EDISON

Imugene

Transformative acquisition

Checkpoint inhibitor vaccine programme accelerated

Pharma & biotech

Imugene has in-licenced a pipeline of B-cell vaccines that complements and advances its in-house programme. The deal has brought forward significant value-creation opportunities while maintaining Imugene's focus on B-cell vaccine technologies. It accelerates the key PD-1 and PD-1/HER2 combo programmes by two years compared to its original pipeline. The company is well funded to accelerate key clinical studies for the newly combined pipeline. Our valuation is A$147m or 4.1 cents per share.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
06/16	1.5	(2.7)	(0.2)	0.0	N/A	N/A
06/17	1.2	(2.5)	(0.1)	0.0	N/A	N/A
06/18e	1.6	(4.4)	(0.2)	0.0	N/A	N/A
06/19e	2.6	(5.9)	(0.2)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding exceptional items.

B-cell vaccine alternative to checkpoint inhibitors

KEY-Vaxx, the in-licensed PD-1 B-cell vaccine, aims to induce the body to produce polyclonal antibodies that block PD-1 signalling, and thus produce an anticancer effect similar to Keytruda, Opdivo and the other immune checkpoint inhibitor (ICI) monoclonal antibodies that are transforming treatment of a range of cancers. KEY-Vaxx has shown great potential in preclinical studies. It outperformed an industry-standard mouse anti-PD-1 antibody in a mouse model of HER2+ colorectal cancer.

Potential returns outweigh possible pitfalls

There is still a long way to go for KEY-Vaxx, with the first clinical trials not expected until 2019. The key role that PD-1 signalling plays in regulating immune responses will ensure that safety is closely examined in pre-clinical and clinical studies, as there is a theoretical risk that KEY-Vaxx could trigger unregulated autoimmune responses in patients. Encouragingly, there has been no evidence of autoimmune disorders in preclinical studies to date. Despite these risks, the broad potential market for KEY-Vaxx will ensure intense interest in the planned Phase I study from potential pharma partners. A successful clinical study of KEY-Vaxx with evidence of efficacy would be transformative for Imugene, in our view.

HER2 vaccines: PoC plus therapeutic potential

Imugene now has two HER2 B-cell vaccines in clinical trials, one in-licensed from Ohio State University (OSU) called B-Vaxx, plus its in-house HER-Vaxx programme. Both vaccines have completed Phase I studies showing that they stimulated production of polyclonal antibodies against HER2, with encouraging indications of efficacy, thus providing proof of concept (PoC) for the B-cell vaccine technology as well as suggesting therapeutic potential in HER2+ cancers.

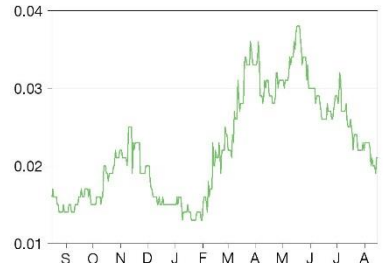
Valuation: A$147m or 4.1 cents per share

We value Imugene at A$147m or 4.1 cents per share, including milestones and royalties for HER-Vaxx plus an indicative valuation of KEY-Vaxx. With pro forma cash of A$27m following a recent fund raise, it is funded beyond our FY20 forecast horizon.

16 August 2018

Price	**A$0.02**
Market cap	**A$71m**
	US$0.76/A$
Net cash* (A$m) at 30 June 2018 *Pre-capital raise	7.8
Shares in issue	3,559.8m
Free float	69%
Code	IMU
Primary exchange	ASX
Secondary exchange	N/A

Share price performance



52-week high/low	A$0.01	A$0.01

Business description

Imugene is developing B-cell vaccines that aim to induce polyclonal antibody responses against important cancer targets, as an alternative to monoclonal antibodies. HER-Vaxx, a proprietary HER2 +ve cancer vaccine, is in a Phase Ib dose-finding study ahead of a gastric cancer Phase II.

Next events

Complete KEY-Vaxx CMC manufacturing	H218
HER-Vaxx Phase Ib patient data available	H218
Commence recruiting HER-Vaxx Phase II	Q119

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Imugene is a research client of Edison Investment Research Limited

Investment summary: Immunotherapy play

Company description: Anti-tumour vaccine effect

Imugene is an Australian biotechnology company developing B-cell vaccines to treat cancer. Its lead products are HER-Vaxx, a gastric cancer vaccine, and KEY-Vaxx, which aims to replicate the efficacy of ICI monoclonal antibodies (mAbs) using a vaccine approach. The company is a pure-play cancer opportunity in the highly valuable area of cancer immunotherapy. If KEY-Vaxx shows potential in the Phase I study planned to commence in 2019, or if one of the two ongoing Phase Ib/II studies of its two different HER2 vaccines shows a strong efficacy signal, it might enable a major deal with a big pharma company. The global market for gastric cancer is over 900,000 patients annually, while the two leading ICI drugs, Keytruda (Merck) and Opdivo (BMS), are each on track to report global sales in excess of US$6bn in 2018.

Valuation: A Phase II deal is the goal

If any of its ongoing or planned clinical trials show a strong efficacy signal with a good safety profile, Imugene could gain a big pharma partner. Assuming a US$84m upfront, regulatory milestones of US$260m for a deal combining HER-Vaxx and KEY-Vaxx, with potential royalties of 15% starting in 2025 for HER-Vaxx or 2027 for KEY-Vaxx, and ending in 2039 (due to 12 years of data exclusivity for biologicals in the US and the likelihood of additional patents on KEY-Vaxx and the new HER-Vaxx composition), Imugene has an indicative equity value on discounted cash flow of A$147m, including pro forma net cash of ~A$27m. This assumes a Phase Ib/II probability of reaching the market of 20% for HER-Vaxx and 10% for KEY-Vaxx, and a 50% probability of a 2021 licensing deal. Our standard 12.5% discount rate is used. We assume Imugene pays an 18% share of its income from HER-Vaxx to Biolife until 2026, and a low single digit royalty on net sales of KEY-Vaxx to OSU. Our valuation is equivalent to 4.1c per share (undiluted) or 4.0 cents per share after diluting for the 555m options on issue (most of the options are out of the money).

