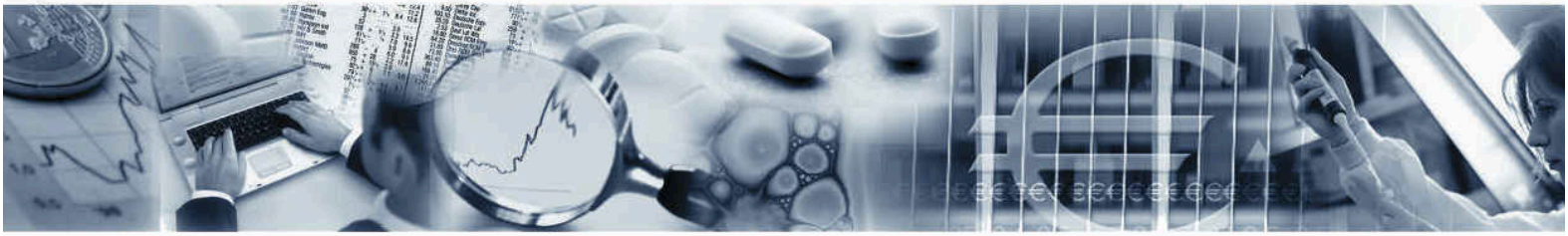

Update Report

Prima BioMed

Strengthening Leadership in LAG-3

Chief Research Analyst

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Date: 14 August 2017

Name:	**Prima BioMed**
Country:	**Australia**
Price:	**AUD 0.021**
ISIN Code:	**US74154B2034**
Reuters Code:	**PRR.AX, NASDAQ: PBMD**
Market Cap (AUD m):	**49.1**
EV (AUD m):	**30.8**
Cash & cash eq. (AUD m):	**18.3 *)**
Shares outstanding (m):	**2,340**
Volume:	**3,046,048**
Free float:	**100%**
52-week Range:	**0.02-0.042**

) includes recent USD 5m capital raising

	2014A	2015A	2016A
Total Revenues	3.1	2.1	2.0
Net (Loss)/Profit	(13.4)	(32.2)	(62.0)
Net loss per share (cents)	(0.93)	(2.02)	(2.77)
R&D costs	11.9	9.0	7.1
Cash increase/(decrease)	(8.6)	(8.5)	15.1
Cash and marketable sec.	14.2	6.8	20.9

Executive Summary

- Prima BioMed Ltd (ASX:PRR, NASDAQ: PBMD) is a leading biotech company in the development of personalized immunocellular therapeutics for the treatment of cancer. With the acquisition of French private biotech company Immutep late 2014, the company has evolved into a front runner in the so called LAG-3 technology. LAG-3 is a major factor involved in the regulation of T-cells in immune responses.

- Its lead product IMP321 is in Phase IIb development against metastatic breast cancer (MBC) and also in Phase I development in melanoma in combination with pembrolizumab (Keytruda). It also has two partnered programs with Novartis and GSK. Recently, updated clinical data were published for its trial in metastatic melanoma patients, which showed that IMP321 is safe and well tolerated. Also a third cohort of six patients with metastatic melanoma is expected to be fully recruited in the next few weeks.

- With IMP321, Prima also announced interim data from its Phase IIb trial in metastatic breast cancer. Data from all 15 patients in the safety run-in phase demonstrated that IMP321 showed sustained immune activation with a 47% tumor response rate. This is in line with the response rate in the open-label Phase I study that IMP321 plus paclitaxel is able to double the expected six month response rate in HER-2 negative metastatic breast cancer patients receiving standard-of-care paclitaxel.

- In the beginning of this year, the company announced that it has developed a new candidate, IMP761. IMP761 is the first agonist antibody of LAG-3. So far, therapeutic antibodies with agonistic properties have not been described for any of the three major immune checkpoints, CTLA-4, PD-1 or LAG-3. IMP761 promises the first opportunity for fine tuning of the immune

response to an immune checkpoint target, which could benefit sufferers of certain autoimmune diseases

- The interest in LAG-3 from major pharmaceutical companies like Merck, BMS, GSK and Novartis is clearly increasing. This makes it likely that Prima BioMed will be able to make a substantial deal on IMP321 supported by potentially strong data from the Phase II clinical trials in metastatic breast cancer and melanoma. With two own clinical programs and two advanced partnerships (Novartis and GSK), Prima BioMed clearly is very well positioned in this area. We feel that each of these programs have blockbuster potential.

- Based on our adjusted NPV valuation, we believe Prima BioMed is substantially undervalued at the current share price of AUD 0.021. We have calculated the present valuation of the company should be AUD 234 million or AUD 0.10 per share.

