research. Note: #1.973m ADS warrants converted to ordinary shares at the long term exchange rate. *Both vested and unvested performance rights have been included.

We include risk-adjusted milestones payable by current partners GSK for IMP731 and Novartis for IMP701, plus milestones from prospective deals for efti. The breadth of the LAG-3 pipeline means there could be further upside if Immutep or its partners launch additional products into the clinic or broaden the indications being studied.

Financials

Immutep reported a net loss of A$12.7m in FY18, 36% higher than the A$9.4m loss reported in FY17. Expenses associated with R&D projects rose by 33% to A$10.0m, corporate and administrative expenses rose by 67% to A$7.2m. While the expenses were broadly in line with our expectations, we have modestly increased our forecast expenditure for FY19. These changes see

our forecast FY19 EBITDA loss increase to A$7.6m (vs A$7.1m). We forecast an A$15.3m EBITDA loss in FY20, with lower milestone revenue anticipated in that year. Operating cash outflow was A$7.8m in FY18 compared to A$8.5m in FY17, with the higher after-tax loss in FY18 mainly due to non-cash expenses.

Immutep's gross cash position at the end of June 2018 was A$23.5m. Our forecasts assume that Immutep receives a risk-adjusted US$6m (A$8m) milestone payment from GSK in FY19 under the IMP731/GSK2831781 licence agreement, which would extend its cash reach to the end of FY20.

Sensitivities

Immutep is exposed to the same clinical, regulatory and commercialisation risks as all biotech companies. The key sensitivity is clinical progress of its pipeline of LAG-3 candidates, primarily the internally funded efti. While Immutep has funds to complete the efti Phase II study in mBC, it would require a partnership or alternative forms of funding to advance this indication further. Existing partnerships with big pharma reduce the financial and execution risk for IMP701 and IMP731; in addition, if the proof of concept study of IMP731 in ulcerative colitis reveals evidence of efficacy, it could lead GSK to extend the study to additional indications including rheumatoid arthritis, psoriasis and multiple sclerosis, which could increase the potential peak sales and therefore the value of the product.