Financials: Cash to initiate Phase Ib

Imugene reported an operating loss of A$2.5m for the year ending 30 June 2017 and a further A$1.6m loss for the six months ending 31 December 2017. Our total operating loss estimates for FY19 and FY20 grow to A$6.0m and A$8.2m respectively, mainly due to increased R&D expenditure as Imugene ramps up its clinical trial programme, partly offset by the Australian government's R&D rebate scheme. We estimate pro forma cash of ~A$27m at the beginning of FY19, including A$20.1m (gross) proceeds of the capital raise that closed in July. On our estimates, this is sufficient to fund operations beyond our FY20 forecast horizon, including the HER-Vaxx gastric cancer Phase II, KEY-Vaxx preclinical and Phase I studies, as well as a modest contribution to the ongoing National Institutes of Health funded Phase I/II study of the OSU HER2 B-cell vaccine, B-Vaxx.

Sensitivities

Imugene is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. Our model assumes that HER-Vaxx, B-Vaxx and KEY-Vaxx will be out-licensed; therefore, our valuation is sensitive to potential licensing timing and actual deal terms. Imugene is an early-stage drug developer, therefore in the foreseeable future most value creation will depend on successful R&D progress and any potential partnering activities, although the timing of licensing deals is typically difficult to forecast. Our valuation of KEY-Vaxx is based on an indicative sales estimate; this would likely be revised if the adaptive Phase I study provides insight as to potential indications.

A transformative deal for Imugene

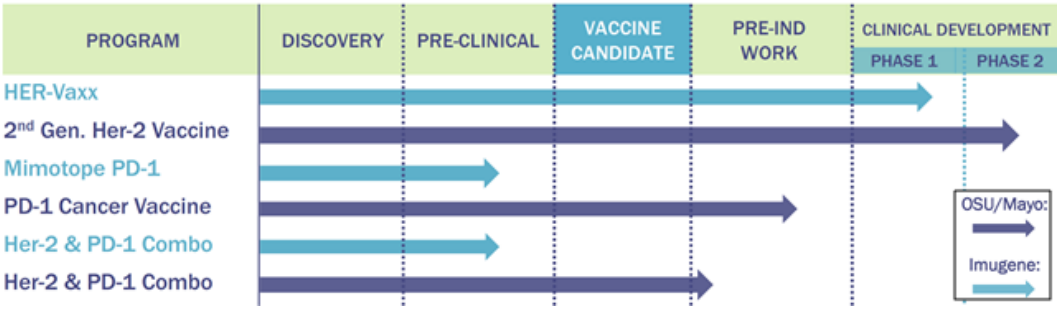
Imugene has undertaken a transformative transaction, with the in-license of a complementary second generation B-cell vaccine programme developed by Professor Pravin Kaumaya of OSU Comprehensive Cancer Centre, and Dr Tanios Bekaii Saab of the Mayo Clinic[1]. The acquired pipeline includes:

- A PD-1 peptide vaccine candidate that has commenced IND-enabling pre-clinical studies, and which has the potential to be a game-changer for Imugene, given that PD-1/L1 immune checkpoint inhibitor mAbs have transformed the treatment of a range of cancers.
- A HER2 vaccine in a US-based Phase I/II study that is partly funded by a National Cancer Institute grant.
- A pipeline of pre-clinical candidates including HER-1 (EGFR), HER-3 and IGF-1R peptide cancer vaccines and a VEGF peptide mimic.

Exhibits 1 and 2 show how the in-licensed programmes fit in to Imugene's expanded candidate pipeline.

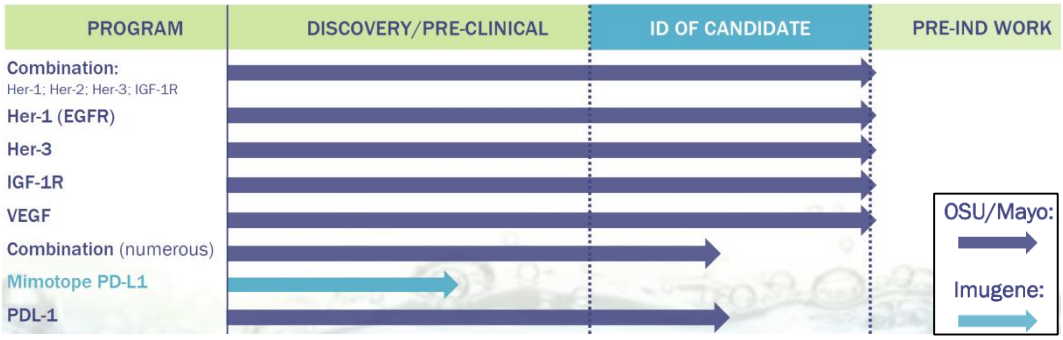
The lead products in the OSU/Mayo pipeline use the same underlying approach (B-cell peptide vaccines) and are focused on the same biological targets (HER2 and PD-1) as Imugene's lead programmes, but they target different peptide epitopes and use different vaccine formulation technologies. Both vaccine programmes link an immunogenic protein with the peptide and incorporate an adjuvant to trick the body into producing antibodies against the normal self HER2 of the PD-1 protein (known as breaking immune tolerance).

Exhibit 1: Expanded Imugene lead candidate pipeline with OSU/Mayo transaction



Source: Imugene

Exhibit 2: Expanded Imugene discovery/preclinical pipeline with OSU/Mayo acquisition



Source: Imugene

1 PD-1 intellectual property (IP) licensed from OSU/Mayo Clinic. All other targets IP (HER-1, HER-3, IGF-1R and VEGF) licensed from OSU only.

OSU's potentially game-changing PD-1 programme is more advanced

A key attraction of the OSU pipeline is that its PD-1 peptide vaccine programme is about two years ahead of Imugene's in-house PD-1 mimotope discovery programme. OSU has selected a lead vaccine candidate, which Imugene refers to as KEY-Vaxx. KEY-Vaxx is ready for IND-enabling formal preclinical toxicology and efficacy studies and is on track to enter its first clinical trial in 2019.

In studies in a preclinical model of HER2+ colorectal cancer, the PD-1 vaccine inhibited tumour growth to a greater extent than an industry standard anti-PD-1 mAb. Combining the PD-1 vaccine with the HER2 vaccine inhibited tumour growth even more. There were no significant toxic side effects from the combination therapy.

If KEY-Vaxx is able to replicate this good efficacy and low toxicity in cancer patients, it could have potential application as part of combination immunotherapy regimens in a wide range of cancers.