Immune Checkpoint Inhibitors On the Rise

Cancer survival rates are generally increasing in the United States and Europe. According to the National Cancer Institute, approximately 39% of all Americans will develop cancer at some point in their lifetime. However, the overall mortality rate of those diagnosed with cancer has declined, in part due to improvements in therapeutic approaches. The development of immunotherapies reflects a new approach to cancer treatment involving activation of the immune system against cancer. Immune checkpoint inhibitors, in particular, have demonstrated considerable promise in their recent approval for the treatment of melanoma, non-small cell lung cancer, and other cancers. Immune Checkpoint Modulators blocks the ability of certain proteins, called immune checkpoint proteins, to limit the strength and duration of immune responses. These proteins normally keep immune responses in check by preventing overly intense responses that might damage normal cells as well as abnormal cells. But, researchers have learned that tumors can commandeer these proteins and use them to suppress immune responses. LAG-3 is an example of an Immune Checkpoint (others include CTLA-4, TIM3 and PD-1).

Unlike other immunotherapies or cancer vaccines that work by strengthening the immune system or training it to attack tumor cells, checkpoint inhibitors work to defeat a cancer resistance mechanism that causes immune cells to see tumor cells as “self”. Once this veil or “brake” is lifted, the immune response may be enough to defeat the cancer cells on its own, but a wide ranging array of therapeutic combinations is being tested. Blocking the activity of immune checkpoint proteins releases the "brakes" on the immune system, increasing its ability to destroy cancer cells. Several immune checkpoint inhibitors have been approved by the Food and Drug Administration (FDA). Checkpoint inhibitor interest started with iplimumab (Yervoy), which is an antibody directed to the CTLA4 receptor, an important inhibitory regulator of T-cell activation. More recently, the drugs Nivolumab (Opdivo) and pembrolizumab (Keytruda) have received a lot of attention – they

are checkpoint inhibitors that are mediated by Program Cell Death pathways. Keytruda received breakthrough therapy status by the FDA in 2014 for the treatment of NSCLC. CTLA4 acts as a "switch" to inactivate these T cells, thereby reducing the strength of immune responses; ipilimumab binds to CTLA4 and prevents it from sending its inhibitory signal. Opdivo and Keytruda, work in a similar way, but they target a different checkpoint protein on activated T cells known as PD-1. Nivolumab is approved to treat some patients with advanced melanoma or advanced lung cancer, and pembrolizumab is approved to treat some patients with advanced melanoma. Researchers have also developed checkpoint inhibitors that disrupt the interaction of PD-1 and proteins on the surface of tumor cells known as PD-L1 and PD-L2.

Several researchers estimate that the market for immunotherapeutic approaches in cancer treatment is expected to exceed USD 30 billion by 2023, driven by novel agents, combination therapy, longer treatment times and the emergence of predictive Biomarkers. Within cancer immunotherapy, immune checkpoint inhibitors are taking the bulk of the market with and expected CAGR more than 50%.

The growth is driven by:

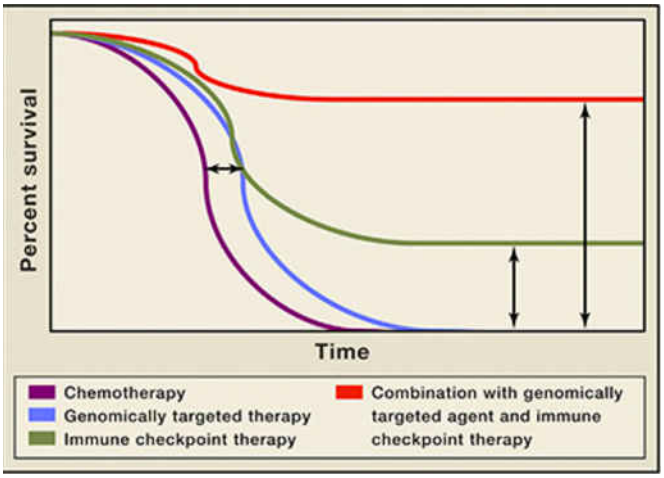
- High adoption rates in Western countries, given immunotherapies have a largely well tolerated adverse event profile compared with conventional chemotherapy;

- Immunotherapy treatment months/patient to likely materially expand due to improved progression free survival (PFS) associated with immunotherapy, multiple lines of therapy during a patient's disease and maintenance usage;

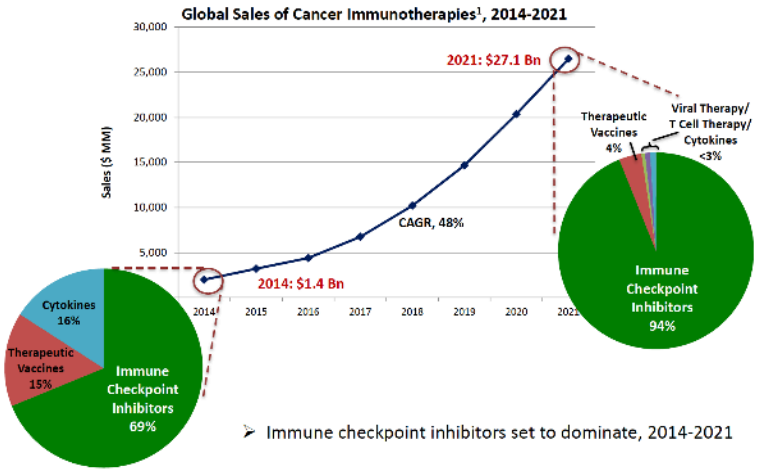
- Likely use of repeat immunotherapy based approach in patients who lose their partial response, given well tolerated adverse event profile and mechanistic rationale;

