EDISON

Immutep

Merck collaboration

Merck collaboration opens new opportunities

Pharma & biotech

Immutep has entered a clinical trial collaboration and supply agreement with Merck & Co (MSD) for a Phase II study to evaluate eftilagimod alpha (IMP321) plus Keytruda in lung, head and neck and ovarian cancers. It is positive to see Immutep collaborating with a leading immunotherapy company, with three new indications added to its ongoing studies in breast cancer and melanoma. It has raised A$6.9m through a placement and has opened a share purchase plan to raise up to A$10m. We increase our valuation to A$439m (vs A$272m) or A$0.14/share (vs A$0.12/share).

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS* (c)	P/E (x)	Yield (%)
06/16	1.9	(13.7)	(0.6)	0.0	N/A	N/A
06/17	4.1	(8.4)	(0.4)	0.0	N/A	N/A
06/18e	3.5	(12.9)	(0.6)	0.0	N/A	N/A
06/19e	10.9	(6.4)	(0.2)	0.0	N/A	N/A

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

Phase II in collaboration with Merck to begin H218

Immutep and Merck will collaborate in the TACTI-002 Phase II study of IMP321 plus Keytruda in up to 120 patients with non-small cell lung cancer (NSCLC), head and neck cancer or ovarian cancer. In clinical studies IMP321 has been shown to stimulate the immune system and turn “cold” tumours “hot”. There is good potential for response rates in these three cancers to be increased by combining the immune activation activity of IMP321 with an immune checkpoint inhibitor such as Keytruda, particularly in patients with low levels of PDL1 expression in tumours.

TACTI-mel Phase I study expanded, data update in Q2

The three-dose escalation cohorts in the TACTI-mel study of IMP321 plus Keytruda in melanoma are fully recruited and the Database Safety and Monitoring Board has confirmed that the highest dose (30mg) is safe and well tolerated. In 2017 the company reported an encouraging 33% response rate in the first two cohorts of patients who had a suboptimal initial response to Keytruda monotherapy; further data, including initial cohort three results, are expected in Q218. Immutep has recruited the first subject in an additional cohort of six patients to be dosed with IMP321 from the first cycle of Keytruda therapy vs the fifth cycle previously.

SPP to extend funding runway beyond AIPAC readout

The AIPAC breast cancer Phase II is expected to fully recruit in mid-2018 and report top-line progression free survival data by mid-2019. The cash from the institutional placement (A$6.9m before costs) and share purchase plan (SPP) (up to A$10m) aims to extend the funding runway to late CY19, excluding any further milestone payments from partners Novartis and GlaxoSmithKline. Milestone revenue (we model ~A$8m in FY19) would extend the cash runway.

Valuation: Increased to A$439m, 14c per share

We have rolled forward our DCF model, added the three new IMP321 indications and updated our forecasts for the capital raise and H118 results. Our valuation has increased to A$439m (vs A$272m) or A$0.14/share (vs A$0.12/share).

29 March 2018

Price	**A$0.023**
Market cap	**A$62m**
	US$0.76/A$
Gross cash (A$m) at 31 December 2017	13.7
Shares in issue	2,725.5m
Free float	87%
Code	IMM
Primary exchange	ASX
Secondary exchange	NASDAQ

Share price performance

%	1m	3m	12m
Abs	9.1	0.0	(25.0)
Rel (local)	6.7	0.1	(28.6)
52-week high/low	A$84.5	A$35.5	

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 cohort 3 safety and activity data	Q218
Fully recruit AIPAC breast cancer Phase II	mid-2018
Initiate TACTI-002 Phase II	H218

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Edison profile page

Merck collaboration opens up new indications

On 12 March Immutep announced that it had entered a clinical trial collaboration and supply agreement with MSD for a Phase II study of IMP321 plus Merck's anti-PD1 immune checkpoint inhibitor (ICI) Keytruda in patients with NSCLC, head and neck cancer or ovarian cancer.