An effective PD-1 B-cell vaccine would be a game changer for Imugene and would give it a place at the table in the biggest game in town in cancer therapy. PD-1/L1 mAbs have transformed the treatment of a range of cancers, and the scope is continually being extended through combination therapies. The two leading anti-PD-1 ICI mAbs, Keytruda and Opdivo, each achieved sales of over US$1.6bn in the June quarter of 2018 and each is on track to exceed US$6bn of sales in 2018.

A patent application filed in March 2018 under the international Patent Cooperation Treaty would provide IP protection until at least 2038, if granted.

Two HER2 programmes in the clinic

Both Imugene's in-house HER-Vaxx programme and the OSU HER2 vaccine are at a similar stage of development, having completed successful Phase I studies. Both were well tolerated and successfully stimulated anti-HER2 antibody production. They also both showed encouraging signs of efficacy in these early clinical studies, with high disease control rates and a partial tumour response reported in each study.

The HER2 vaccine in-licensed from OSU has identified the optimal biological dose (OBD) in a Phase I dosing study and is recruiting a 12-patient extension cohort that is intended to form part of a 48-patient non-randomised Phase II study.

Imugene has initiated a Phase Ib trial of its HER-Vaxx product in gastric cancer patients in Asia, with a randomised Phase II study expected to commence in Q119.

Why B-cell vaccines

B-cell vaccines link an immunogenic protein with the peptide and incorporate an adjuvant to induce the body into producing antibodies against the normal self-proteins, such as HER2 or PD-1 (known as breaking immune tolerance). The antibodies produced following the vaccination are a 'polyclonal' mixture of antibodies that bind to different parts of the vaccine antigen. This makes them somewhat different to the monoclonal antibody drugs, even though they bind to the same target in the body.

The use of B-cell vaccines to stimulate the patient's immune system to produce polyclonal antibodies may have advantages over synthetic antibodies, including:

- Lower cost of production: peptide vaccines are much cheaper to manufacture than mAb drugs.
- The polyclonal antibody response may reduce the risk of the tumour becoming resistant to the therapy and could potentially improve efficacy.
- The vaccine stimulates continuous antibody production via a lasting immune response that may inhibit tumour recurrence.

- The natural polyclonal antibodies produced following vaccination are potentially safer than synthetic mAb and may avoid toxic side effects of mAb administration, which can include ventricular dysfunction, congestive heart failure or anaphylaxis.
- Subcutaneous or intramuscular injection of the vaccine is more convenient than intravenous infusion of mAb drugs.

B-cell peptide vaccines are distinct from T-cell peptide vaccines, which bind to class I MHC molecules on antigen-presenting cells and are recognised by cytotoxic T-cells. Although several T-cell vaccines have shown limited therapeutic benefits in clinical trials, they did not cause striking tumour regression[2].

KEY-Vaxx showed impressive efficacy in animal models

After investigating a number of PD-1 peptide vaccine constructs, OSU recently selected a lead PD-1 B-cell vaccine candidate, which Imugene refers to as KEY-Vaxx. KEY-Vaxx comprises amino acids 92-110 of the PD-1 receptor covalently linked to a promiscuous T-cell epitope derived from the measles virus fusion protein, and formulated together with an adjuvant in Montanide ISA 720 (a water-in-oil water emulsion) to stimulate strong production of anti-PD-1 antibodies.

KEY-Vaxx showed impressive efficacy in an industry-recognized mouse colon cancer model, where it inhibited cancer growth to a greater extent than the gold-standard mouse PD-1 mAb, which management advises was used in preclinical model testing of Keytruda and Opdivo. Exhibit 3 shows that whereas the PD-1 mAb inhibited tumour growth by 39%, the PD-1 vaccine was markedly more effective, inhibiting tumour growth by 65%.

Exhibit 3 also shows that in the animal model described above, combined vaccination with both the PD-1 vaccine and the OSU HER2 vaccine inhibited tumour growth to an even greater extent (90% inhibition for the combo vs 65% for the PD-1 vaccine alone). There were no significant toxic side effects from the combination therapy.

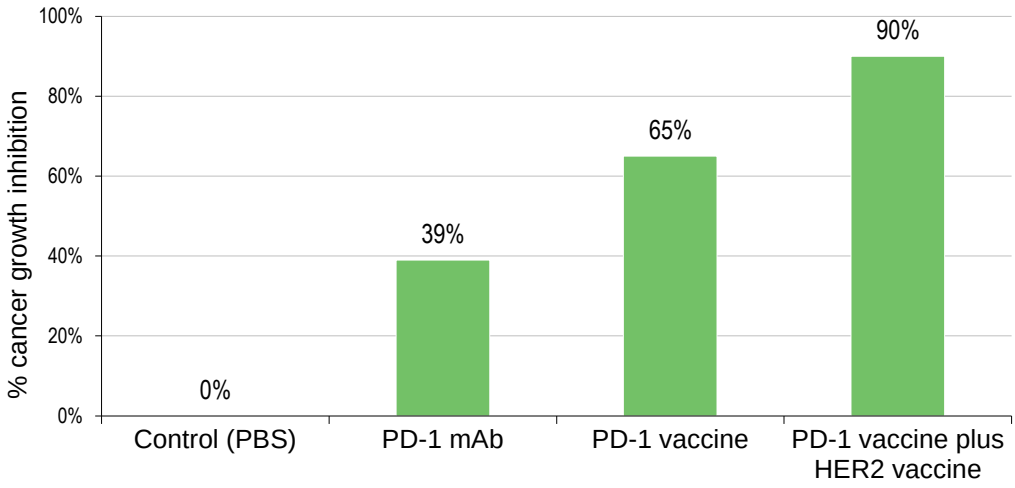
It is important to note that the antibodies generated to the human PD-1 epitope in mice cross react between both mouse and human PD-1, thus validating this impressive result.

The results in the mouse model suggest the anticancer efficacy of the PD-1 B-cell vaccine could potentially rival the efficacy of the PD-1 mAbs such as Keytruda and Opdivo.

This is only unproven potential at this stage, but the preclinical results and the encouraging signs of efficacy seen in HER2 B cell vaccine clinical studies offer tantalising signs that this programme has great promise.