- Combination strategies with chemo/radio/MAb/cryotherapy or other checkpoint

inhibitors (like IMP32 for melanoma as a combination therapy with Keytruda and for MBC in combination with paclitaxel) will likely expand the potential indications for checkpoint agents. These combination therapies also have considerably improved survival rates as the graph below shows.



Source: Cell, April 2015



Source: DR/Decision Resources LLC

Competitive Landscape LAG-3with enrolment of more than 3,900 patients

Company	Program	Indication	Phase	Pat.	Comments	Study Completion
Prima BioMed	**IMP321**	**Metastatic Breast Cancer**	**IIb**	**226**	**Adenocarcinoma Breast Stage IV. 2arms: Paclitaxel + IMP321 at the RPTD and Active Comparator: Comparator: Paclitaxel + Placebo**	**2019**
Prima BioMed	**IMP321**	**Metastatic Melanoma**	**I**	**18**	**Multicentre, Open Label, Dose Escalation, Phase 1 Study in Patients With Unresectable or Metastatic Melanoma**	**2018**
Novartis (partnership Prima)	**LAG525**	**Various Cancers**	**I/II**	**416**	**May 9, 2015: Safety and Efficacy of LAG525 Single Agent and in Combination With PDR001 in Patients With Advanced Malignancies**	**Apr 2018**
Bristol Myers Squibb	BMS986016	Solid Tumors	I/IIa	360	Sep 25 2013: Phase I/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Mab Alone and in Comb with Anti-PD-1 Nivolumab,in Solid Tumors	Oct 2019
Bristol Myers Squibb	BMS986016	Hematologic Neoplasms	I/IIa	132	Feb 12, 2014: Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy in Combination With Anti-PD-1 Nivolumab, in Relapsed or Refract B-Cell Malignancies	May 2020
Bristol Myers Squibb	BMS986016	Glioblastoma	I	68	Jan 2016: A Phase I Trial of Anti-LAG-3 or Anti-CD137 Alone and in Combination With Anti-PD-1 in Patients With Recurrent GBM	Dec 2019
Bristol Myers Squibb	BMS986016	NSCLC	II	504	April 21, 2016: A Phase 2, Fast Real Time Assessment of Combination Therapies in Immuno-Oncology Study in Subjects With Advanced NSCLC (FRACTION-Lung)	April 2021
Bristol Myers Squibb	BMS986016	Various Advanced Cancer	I/II	500	Combination therapy with Nivolumab/ipilumab/daratumumab. Recruitment since October 2015	Dec 2019
Bristol Myers Squibb	BMS986016	Metastatic Colon Cancer	II	340	Combination therapy with Nivolumab/Ipilumab/Daratumumab/Cobi Recruitment since March 2014	Dec 2018
Bristol Myers Squibb	BMS986016	Advanced Renal Cancer	II	200	Combination therapy with Nivolumab/Ipilumab Recruitment since January 2017	Jan 2022
Bristol Myers Squibb	BMS986016	Advanced Gastric Cancer	II	300	Combination therapy with Nivolumab/Ipilumumab Recruitment since November 2016	Nov 2021
Merck	MK4280	Solid Tumors	I	260	March 22, 2016 : A Phase 1 Trial as Monotherapy and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors	Oct 2020
GlaxoSmithKline (partnership Prima)	**GSK2831781**	**Psoriasis**	**I**	**67**	**July 17, 2014: A Randomised, Double Blind Placebo-Controlled, Single Asc Dose Study of Safety, Tolerability, Pharmacokinetics of a IV Dose in Healthy Subjects and Patients With Psoriasis**	**Aug 2018**