The Phase II study, referred to as TACTI-002, will recruit up to 120 patients in the US and Europe across the three indications in an open label single-arm Simon two-stage design. In the first stage of a Simon two-stage study, a small number of patients with each disease type is treated. If a predefined threshold response rate is observed in this initial cohort, a larger number of patients is recruited in the second stage of the study. If the response rate in the first stage does not reach the predefined threshold for a particular indication, no further patients with that cancer type are recruited.

It seems likely that the indications that were chosen for the TACTI-002 study are the ones where Merck and Immutep see the greatest potential benefit from combining a therapy such as IMP321, which can turn immunologically cold tumours hot, with Keytruda to increase the response rate. It is noteworthy that response rates reported for single-agent ICI therapy in ovarian and head and neck cancers have been quite low (10-16%), while in NSCLC response rates have been low in patients with low levels of PDL1 expression in their tumours.

No details regarding the financial terms of the collaboration have been disclosed. We assume that Merck will provide the Keytruda medication, while Immutep will manage the study and be responsible for most of the other trial costs. We estimate that Immutep's contribution to the trial is likely to be around US$10m if the full number of 120 patients is recruited.

Lung cancer represents a large potential market

According to the National Cancer Institute, lung cancer is the second most common cancer (after breast cancer), with 222,500 new cases per year in the US. The poor prognosis for lung cancer patients (five-year survival rate 18%) means it is responsible for more deaths than any other cancer, with 156,000 deaths each year in the US. The collaboration with Merck is targeting NSCLC which accounts for ~85% of cases of lung cancer.

A number of ICI therapies have already been approved for treating NSCLC. Keytruda itself already has first-line approvals both as a single agent and in tandem with chemotherapy.

Keytruda monotherapy is approved as a first-line therapy in NSCLC patients who have a high level of PDL1 expression (>50%) in their tumours. In this setting Keytruda achieved an overall response rate (ORR) of 45% vs 28% for chemotherapy control.

In combination with chemotherapy, Keytruda is approved as a first-line treatment for NSCLC patients regardless of PDL1 tumour expression status, having achieved an ORR 55% vs 29% for chemotherapy alone.

Given the large number of lung cancer patients, any treatment that improves response rates in this patient group could be particularly valuable. We note that the good tolerability observed for IMP321 in studies so far could see it used (if effective) as part of triple combos of Keytruda/chemo/IMP321 to further improve response rates. The good tolerability could also see the IMP321/Keytruda combination used as an alternative to Keytruda/chemotherapy.

No ICI therapies approved in ovarian cancer to date

Ovarian cancer accounts for 22,400 new cases and 14,100 deaths in the US each year, with a five-year survival rate of 47%. No ICI drugs have been approved for ovarian cancer. Response rates reported for single-agent ICI therapy from early-stage trials have been modest at ~10-15%[1].

We see the potential for accelerated approval of an IMP321/Keytruda combination in ovarian cancer if the combination substantially improves response rates, given the high unmet need in this disease.

The most advanced ICI trial in ovarian cancer is Phase III JAVELIN Ovarian 200 study of Pfizer's Bavencio (avelumab), anti-PD-L1 ICI drug alone or in combination with pegylated liposomal doxorubicin chemotherapy (NCT02580058). This 550-patient study has an estimated completion date of March 2018, so top-line data could be available in the next few months.

Low response rates to ICI therapy in head and neck cancer

There are 63,000 new cases of head and neck cancer and 13,300 deaths in the US each year, with a five-year survival rate of ~60%. Keytruda and Bristol-Myers Squibb's ICI drug Opdivo (nivolumab) were both approved in 2016 for patients with advanced head and neck cancer. However, the response rates to single-agent ICI therapy in this condition are low. Keytruda reported an ORR of 16% and complete response rate of 5% in a single-arm pivotal trial in 174 patients, whereas Opdivo achieved an ORR of 13% vs 6% in a chemotherapy control group.