2 Kametani et al. Antibodies 2015, 4, 225-239; doi:10.3390/antib4030225

Exhibit 3: % cancer growth inhibition in colorectal cancer preclinical model



Source: Edison Investment Research, Imugene. Note: The chart shows inhibition of cancer growth 16 days after infusion of cancer cells. The CT26/HER2 colon cancer cells used in the study are HER2 positive.

Potential for combination therapies is a big appeal of KEY-Vaxx

One of the key appeals of KEY-Vaxx is that if it demonstrates efficacy in clinical studies with acceptable tolerability, then the convenient sub-cutaneous dosing schedule and low cost of goods could make it well suited for use in combination with other therapies in a wide range of cancers.

While ICI drugs have had remarkable success in treating a range of cancers, typically less than a third of patients respond when these drugs are used as single agents (monotherapy).

Exhibit 4 illustrates that one way to improve response rates to ICI therapy is through combination with a treatment that kills cancer cells and releases cellular debris, and thus triggers an immune response (sometimes referred to as immunogenic cancer cell death or turning immunologically cold tumours hot). By taking the brakes off the activity of effector T cells, the ICI therapy is then able to strengthen this immune response.

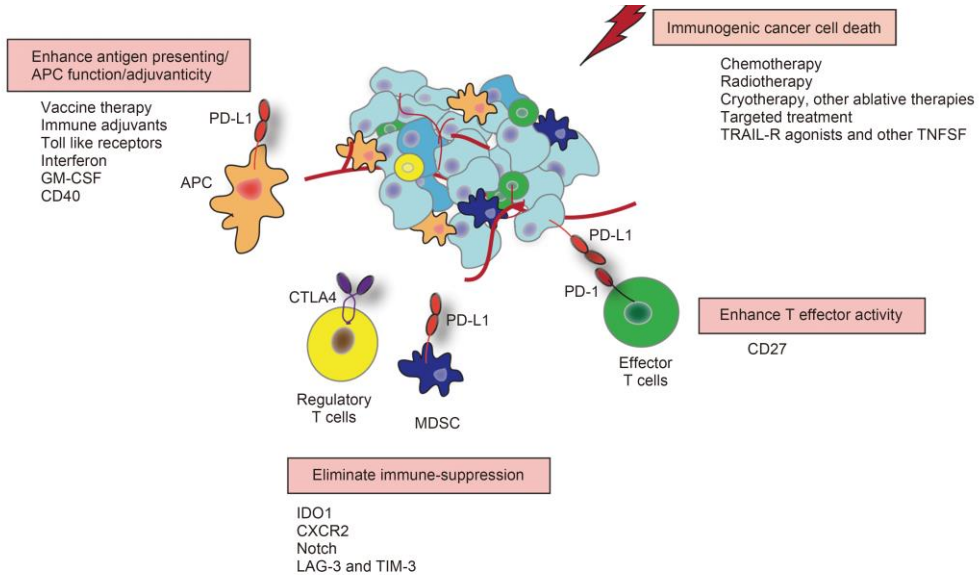
A wide range of treatment modalities induce immunogenic cancer cell death and thus could play a role in ICI combination therapy regimens, including chemotherapy, radiotherapy and targeted therapies (such as anti-HER2 antibodies).

As an illustration of the potential of ICI combos to improve response rates, we note that, in newly diagnosed metastatic lung cancer the overall response rate (ORR) to the Keytruda/chemo combo in the KEYNOTE-189 study was 49.4%[3], which is substantially higher than the 27.3% ORR to Keytruda monotherapy reported in a similar patient population in the separate KEYNOTE-042 study.

The strong inhibition of cancer growth seen when KEY-Vaxx is combined with the HER2 vaccine, as shown in Exhibit 3, above, is evidence of the potential efficacy of such combinations.

3 Gandhi et al. N Engl J Med 2018;378:2078-92.

Exhibit 4: Potential combination strategies to improve response rates to ICI therapy



Source: Harris et al. Cancer Biol Med 2016 13(2). doi: 10.20892/j.issn.2095-3941.2016.0015

Tweaking the immune system can be risky, but no worrying signs so far

At this early stage of development there are a number of risks facing the PD-1 B-cell vaccine programme. KEY-Vaxx aims to break tolerance and stimulate ongoing production of antibodies against the normal or 'self' PD-1 receptor and thus block the action of this inhibitory immune checkpoint and take the brakes off anti-tumour immune responses. On the one hand, the level of anti-PD-1 antibodies produced in patients might be too low to have the desired therapeutic effect. On the other hand, the PD-1/L1 axis plays an important role in regulating the immune system to maintain self-tolerance and preventing autoimmune reactions, so there is a risk that a vaccine that inhibits the activity of PD-1 could result in autoimmune disease or an inflammatory disorder.

We have already seen that anticancer therapy with ICI mAbs such as Opdivo and Keytruda can stimulate off-target immune responses leading to excessive inflammation in organs such as the colon (colitis), lungs (pneumonitis) or other organs. If KEY-Vaxx does trigger similar toxic side effects, there is a risk they could continue for a considerable period, because it is likely to take several months for the production of polyclonal anti-PD-1 antibodies to wane after vaccination with KEY-Vaxx ceases.

To check for this possibility, the animals in the PD-1/HER2 vaccine combination study were examined closely for signs of toxicity, including detailed analysis of organs including spleen, liver, heart, lung and kidney, which were collected from the mice at the end of the study. It is encouraging that the vaccine combination was very well tolerated. The mice did not show any signs of ill health such as scruffiness, lesions or lethargy, there were no biochemical abnormalities and no significant lesions were noted in any of the organs submitted for histologic examination.

The HER2 B-cell vaccines have shown signs of efficacy in clinical studies despite the levels of polyclonal anti-HER2 antibodies stimulated by the vaccine being at least an order of magnitude lower than the levels used in anticancer therapy with Herceptin, which also acts on HER2. If KEY-Vaxx similarly shows efficacy despite generating lower levels of anti-PD-1 polyclonal antibodies than mAb ICI drugs, it is possible it might also have fewer toxic side effect than the ICI mAb.

While it is encouraging that there were no signs of toxicity in the mouse models, we expect the safety of the PD-1 vaccine would need to be confirmed in studies in non-human primates before a Phase I study could commence.