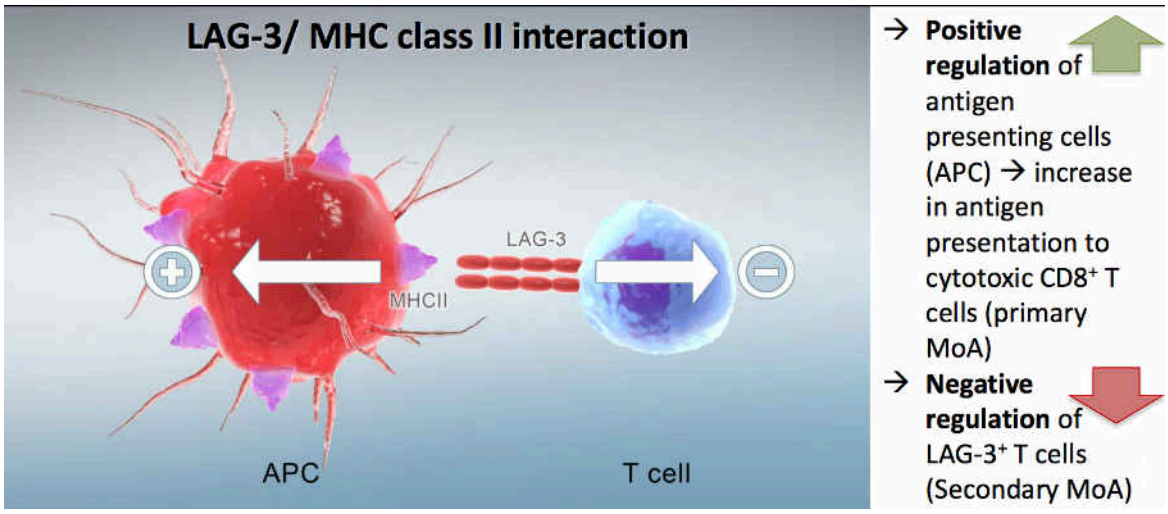
Source: Van Leeuwenhoeck Research, Company Reports

As the table above shows, various large pharmaceutical companies are taking an interest in LAG-3

Prima BioMed is very well positioned with two own clinical programs and two advanced partnerships with Novartis and GSK. IMP321 and IMP731 are unique in terms of mechanism of action and currently do not face a direct competition. LAG-3 as a target is clearly (given clinical development and data) moving to the forefront. Data from BMS was presented at SITC (Nov 2016) and ASCO 2017. We expect more data at the next key conferences.

Clinical Overview LAG-3 Pipeline

The LAG-3 platform provides a good combination for a total approach in cancer immunotherapies. LAG-3 stands for "Lymphocyte Activation Gene-3" and is involved in the regulation of T cells in immune responses. On activated T cells it is an inhibitory receptor that down-modulates their proliferation and activation. LAG-3 is one of the few key molecules that have been identified as being responsible for the regulation of T cells. LAG-3 is important as it plays a number of roles that can both activate or suppress immune responses, which makes it an attractive target for immunotherapy, both in cancer treatment and autoimmunity. Both fields are similar in essence as human tumors are frequently deeply infiltrated by active T cells, and the tumor could then be considered as an autoimmune site where the T cell response has just not been strong enough to eliminate these abnormal tissue cells. In immuno-oncology multiple tumor masses disappear in advanced metastasized cancer by just unleashing the power of this tumor infiltrating T cell.

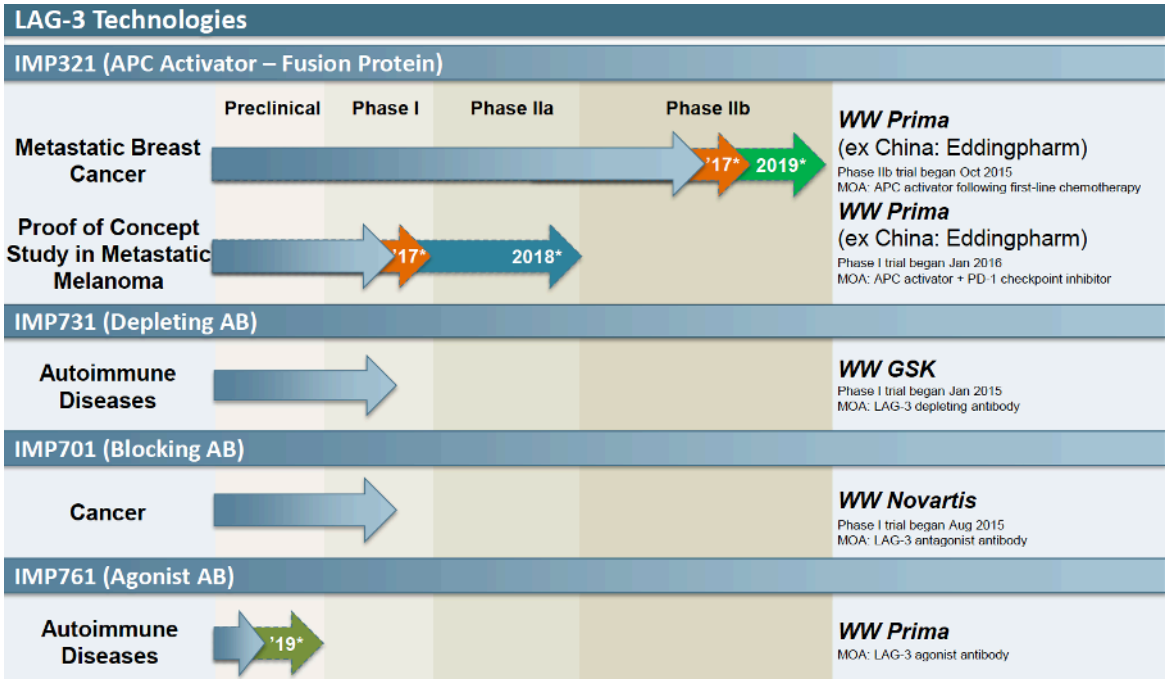


With the LAG-3 antibodies IMP731 and IMP701 the effect is to release the brakes on the immune system, whereas the LAG-3 activator IMP321 has the function to push the accelerator as a strong