Viralytics/Merck deal is consistent with our valuation of Immutep

It is relevant to note that in February Merck agreed to acquire the Australian cancer immunotherapy company Viralytics for A$502m (US$394m). The agreed price of A$1.75 per share was a 160% premium to the one month volume weighted average price of Viralytics' shares. Viralytics is developing the Cavatak oncolytic virus in multiple Phase I and Phase II trials, including in combination with Merck's Keytruda and BMS's anti-CTLA4 drug Yervoy (ipilimumab). Ongoing trials are targeting melanoma, NSCLC and bladder cancer, while Phase I studies in colorectal cancer liver metastases and head and neck cancer are planned to commence in 2018.

In an interesting parallel with Immutep, Viralytics entered a clinical trial collaboration agreement with Merck in November 2015 to evaluate the safety and efficacy of Cavatak combined with Keytruda in NSCLC and metastatic bladder cancer patients. In a similar strategy to the IMP321/Keytruda combination, Viralytics was seeking to increase tumour response rates by combining Cavatak immunotherapy with Keytruda.

Our A$439m valuation of Immutep is approximately six times higher than the estimated post-SPP market capitalisation of the company of ~A$74m (at the current market price of 2.3c per share). Given the parallels in the drug development strategies of the two companies, the Merck/Viralytics transaction gives us comfort that our valuation of Immutep is reasonable.

1 Gaillard et al. Gynecologic Oncology Research and Practice (2016) 3:11

Novartis expands partnered anti-LAG-3 programme to include a Phase II trial

Novartis is developing LAG525, an anti-LAG-3 antibody that is based on a programme that it in-licensed from Immutep. LAG525 blocks the LAG-3-mediated inhibitory signal given to tumour-infiltrating T cells and thus activates T-cell proliferation.

Novartis is conducting a 515-patient Phase I/II trial of LAG525. The trial (clinicaltrials.gov identifier: NCT02460224) is testing LAG525 in combination with Novartis's in-development anti-PD-1 ICI PDR001. The Phase II component of the study was initially targeting patients with melanoma, NSCLC and renal cancers, but in September 2017 the protocol was expanded to enrol patients with mesothelioma and triple-negative breast cancer. The trial began in June 2015 and has an estimated completion date of April 2019 (previously October 2018).

In January Novartis initiated a 160-patient open label Phase II study of PDR001+LAG525 in multiple tumour types. The trial (clinicaltrials.gov identifier: NCT03365791) is enrolling patients with gastric, lung, prostate, oesophageal and ovarian cancers, as well as neuroendocrine tumours and lymphoma.

To our knowledge, Novartis has not yet published any results from the initial LAG525 combination study, but the recent initiation of the second LAG525 clinical trial is evidence that the LAG525 programme is progressing as anticipated.

IMP731/GSK2831781 Phase I in psoriasis ongoing

GlaxoSmithKline (GSK) is conducting a Phase I trial of GSK2831781, which is based on LAG-3 technology in-licensed from Immutep. GSK2831781 is a cytotoxic monoclonal antibody (mAb) that will kill the few LAG-3+ activated T cells that infiltrate autoimmune disease sites. The estimated completion date for the study is listed as March 2018 on the GSK clinical studies register, so the trial may have recently been completed and there may be some newsflow from this project in the near term.

The trial was designed to measure the activity of escalating doses of GSK2831781 in patients with the autoimmune disease plaque psoriasis, including the proportion of patients achieving 50% and 75% improvement from baseline in Psoriasis Area Severity Index, and change from baseline in Psoriatic Lesion Severity Scores. This suggests that the Phase I trial could potentially produce early evidence of activity of the therapy in psoriasis patients.

Following a portfolio review, GSK announced in July 2017 that around 30 drug development programmes were to be terminated or divested. The LAG-3 programme has been retained, which suggests the company is satisfied with the way the Phase I trial is progressing.

IMP761 LAG-3 agonist in preclinical development

Immutep has developed IMP761, which is a humanised mAb that acts as an agonist to stimulate the activity of the LAG-3 receptor. The mechanism of action is different from other known LAG-3 antibodies; 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 therapeutic LAG-3 antibodies are antagonist antibodies which block LAG-3 signalling and thereby prevent the downregulation of T cell immune responses.