There is 100% homology between the KEY-Vaxx peptide and the corresponding region of the PD-1 protein in the monkey species that is typically used for non-human primate safety studies, so we expect the safety and toxicity profile seen in these studies to be examined closely by the regulators before it is cleared for use in clinical studies. Demonstration of safety and tolerability in non-human primates would be an important milestone for the KEY-Vaxx development programme

OSU Her-2 B-Vaxx programme

The most advanced B-cell vaccine in-licensed from OSU, in terms of clinical development, targets the oncoprotein HER2, a cell surface growth signal. HER2 is a well understood cancer target that is expressed at high levels in about 15–25% of breast and gastric cancers[4], and is also overexpressed in significant proportion of oesophageal, ovarian, uterine, endometrial and lung cancers[5]. HER2 is targeted by the approved monoclonal therapeutics Herceptin (trastuzumab, Roche), Perjeta (pertuzumab, Roche) and Kadcyla (trastuzumab emtansine, Roche). Herceptin is used in breast and gastric cancers. Perjeta in combination with Herceptin and chemotherapy adds 15.7 months to median breast cancer survival. Sales of Herceptin alone in 2017 totalled US$6.7bn worldwide.

B-Vaxx, the HER2 B-cell vaccine in-licensed from OSU, is based on a combination of two peptides corresponding to amino acids 266-296 and 597-626 of the HER2 molecule, which overlap the binding sites of Perjeta and Herceptin, respectively. The binding of Herceptin and Perjeta block the 'growth-promoting' activity of the HER2 molecules on the surface of the cancer cells. The polyclonal antibodies stimulated by the HER2 vaccine appear to act in the same way.

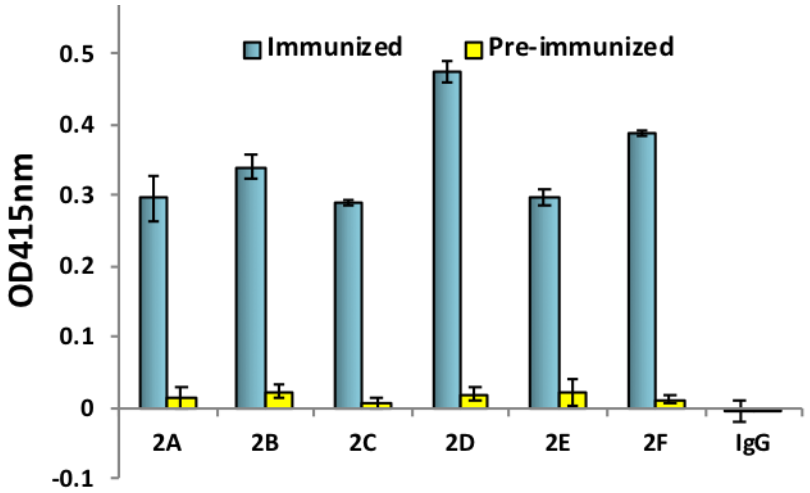
The OSU HER2 vaccine has completed the dose-escalation phase of a Phase I trial, which has identified the OBD for use in Phase II. Patients are being recruited in a 12-patient extension cohort that is intended to form part of a 48-patient non-randomised Phase II study in patients with breast, colon, ovarian and gastrointestinal stromal tumour cancers. Three subjects had been enrolled as of May 2018. This study is partly funded by the US National Institutes of Health. Interim data are expected by December 2019.

The Phase I study produced encouraging signs of efficacy, with 10 out of 24 evaluable subjects achieving stable disease or better, including one patient with a partial response. All eight evaluable subjects treated at the OBD generated antibodies that bind to recombinant HER2 protein (Exhibit 5).

4 Jørgensen, J. T. Role of human EGFR 2 in gastric cancer. World J. Gastroenterol. 20, 4526–35 (2014).

5 Foy et al. OncoImmunology 1:7, 1048–1060; October 2012.

Exhibit 5: OSU HER2 vaccine stimulated anti-HER2 antibodies in patients in Phase I



Source: Imugene

In-house HER-Vaxx programme

Imugene also has an in-house HER2 vaccine, HER-Vaxx, which is in a Phase I/II study in gastric cancer. Like the OSU HER2 vaccine, HER-Vaxx aims to stimulate the production of high levels of polyclonal antibodies against HER2. HER-Vaxx contains three peptides that stimulate the patient's immune system to produce antibodies against the P4, P6 and P7 sites on the HER2 molecule. Data from previous preclinical studies showed that polyclonal antibodies produced following vaccination with HER-Vaxx were more potent than the marketed mAb Herceptin at blocking the 'growth-promoting' activity of the HER2 molecules and thereby inhibiting the growth of breast cancer cells. The polyclonal antibodies may also trigger an immune response against the HER2-expressing cells, so called antibody-directed cell cytotoxicity.

A Phase I study of a previous formulation of HER-Vaxx was conducted in 10 patients with metastatic breast cancer[6]. The main conclusion identified by the lead investigator was that HER-Vaxx 'broke tolerance', that is, it stimulated clear antibody responses against all three peptide sites with some evidence of a wider immune effect. Eight out of 10 subjects generated anti-HER2 antibodies and six out of 10 subjects experienced stable disease or better, including one partial response.

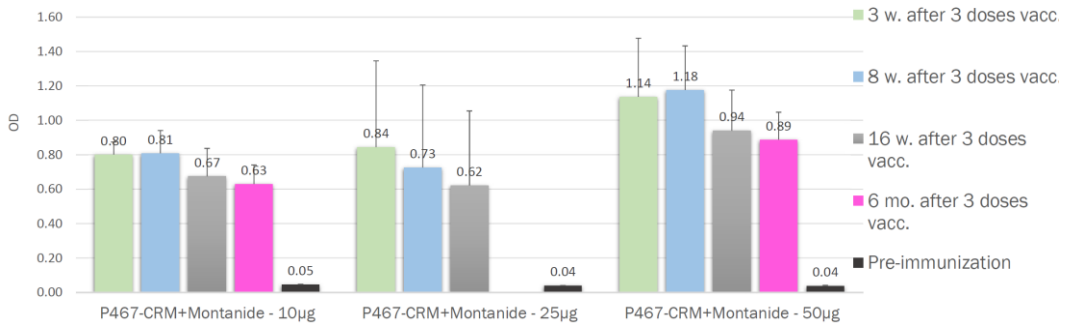
The original formulation of HER-Vaxx that was tested in that Phase I breast cancer trial contained the three separate P4, P6 and P7 peptides incorporated into a virosome, an artificial virus. Imugene has subsequently reformulated the vaccine to increase its immunogenicity, including by combining the three peptides into one long peptide strand and replacing the virosome with a clinically and commercially validated vaccine carrier protein called CRM_{197} together with an adjuvant. Advantages of the new CRM_{197} formulation include a notably faster and stronger immune response (in preclinical studies) and a cheaper, simpler and more reliable manufacturing process[7]. A new patent covering the formulation will extend IP coverage to 2036 if granted (the patent was granted in Australia in June 2017).