immune activator. It therefore makes perfect sense for each of the three products to be developed in parallel, as they are complimentary therapies with their use dependent on the condition of the individual patient.

Although each of the products are standalone products they can be potentially combined with other immuno-therapies, such as checkpoint inhibitors or chemotherapy, and these combination therapies are increasingly being recognised in the scientific and medical community as optimal approaches for fighting cancer.

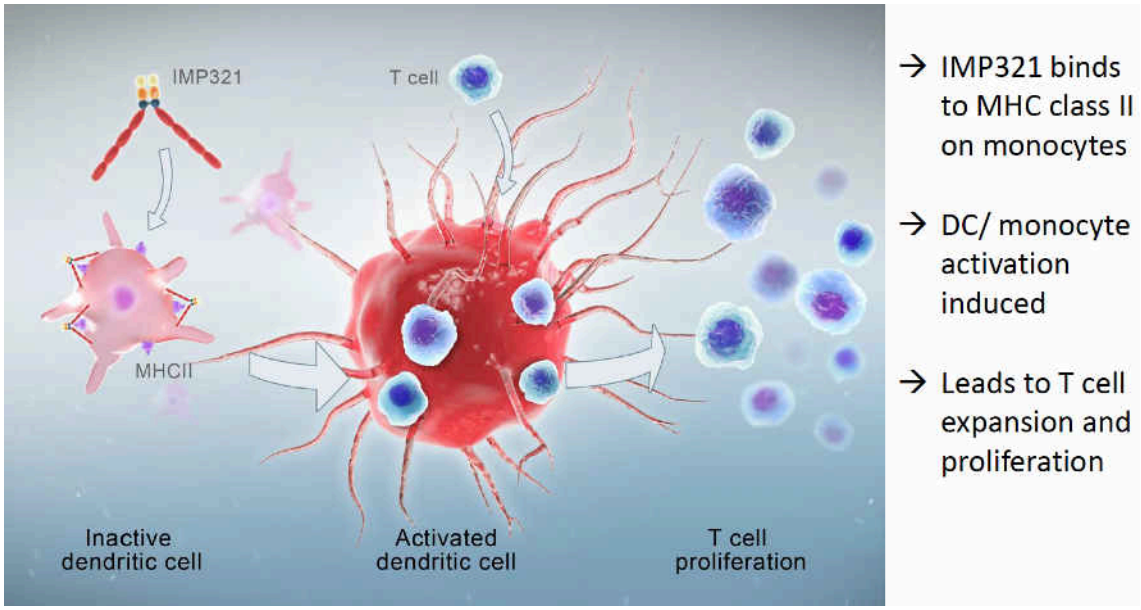
Clinical Overview



Source: Prima BioMed

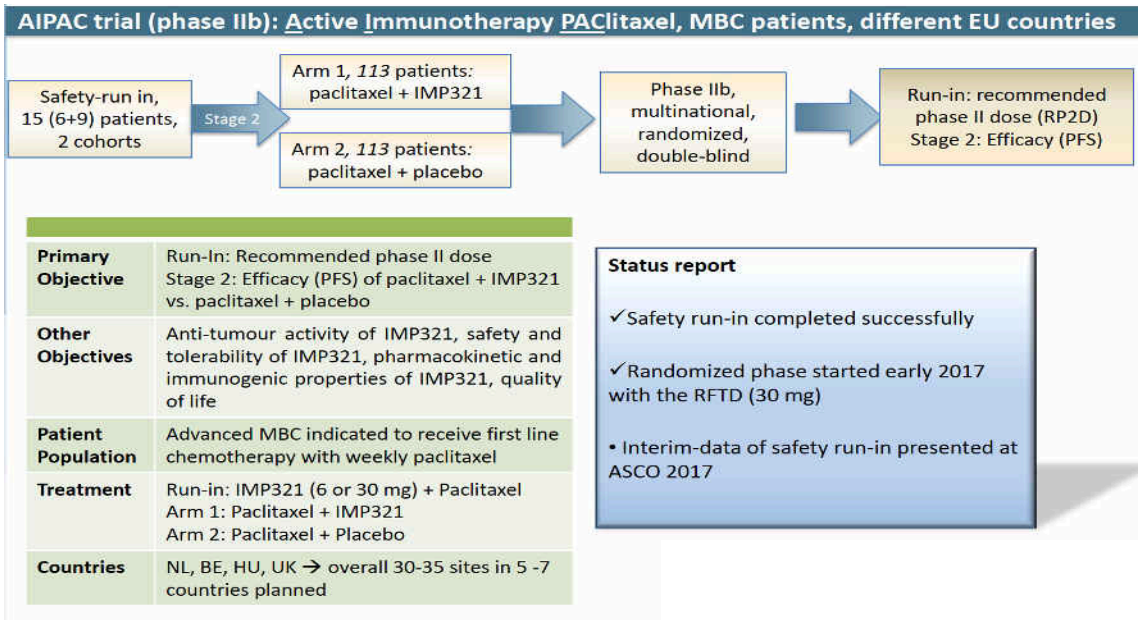
IMP 321:Combination Therapy in Development for MBC and Melanoma