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

IMP761 is undergoing preclinical development to better understand its potential applications; new preclinical data are expected to be reported in 2018.

Valuation

Our valuation of Immutep has increased to A$439m (previously A$272m) or 14c per share (undiluted) (vs 12c per share). On a fully diluted basis our valuation is 10c per share (vs 8c per share previously), after taking into account the options, warrants and convertible notes on issue. Exhibit 1 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 (~A$6.9m) institutional placement in March. We have also assumed that the current SPP will raise A$10m (before costs) through the issue of 476.2m shares at A$0.021 per share, which would increase the 2,725.5m shares that are currently on issue following the institutional placement to a total of 3,202m.

We forecast the gross cash balance at end FY18 to be A$21.2m. 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$7.5m as shown in Exhibit 1. We note that this is different to the accounting treatment of the convertible note, which includes only the A$6.2m 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$15.5m as shown in Exhibit 3.

We have added NSCLC, ovarian cancer and head and neck cancer indications for IMP321 in combination with Keytruda following the announcement of the planned TACTI-002 Phase II study in these indications. We assume a modest 15% probability of success in these indications, which we may revise upwards as more information becomes available. We base our estimate of market size on the number of deaths from these cancers (rather than the number of new cases). We assume a 20% peak penetration for ovarian and head and neck cancers, and a lower 10% penetration in NSCLC due to the number of competing immunotherapies in the market and assume a pricing of US$60k per patient in the US market. We assume that US market represents 50% of global sales.

Our peak sales estimates for IMP321 in melanoma and for IMP701/LAG525 and IMP731 are unchanged.

Exhibit 1: DCF valuation of Immutep

Value driver	Launch date	Likelihood of success	Peak sales (US$m)	Royalty	Value (A$m)	Value per share (A$)
IMP321-MBC*	2021 (EU), 2024 (US)	35%	971	17.5%	204.9	0.06
IMP321+anti-PD1 ICI-melanoma	2025	15%	480	17.5%	31.7	0.01
IMP321+Keytruda NSCLC	2025	15%	2,300	17.5%	153.8	0.05
IMP321+Keytruda ovarian	2025	15%	500	17.5%	32.7	0.01
IMP321+head and neck	2025	15%	470	17.5%	31.0	0.01
IMP321 milestones - assume partnered post PII in MBC	US$225m estimated risk-adjusted milestones from out-licensing North American and European rights.				53.0	0.02
IMP731-autoimmune disease	2023	15%	1,079	8%	46.3	0.01
Potential IMP731 milestones from GSK	US$90m of total US$100m in risk-adjusted milestones from GSK				19.2	0.01
IMP701-solid tumours (lung cancer)	2025	15%	2,440	5%	47.9	0.01
Potential IMP701 milestones from Novartis	US$20m in risk-adjusted milestones from Novartis				3.2	0.00
Grants					2.7	0.00
R&D expenses					(20.6)	(0.01)
Admin expenses					(15.6)	(0.00)
Capex					(0.0)	(0.00)
Tax					(159.1)	(0.05)
Net cash	End FY18 net cash (including A$13.75m convertible note at face value, assumes SPP raises A$10m)				7.5.0	0.00
Total					**438.6**	**0.14**

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

Exhibit 2 shows that in addition to the 3,202m Immutep shares that would be on issue if, as we assume, the SPP raises A$10m. 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 14c per share undiluted valuation. Exhibit 2 shows that after taking into account these potential shares, our diluted valuation is 10c per share. Depending on trial progress and the timing of milestone payments from partners, Immutep may require additional funding to complete the IMP321 clinical trials; our diluted valuation of 10c per share does not take into account potential dilution from any future capital raising.

Exhibit 2: Potential further dilution and value per share

	Average exercise price (A$)	m
Current number of shares		3,202
Ridgeback convertible note potential shares	0.020	688
Ridgeback warrants	0.024	380
Listed options	0.200	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		4,748
Net cash raised from options and CN exercise		A$37
Valuation (above plus additional cash)		A$475
Diluted value per share		**A$0.10**

Source: Edison Investment Research. Note: *Both vested and unvested performance rights have been included

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.