Exhibit 6 shows that the new HER-Vaxx formulation induces long-lasting production of anti-HER2 polyclonal antibodies in mice.

6 Wiedermann et al 2010. Breast Cancer Res Treat. 119 (3):673-83.

7 Tobias et al. BMC Cancer. 2017 Feb 9;17(1):118

Exhibit 6: HER-Vaxx stimulates strong anti-HER2 immune responses that last at least six months in mouse model



Source: Imugene. Note: P467+CRM+Montatnide= HER-Vaxx

Phase Ib/II HER-Vaxx trial in gastric cancer

Imugene is conducting a Phase Ib trial of HER-Vaxx in gastric cancer patients, which will be followed by a randomised Phase II study. Management sees gastric cancer as a faster indication to develop, relative to breast cancer, with a large potential gastric cancer market and high unmet medical need. The company has based its HER-Vaxx trials in Asia, and recently in 2018 in Eastern Europe. Asia represents the largest target market for gastric cancer therapies. Of the 952,000[8] new cases of gastric cancer that were estimated to have occurred globally in 2012, 700,000 occurred in Asia, including 108,000 cases in Japan and 405,000 cases in China. Gastric cancer is less common in the other major pharmaceutical markets, with 28,000 cases in Western Europe and 24,500 cases in North America.

The Phase Ib lead-in trial is testing three different doses of HER-Vaxx in 18 patients (three groups of six) in combination with standard of care chemotherapy. The key endpoints of the Phase Ib trial are to:

- identify the optimal dose of HER-Vaxx to use in the Phase II part of the study (recommended Phase II dose or RP2D);
- confirm safety and identify any HER-Vaxx toxicity; and
- monitor immune responses to the vaccine.

Patient data from the Phase Ib trial are expected to be available in H218. It will be followed by a randomised Phase II trial to test the efficacy, safety and immune response of the selected dose in 68 gastric cancer patients. The efficacy endpoints of this randomised, placebo-controlled trial will be influenced by the Phase Ib results, but are likely to be progression-free survival and/or overall survival. Immune response will be a secondary endpoint.

PD-1/HER2 vaccine combination trial in the wings

Imugene has stated that it intends to investigate the potential for combining KEY-Vaxx with HER-Vaxx or B-Vaxx in HER2-positive cancers after its initial Phase I trial of KEY-Vaxx has completed. Such a trial would investigate whether the synergistic efficacy seen with combined HER2/PD-1 B-cell vaccination in animal models translates to efficacy in cancer patients.

This would be a proof-of-concept study as KEY-Vaxx could potentially be combined with a wide range of anticancer therapies if it shows efficacy together with good tolerability.

8 http://globocan.iarc.fr

Lots of potential in the OSU preclinical pipeline

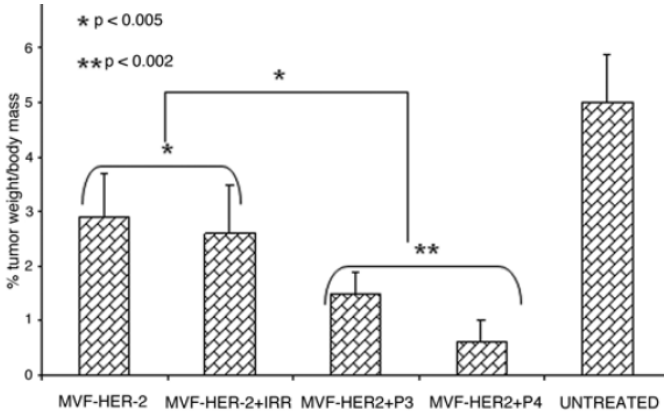
In addition to the lead PD-L1 and HER2 B-cell vaccines, Imugene has in-licensed from OSU a number of other B-cell vaccines, as well as peptide mimics that can inhibit growth factor signalling, including programmes targeting HER-1, HER-3, VEGF, IGF-1R and CD28. While in the near term we expect Imugene to focus on developing its HER2 and PD-1 B-cell vaccines, a number of these pipeline products have shown considerable promise in preclinical studies and could potentially add significant value.

One interesting example from the preclinical pipeline is VEGF-P4, a peptide mimic corresponding to amino acids 76-96 of the vascular endothelial growth factor receptor VEGFR2. VEGF-P4 binds with high affinity to VEGFR2, thereby blocking the binding of endogenous VEGF to its major receptor, resulting in anti-tumour effects by inhibiting the formation of new blood vessels needed to support tumour growth. VEGF signalling is a well-recognised cancer target; a number of approved cancer drugs block VEGF signalling, including Avastin (bevacizumab) and Sutent (sunitinib).

The combination of OSU's HER2 vaccine with VEGF-P4 dramatically inhibited tumour growth in a mouse model of breast cancer. Whereas HER2 vaccination alone inhibited tumour growth in mice by about 40%, combining HER2 vaccination with the VEGF-P4 peptide mimic inhibited tumour growth by almost 90%[9].

These data suggest that VEGF-P4 warrants further investigation when Imugene has sufficient resources.

Exhibit 7: Combining HER2 B-cell vaccination with VEGF-P4 peptide mimic dramatically inhibited tumour growth in a mouse model of breast cancer



Source: Foy et al OncoImmunology 1:7, 1048–1060; October 2012. Note: MVF-HER-2 is mice that had been vaccinated with the HER2 B-cell vaccine; MVF-HER2+P4 mice were vaccinated with the HER2 B-cell vaccine and then treated with the VEGF-P4 peptide mimic; IRR, irrelevant peptide; P3, a different VEGF mimic.

In-house PD-1/L1 mimotopes provide a backup plan

In February 2018 Imugene announced it had completed early development of a new anti-PD-1 mimotope vaccine and would commence a preclinical development programme to test the vaccine for both safety and efficacy. Its programme to develop a B-cell vaccine that targets PD-L1, the ligand that binds to the PD-1 receptor, is still in the discovery phase.