IMP321 is a recombinant protein consisting of a dimer of LAG-3 that has been engineered to be soluble rather than expressed on the surface of cells. It is a first-in-class antigen presenting cell (APC) activator, which has been proven to induce sustained immune responses in cancer patients when used at low dose as a cancer vaccine adjuvant or used at higher doses to get a systemic effect (i.e. general APC activation).



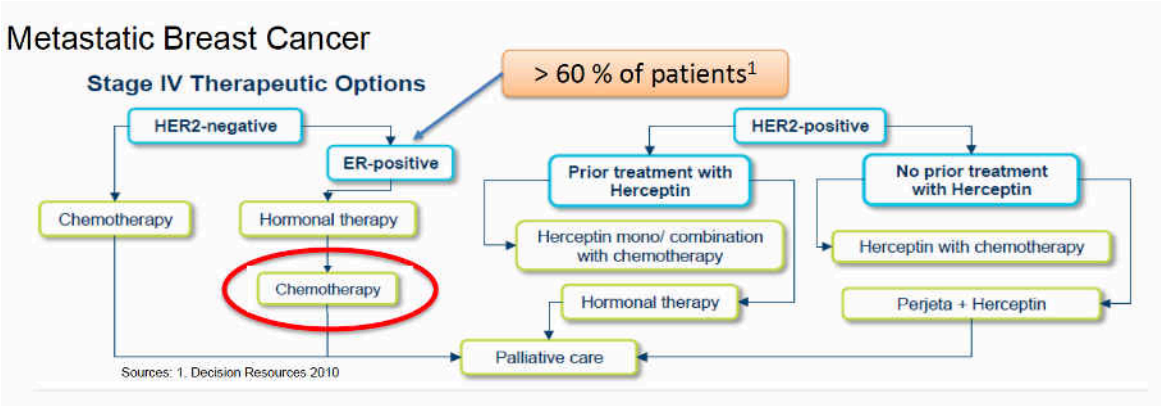
At the recent ASCO, Prima BioMed presented very encouraging interim results from the safety run-in phase of its AIPAC Phase IIb clinical trial as a chemo-immunotherapy for metastatic breast cancer (MBC). AIPAC (Active Immunotherapy PAClitaxel) is Prima's multicentre, Phase IIb, randomised, double-blind, placebo-controlled study in hormone receptor-positive MBC patients receiving IMP321 or placebo as adjunctive to first-line weekly chemotherapy, paclitaxel. The safety run-in phase trialed the safety, immune-monitoring and activity of 15 patients. At both the 6mg and 30mg dose levels, IMP321 was shown to be safe and well tolerated. The higher 30mg dose demonstrated a stronger immune response, and was determined to be the recommended phase II dose (RPTD)

for the ongoing randomised phase of 226 patients. A total of 15 patients received between 1-18 IMP321 injections. The preliminary efficacy results showed that the ORR was 47% accompanied by a Disease Control Rate (DCR) of 87%. The ORR is consistent with the 50% response rate reported from the earlier Phase I trial that tested 6mg dose in combination with paclitaxel in 30 patients. In total, the randomized double blind phase will enroll 226 patients with half receiving paclitaxel chemotherapy plus 30mg of IMP321 while the other half receives paclitaxel plus placebo. Final data for the PFS primary endpoint are expected mid 2019. The EMA already indicated that the trial would be sufficient to file for a marketing authorization if it received certain clinical endpoints.



As a comparison, last May the FDA granted approval for Keytruda in combination with chemotherapy as a first line treatment for NSCLC. The data showed 55% ORR versus 29% for standard chemotherapy. Median PFS was 13 months for the combination therapy with Keytruda and 8.9 months for the standard chemotherapy. This is the first approval for a combination

chemotherapy plus immunotherapy.