We include risk-adjusted milestones payable by current partners GSK for IMP731 and Novartis for IMP701, plus milestones from prospective deals for IMP321. Possible catalysts include efficacy data from the AIPAC dose-finding cohorts, progression of the licensed anti-LAG-3 antibody into Phase II by GSK or news on partnering, all of which could provide upside to our current valuation.

Financials

Immutep's gross cash position at the end of December 2017 was A$13.7m. Since then it has received gross cash proceeds of ~A$6.9m from a placement to institutional investors and has initiated an SPP that aims to raise A$10m. Operating cash burn in H1 FY18 was A$4.5m, 8% higher than in the previous year.

We have increased forecast R&D expenditure in line with the increase spend in H1 FY18 and the announcement of the TACTI-002 Phase II study to commence in H2 CY18. We have also increased forecast SG&A spend in line with increased expenditure in H1 FY18. These changes see our forecast FY18 EBITDA loss increase to A$13.2m (vs A$8.7m). We forecast an A$7.1m EBITDA loss in FY19.

Company guidance is that if the SPP raises A$10m then would have a projected cash reach to late CY19. 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 IMP321. While Immutep has funds to conduct the IMP321 Phase II study in metastatic breast cancer, 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 Phase I study of IMP701 reveals evidence of efficacy, it could lead GSK to extend the study to additional indications including rheumatoid arthritis and multiple sclerosis, which could increase the potential peak sales and therefore the value of the product.

Exhibit 3: Financial summary

A$'000s	2015	2016	2017	2018e	2019e
Year end 30 June	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	1,336	1,949	4,117	3,500	10,855
R&D expenses	(8,952)	(7,060)	(7,526)	(9,752)	(10,752)
SG&A expenses	(5,723)	(6,983)	(4,347)	(6,977)	(7,187)
EBITDA	(13,345)	(12,093)	(7,756)	(13,229)	(7,083)
Operating Profit (before GW and except.)	(13,671)	(12,275)	(7,770)	(13,232)	(7,086)
Intangible Amortisation	(1,015)	(1,993)	(1,688)	(1,712)	(1,558)
Exceptionals	(18,338)	(47,468)	0	0	0
Operating Profit	(33,024)	(61,736)	(9,458)	(14,944)	(8,644)
Other	538	(1,716)	(752)	0	0
Net Interest	192	256	104	367	638
Profit Before Tax (norm)	(12,940)	(13,735)	(8,417)	(12,865)	(6,449)
Profit Before Tax (IFRS)	(32,294)	(63,196)	(10,105)	(14,577)	(8,006)
Tax	142	1,181	737	0	0
Profit After Tax (norm)	(12,798)	(12,554)	(7,680)	(12,865)	(6,449)
Profit After Tax (IFRS)	(32,152)	(62,015)	(9,368)	(14,577)	(8,006)
Average Number of Shares Outstanding (m)	1,490.1	2,016.6	2,072.5	2,079.7	3,201.7
EPS - normalised (c)	(0.9)	(0.6)	(0.4)	(0.6)	(0.2)
EPS - IFRS (c)	(2.2)	(3.1)	(0.5)	(0.7)	(0.3)
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	22,960	20,883	19,045	17,337	15,783
Intangible Assets	22,662	20,852	19,020	17,309	15,751
Tangible Assets	298	32	24	28	32
Other	0	0	0	0	0
Current Assets	8,023	21,671	15,919	24,938	18,485
Stocks	0	0	0	0	0
Debtors	315	168	2,194	2,194	2,194
Cash	6,760	20,880	12,237	21,256	14,803
Other	948	623	1,488	1,488	1,488
Current Liabilities	(4,380)	(1,472)	(2,632)	(2,632)	(2,632)
Creditors	(2,791)	(1,444)	(2,589)	(2,589)	(2,589)
Short term borrowings	(1,508)	(0)	(0)	(0)	(0)

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