While less advanced than the in-licenced KEY-Vaxx, Imugene's in-house PD-1 and PD-L1 mimotope B-cell vaccine programmes provide it with additional options that will enable to continue development in the ICI space if KEY-Vaxx falters.

9 Foy et al. OncoImmunology 1:7, 1048–1060; October 2012. http://dx.doi.org/10.4161/onci.20708

Herceptin biosimilars could impact HER2 uptake or pricing

Herceptin, the biggest-selling drug that targets HER2, is likely to face increasing competition from biosimilars over the next few years. Biocon/Mylan and Celltrion/Hospira have launched Herceptin biosimilars in India and Korea, respectively, while Merck/Samsung Bioepis launched the first Herceptin biosimilar in Europe in March 2018 (Herceptin patent protection expired in Europe in 2014).

The US FDA approved a Herceptin biosimilar developed by Mylan and Biocon in December 2017, but it is not expected to be launched in the US until 2019. Several other companies are seeking FDA approval for their Herceptin biosimilars.

A one-year course of Herceptin was reported to cost between U$64,000 and US$70,000 in the US in 2016[10,11]. The price of Herceptin is likely to decline once biosimilars enter the market, although price falls for biologicals such as Herceptin are expected to be less aggressive than for small molecule generics.

The launch of Herceptin biosimilars in the US may impact the potential pricing or uptake of HER-Vaxx. We model US pricing of US$50,000 per year for HER-Vaxx, with lower prices in most other countries.

Valuation

We last published on Imugene in February 2016. We have updated our model to include the acquired KEY-Vaxx programme and have revised our assumed licensing deal terms based on relevant benchmarks, as described below. We value Imugene at A$147m based on a risk-adjusted discounted cash flow model, which includes net cash plus our estimates of the future milestone payments and royalty streams for HER-Vaxx and KEY-Vaxx. We have extended our cash flow forecasts out to 2039 (supported by 12 years of biologicals market exclusivity in the US and 10 years in Europe) but have not included any terminal valuation. We assume that HER-Vaxx sales decline at 20% per year after market exclusivity expires in 2037. We assume a long-term exchange rate of US$0.76/A$ and apply a 12.5% discount rate.

Our valuation is equal to 4.1 cents per share on an undiluted basis and 4.0 cents per share after diluting for the 555m options on issue (exercise prices range from 1.25 to 4.1 cents).

Our valuation of the HER2 B-cell vaccine programmes is based on HER-Vaxx in the gastric cancer indication, which is the subject of the randomised Phase II trial that is expected to commence in Q119. The detailed assumptions for individual gastric cancer markets are shown in Exhibit 9. If the OSU HER2 vaccine was to become the lead HER2 candidate, the valuation would be similar.

For our valuation of KEY-Vaxx we assume an indicative present-day sales potential of US$1,000m as the lead indication is not yet known. Given that the two leading anti-PD-1 drugs, Keytruda and Opdivo, are both on track to exceed US$6bn of sales in 2018, we believe this is a conservative estimate of the sales that KEY-Vaxx could potentially achieve if it is shown to be safe and effective.

Exhibits 8 and 9 show our market assumptions for HER-Vaxx and KEY-Vaxx and the rNPV for each product. We have offset the risk-adjusted trial cost against revenue for each indication.

10 Sonenshein J. https://www.marketwatch.com/story/the-staggering-cost-of-breast-cancer-2016-05-25

11 Silverman E. STAT website. https://www.statnews.com/pharmalot/2016/05/20/genentech-herceptin-prices/

Exhibit 8: Imugene sum-of-the-parts DCF

	Base case likelihood (%)	rNPV (A$m)	rNPV/sh (A$)	Assumptions
HER-Vaxx in gastric cancer	20%	67.0	$0.019	Present-day sales potential in gastric cancer US$649m, growing to global peak sales of US$930m in 2030, assuming 3% market growth rate. Detailed market assumptions shown in Exhibit 9, which assumes 20% of gastric cancers are HER2+, 75% of which are eligible for HER-Vaxx therapy; market launch 2025; assume receives 15% gross royalty, pays 18% of royalty and milestone income to Biolife until 2026. R&D cost: A$8m for Phase II, then out-license.
KEY-Vaxx indicative valuation	10%	65.9	$0.019	Present-day indicative sales potential US$1,000m, growing to global peak sales of US$1,510m in 2032, assuming 3% market growth rate; market launch 2027; assume net 12% royalty after pay-aways to OSU. R&D cost: A$10m to FY21, then out-license
SG&A		-13.1	-$0.004	
Portfolio total		**119.7**	**$0.034**	
Pro forma cash (30 June 2018)		26.9	$0.008	
Enterprise total		**146.6**	**$0.041**	

Source: Edison Investment Research. Note: NPV adjusted for tax at an effective tax rate of 25%. We assume the addressable markets grow at 3% per year.

Exhibit 9: Present-day market opportunity for HER-Vaxx in gastric cancer (in 2018 dollars)

Market (US$ unless otherwise stated)	Cases	Eligible	Uptake (%)	Number treated	Price (US$000s)	Sales potential in 2018 (US$m)
US	21,200	3,180	30%	954	50.0	48
Japan	107,900	16,185	30%	4,856	65.0	316
Western EU	62,240	9,336	40%	3,734	40.0	149
Eastern EU	18,360	2,754	25%	689	25.0	17
Eastern Europe and Russia	59,000	8,850	25%	2,213	25.0	55
China	405,000	60,750	5%	3,038	12.5	38
Other E Asia	40,000	6,000	5%	300	12.5	4
Other	238,300	35,745	5%	1,787	12.5	22
Total	**952,000**	**142,800**		**17,570**		**649**

Source: Market data references[12,13] and Edison Investment Research

Assumed licensing deal terms are based on relevant benchmarks over the last few years (sourced from EvaluatePharma and the industry group BIO). There is a lack of directly comparable deals. Therefore, we looked first at deal terms within the targeted therapy space, which included average upfront/milestones of US$122m/US$757m (Exhibit 10). Additionally, based on data in a report produced by BIO, we calculated that among 124 global licencing deals for Phase II therapeutics from 2013 to 2017 (for all diseases) the average upfront/milestones were US$46m/US$281m. Averaging these two data sources we assume upfront/milestones of US$84m/US$520m for a licence deal for Imugene's product pipeline. We assume half of the milestone payments in the benchmark licence deals (ie US$260m) are for clinical and regulatory milestones and half are sales-based milestones. We do not include the potential sales-based milestones in our forecasts, and instead model a 15% gross royalty rate on net sales.