The primary target population for IMP321 are patients with HR+ and HER2neu MBC. Breast cancer that is ER+ or PR+ falls under the category of hormone receptor-positive (HR+) breast cancer. HER2+ cancer tends to be less responsive to hormonal treatment. This could be because HER2+ breast cancer tends to be more aggressive than other types of breast cancer. 30% of breast cancer patients are metastatic with 2 out of 3 HR+. After hormone therapy, patients receive taxane or anthracycline based chemotherapy. The average PFS/OS is 5-9 months versus 24 months, so there is a high unmet medical need for which no major improvements were shown in the last few years.

Next to the AIPAC breast cancer trial, Prima has a Phase I combination therapy trial in metastatic melanoma termed TACTI-mel in development. TACTI-mel is using IMP321 to increase the efficacy in melanoma patients who have had a suboptimal initial response to Keytruda. Interim data results from the first patient cohort released in December 2016 indicate IMP321 at the 1mg dose level is safe and well tolerated. Out of the six patients in the first cohort (all with suboptimal response to KEYTRUDA® monotherapy) two patients had a partial or complete radiological tumour response according to immune related response criteria (irRC). The positive safety profile was also confirmed in the second cohort dosed with 6 mg of IMP321. None of the 6 patients treated with KEYTRUDA® plus IMP321 at this higher dose level experienced any serious adverse

reaction nor dose limiting toxicity. As a result, the independent Drug Safety Monitoring Board (DSMB) has granted approval for the third cohort, at the 30mg dose level, to commence with the first patient to be dosed in due course. Recruitment of this third and highest dose cohort is expected to be completed in 2017Q3

TACTI-mel trial: Two ACTive Immunotherapeutics in melanoma

18 patients, 3 cohorts of 6 patients → IMP321 + anti-PD-1 (Keytruda®) → Phase I, multicenter, open label, dose escalation → Recommended Phase II dose Safety and tolerability

Primary Objective	Recommended dose for phase II (RP2D) with IMP321 + pembrolizumab Safety + tolerability
Other Objectives	PK and PD of IMP321, response rate, time to next treatment, PFS
Patient Population	Unresectable or metastatic melanoma with asymptomatic or suboptimal response after 3 cycles of pembrolizumab

Status report

✓First dose escalation (1 → 6 mg) successfully confirmed by DSMB in Dec 2016

✓Enrollment of cohort 2 (6 mg) completed in Mar 2017

• Full enrollment completion expected in 2017

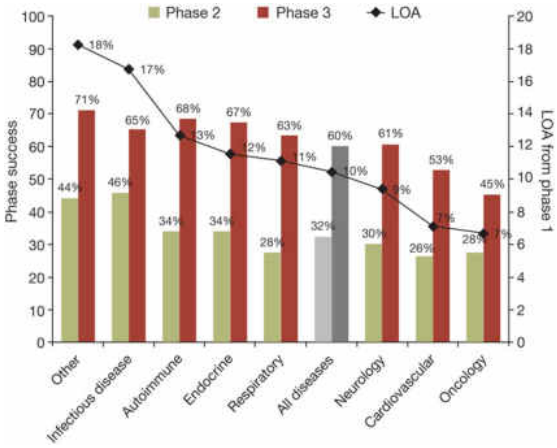
6 sites in Australia

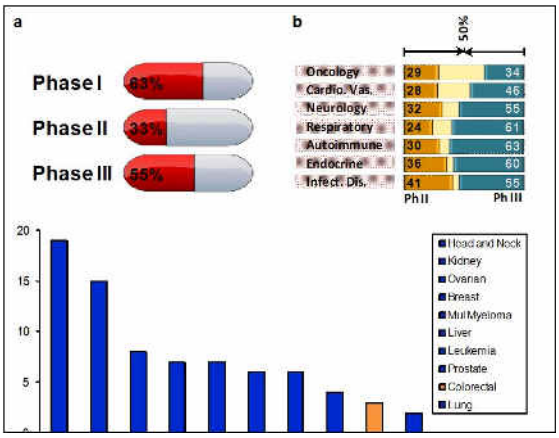
TACTI-mel (Two ACTive Immunotherapeutics in melanoma) is a multicentre, open label, Phase I study in which patients with unresectable or metastatic melanoma will be dosed with IMP321 in combination with the PD-1 checkpoint inhibitor pembrolizumab (KEYTRUDA®). The study will evaluate safety as the primary endpoint and anti-tumour activity and the immune response to the combination as secondary endpoints.

Valuation LAG-3 pipeline: Blockbuster potential

We value Prima BioMed at AUD 234 million or AUD 0.10 per share using a risk-adjusted NPV valuation. This is valuing the potential of the LAG-3 clinical programs IMP321, IMP731 and IMP701.

In estimating a value for each separate clinical program in Prima's pipeline and its partnerships, we made use of several studies that were done on the clinical development success rates for investigational drugs and specifically on immune therapy. No data were available specifically for Immune Checkpoint Inhibitors. Therefore, we used the data available for monoclonal antibodies as another example of immune therapy. These results were published in Nature Biotechnology[1] and Pharmaceutical Outsourcing[2].