Exhibit 9: Financial summary

A$000s	2016	2017	2018	2019e	2020e
Year-end 30 June	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	1,949	4,117	6,854	10,898	2,778
R&D expenses	(7,060)	(7,526)	(9,990)	(10,990)	(10,440)
SG&A expenses	(6,983)	(4,347)	(7,242)	(7,459)	(7,683)
EBITDA	(12,093)	(7,756)	(11,435)	(7,551)	(15,345)
Operating Profit (before GW and except.)	(12,275)	(7,770)	(11,446)	(7,554)	(15,350)
Intangible Amortisation	(1,993)	(1,688)	(1,798)	(1,650)	(1,501)
Exceptionals	(47,468)	0	0	0	0
Operating Profit	(61,736)	(9,458)	(13,244)	(9,204)	(16,851)
Other	(1,716)	(752)	323	0	0
Net Interest	256	104	177	704	498
Profit Before Tax (norm)	(13,735)	(8,417)	(10,946)	(6,850)	(14,851)
Profit Before Tax (IFRS)	(63,196)	(10,105)	(12,744)	(8,500)	(16,352)
Tax	1,181	737	(2)	0	0
Profit After Tax (norm)	(12,554)	(7,680)	(10,948)	(6,850)	(14,851)
Profit After Tax (IFRS)	(62,015)	(9,368)	(12,746)	(8,500)	(16,352)
Average Number of Shares Outstanding (m)	2,016.6	2,072.5	2,079.7	3,026.1	3,026.1
EPS - normalised (c)	(0.6)	(0.4)	(0.5)	(0.2)	(0.5)
EPS - IFRS (c)	(3.1)	(0.5)	(0.6)	(0.3)	(0.5)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	20,883	19,045	18,356	16,715	15,223
Intangible Assets	20,852	19,020	18,329	16,680	15,178
Tangible Assets	32	24	26	36	45
Other	0	0	0	0	0
Current Assets	21,671	15,919	28,643	21,784	6,924
Stocks	0	0	0	0	0
Debtors	168	2,194	3,432	3,432	3,432
Cash	20,880	12,237	23,476	16,616	1,756
Other	623	1,488	1,736	1,736	1,736
Current Liabilities	(1,472)	(2,632)	(3,853)	(3,853)	(3,853)
Creditors	(1,444)	(2,589)	(3,664)	(3,664)	(3,664)
Short term borrowings	(0)	(0)	0	0	0
Short term leases	0	0	0	0	0
Other	(28)	(43)	(190)	(190)	(190)
Long Term Liabilities	(5,765)	(5,799)	(9,623)	(9,623)	(9,623)
Long term borrowings incl. conv. note	(5,027)	(5,779)	(6,646)	(6,646)	(6,646)
Long term leases	0	0	0	0	0
Other long term liabilities	(737)	(20)	(2,978)	(2,978)	(2,978)
Net Assets	35,317	26,532	33,522	25,022	8,670
CASH FLOW					
Operating Cash Flow	(11,594)	(8,611)	(7,954)	(7,551)	(15,345)
Net Interest	284	104	177	704	498
Tax	0	0	0	0	0
Capex	(27)	(7)	(12)	(12)	(13)
Acquisitions/disposals	130	0	0	0	0
Financing	27,229	(9)	18,898	0	0
Dividends	0	0	0	0	0
Other	0	0	(493)	0	0
Net Cash Flow	16,022	(8,522)	10,616	(6,859)	(14,860)
Opening net debt/(cash)	(5,251)	(15,852)	(6,458)	(16,830)	(9,970)
HP finance leases initiated	0	0	0	0	0
Other	(5,421)	(872)	(244)	0	0
Closing net debt/(cash)	(15,852)	(6,458)	(16,830)	(9,970)	4,889

Source: Immutep accounts, Edison Investment Research

Contact details	Revenue by geography
Level 12, 95 Pitt Street, Sydney, NSW 2000 +61 (0)2 8315 7003 www.immutep.com	N/A

Management team

Chairman: Dr Russell Howard	CEO and MD: Marc Voigt
Dr Russell Howard is an Australian scientist, executive manager and entrepreneur. He has held positions at several research laboratories, including the National Institutes of Health in the US, where he gained tenure. In industry, Dr Howard worked at Schering-Plough's DNAX Research Institute in Palo Alto, CA; was the president and scientific director of Affymax and co-founder and CEO of Maxygen.	Appointed in October 2011, having joined as GM of European operations. Previously CFO/CBO at Revotar Biopharmaceuticals and Medical Enzymes, and an investment manager for a German biotech venture fund. Holds an MBA from Free University of Berlin. Based in Berlin, where Immutep's European operations are located. Mr Voigt was appointed CEO in July 2014.
CSO/CMO: Dr FrédéricTriebel, MD PhD	**General Counsel and Company Secretary: Deanne Miller**
A founder and medical and scientific director at Immutep, Dr Triebel discovered the LAG-3 gene while working at the Institut Gustave Roissy Paris, where he was involved in running Phase I/II immunology studies and headed up a research group. Previously, from 1991 to 1996, Dr Triebel was a director of an INSERM unit.	Ms Miller has broad commercial experience having held legal, investment banking, regulatory compliance and tax advisory positions. She joined Immutep as General Counsel and Company Secretary in October 2012. She has a Combined Bachelor of Laws (Honours) and Bachelor of Commerce from the University of Sydney.

Principal shareholders	(%)
Australian Ethical Investment	6.7%

Companies named in this report

BMS, Eddingpharm, GSK, Merck, Novartis, WuXi AppTec, Neopharm

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
245 Park Avenue, 39th Floor
10167, New York
US

Sydney +61 (0)2 8249 8342
Level 4
95 Pitt Street, Sydney
NSW 2000, Australia