Source: Nature Biotechnology, 2014

We feel that each of the programs in clinical development has block buster potential, catering to

[1] Michael Hay et al: Clinical development success rates for investigational drugs, Nature Biotechnology 32, 40-51 (2014)

[2] Laslo Otvos: Relative Success Rates by Drug Class, Pharmaceutical Outsourcing August 2014

large markets that are addressed with immune checkpoint inhibitors. Examples like Keytruda (sales 2016: USD 1.4 billion, +150% yoy), and Opdivo (sales 2016: USD 3.8 billion, +300% yoy) show that the uptake of such immune checkpoint inhibitors is very rapid with revenues in the first years growing quickly to more than USD 1 billion each. Analysts project sales of these therapies to be USD 5 billion and USD 8 billion respectively by 2020.

Phase Progression	Therapeutic Category	Molecule Classification	Probable Success Rate
Phase I – II	Oncology	Small Molecule NME	66%
		Peptides/Proteins	48%
		Monoclonal Antibodies	68%
	Non-Oncology	Small Molecule NME	65%
		Peptides/Proteins	65%
		Monoclonal Antibodies	72%
Phase II – III	Oncology	Small Molecule NME	29%
		Peptides/Proteins	31%
		Monoclonal Antibodies	29%
	Non-Oncology	Small Molecule NME	29%
		Peptides/Proteins	42%
		Monoclonal Antibodies	47%

Source: Pharmaceutical Outsourcing 2015

Input risk adjusted NPV

Cancer type	Prevalence (5yr) EUR	Prevalence (5yr) US	Prevalence (5yr) ROW	Pricing (monthly)	Market share
Secondary Breast	180,000	300,000	100,000	12,500	8%
Lung	440,000	410,000	700,000	12,500	8%
Melanoma	400,000	1,000,000	150,000	12,500	8%
Renal	333,000	400,000	235,000	12,500	8%

Source: Van Leeuwenhoeck Inc, National Cancer Institute, EUCAN, Remedica Journals, Metastatic Breast Cancer Network

We calculated specific risk factor per clinical phase: 68% success rate for concluding Phase I, 33% success rate for concluding Phase II and a success rate of 60% for concluding Phase III. This leads to a LOA (Likelihood of Approval) of 20% for IMP321 in Metastatic Breast cancer and 14% for IMP321 in Melanoma. For MBC we have increased the LOA to 23% and for Melanoma to 16% respectively as a result of the positive interim results

Valuation IMP321

In estimating a value for IMP321 in Metastatic Breast Cancer, we made use of a potential market of 50% from a total number of patients of 300,000 in the US, 180,000 in Europe and 100,000 in ROW, with a market launch in Europe in 2020 and 2023 in the US. For IMP321 in Melanoma we estimate launch is possible in 2022 in Europe and 2024 in the US. We calculate a Risk adjusted Discount Rate of 13%. Pricing per month treatment is set at USD 12,500 (USD 150,000 per year) which is comparable with pricing of Keytruda and Optivo. We estimate that Prima BioMed will partner IMP321 in Phase III for an estimated royalty of 15%. We estimate that a peak market share of 8% is possible. This leads to a total valuation of AUD 71 million or AUD 0.031 per share.

Valuation IMP731

In estimating a value of IMP731 in Autoimmune Disease, we apply the LOA of 18% to the potential milestones from GSK totaling USD 100 million. That would value IMP731 solely based on milestones at USD 18 million or AUD 23 million. Additionally, we take into account a royalty of 3-5% on sales. We estimate that market launch would be possible in 2022 with a peak market share of 8% in the market for moderate to severe psoriasis. Discounted at 13%, the total current value of expected royalties is AUD 64 million. Added the value for milestones leads to a total value of AUD 88 million or AUD 0.038.

Break down total valuation Prima BioMed

Program	Market	LOA	Market share	Peak Sales (US Million)	Royalty	Risk Adj. NPV (AUD m)	Per share
IMP321 MBC	2020 EU	23%	8%	700	15%	55.0	0.024
IMP321 Melanoma	2024	16%	8%	500 (EU)	15%	16.0	0.007
IMP731 Psoriasis	400,000	18%	8%	1,200 (EU)	5%	88.0	0.038
IMP701 Cancer	333,000	18%	8%	2,000	3%	75.0	0.032
Total						**234.0**	**0.10**

Analyst: Marcel Wijma MSc

Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoeck Research (VLR) to SNS Securities in 2006, he established an award winning analyst team in biotech/life sciences at SNS Securities. In 2009, Marcel was awarded by Financial Times/Starmine as being one of the Top-3 biotech analysts in Europe. Later that year, Marcel purchased VLR from SNS Securities after which the company was reconstituted. At VLR, he leads the professional VLR research organisation, which is augmented by selected external financial researchers with a specialisation in Life Sciences. Mr. Wijma has a Masters degree in Financial Economics from Erasmus University in Rotterdam.

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