We split the US$84m upfront and US$260m clinical and regulatory milestones between the HER-Vaxx and KEY-Vaxx programmes, weighted according to peak sales. We assume a 50% probability of entering a licence deal, with the probability of subsequent milestones declining gradually to 20% for approval milestones.

12 Jemal, A. et al. Global cancer statistics. CA. Cancer J. Clin. 61, 69–90.

13 Ferlay, J. et al. Cancer incidence and mortality patterns in Europe. Eur. J. Cancer 49, 1374–403 (2013).

Exhibit 10: Comparable Phase I/II oncology deals targeting solid tumours

Date	Licensor	Licensee	Product	Pharmacological class / target	Indications included in the deal	Upfront (US$m)	Deal value (excl. upfront) (US$m)
Targeted antibodies							
10/02/2017	Immunomedics	Seattle Genetics	Govitecan (IMMU-132)	TROP-2	TROP-2 expressing solid tumours (eg breast, lung, bladder)	300	1,757
15/10/2015	Five Prime Therapeutics	Bristol-Myers Squibb	CSF1R antibody (FPA008) in combination with Opdivo	CSF1R	Six undisclosed solid tumours	350	1,390
03/12/2013	Oncomed Pharmaceuticals	Celgene	Up to six anticancer stem cell product candidates (including demcizumab)	DLL4, VEGF	Oncology (including demcizumab for pancreatic cancer)	155	967
06/09/2012	Symphogen	Merck KGaA	SYM004	EGFR (Mab)	All indications (including colorectal and head and neck cancer)	25	597
21/03/2011	Five Prime Therapeutics	Human Genome Sciences	FP-1039	FGFR1	Multiple tumour types; endometrial cancer Phase II underway	50	445
Small molecules							
14/11/2017	Loxo Oncology	Bayer	Larotrectinib and LOXO-195	TRK	TRK fusion cancers (eg lung)	400	1,150
28/07/2015	Hanmi Pharmaceutical	Boehringer Ingelheim	Olmutinib	EGFR (TKI)	EGFR mutation positive lung cancer	50	680
15/12/2014	Geron	Johnson & Johnson	Imetelstat	Telomerase inhibitor	Oncology including haematological malignancies and other therapeutic uses	35	900
1/11/2013	Nerviano	Ignyta	RXDX-101 & RXDX-102	TrK, ROS1 and ALK (TKI)	Solid tumours	6	105
08/12/2011	Pharmacyclics	Johnson & Johnson	PCI-32765	BTK inhibitor	B-cell malignancies, solid tumours, immune disorders	150	825
02/02/2010	Topotarget	Spectrum Pharmaceuticals	Belinostat	HDAC inhibitor	Haematological cancers, solid tumours	30	320
28/04/2009	Ardea Bioscience	Bayer	RDEA119	MEK inhibitor	Solid tumours	35	372
Anti-PD-1 agents							
23/10/2014	CureTech	Medivation	Pidilizumab (CT-011)	PD-1	All indications (including oncology)	5	330

Source: Edison Investment Research, EvaluatePharma, BioCentury, company press releases

Sensitivities

Imugene is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. Our model assumes that HER-Vaxx and KEY-Vaxx will be out-licensed; therefore, our valuation is sensitive to potential licensing timing and actual deal terms. Imugene is an early-stage drug developer, therefore in the foreseeable future most value creation will depend on successful R&D progress and any potential partnering activities, although the timing of licensing deals is typically difficult to forecast. Our valuation of KEY-Vaxx is based on an indicative sales estimate; this would likely be revised if the adaptive Phase I study provides insight as to potential indications.

Financials: Well-funded to FY21

Imugene reported an operating loss for the year ending 30 June 2017 of A$2.5m, and a further A$1.6m loss for the six months ending 31 December 2017. Operating cash outflow for FY18 (12 months ending June 2018) was A$4.4m, including A$3.6m on R&D, partly offset by R&D rebate of A$1.1m (P&L accounts will be released later in August). Our total operating loss estimates for FY19 and FY20 grow to A$6.0m and A$8.2m, respectively, mainly due to increased R&D expenditure

(detailed in Exhibit 8) as Imugene ramps up its clinical trial programme, partly offset by the Australian government's R&D rebate scheme.

Imugene had A$7.8m cash and equivalents at 30 June 2018 and has since received A$20.1m (gross) from a capital raise that closed in July. Allowing for 5% capital raise costs, we estimate pro forma cash at the beginning of FY19 as A$26.9m. Imugene is well funded beyond FY20 based on our estimates. Any future funding requirement (if any) will depend on the rate of R&D expenditure and the timing of licensing transaction. We model Imugene out-licensing its B-cell vaccine programme in FY21, in which case it may not need any additional funding.

Exhibit 11: Financial summary

A$'000s	2016	2017	2018e	2019e	2020e
Year end 30 June	AASB	AASB	AASB	AASB	AASB
PROFIT & LOSS					
Sales, royalties, milestones	0	0	0	0	0
Other (includes R&D tax rebate)	1,525	1,164	1,631	2,606	3,492
Revenue	1,525	1,164	1,631	2,606	3,492
R&D expenses	(2,698)	(2,472)	(3,577)	(6,000)	(9,000)
SG&A expenses	(1,596)	(1,232)	(2,269)	(2,260)	(2,347)
Other	0	0	0	0	0
EBITDA	(2,769)	(2,540)	(4,215)	(5,654)	(7,855)
Operating Profit (before GW and except.)	(2,770)	(2,542)	(4,215)	(5,750)	(7,952)
Intangible Amortisation	0	0	(264)	(253)	(243)
Exceptionals	0	0	0	0	0
Operating Profit	(2,770)	(2,542)	(4,479)	(6,003)	(8,195)
Net Interest	39	35	48	78	203
Profit Before Tax (norm)	(2,731)	(2,507)	(4,431)	(5,925)	(7,992)
Profit Before Tax (reported)	(2,731)	(2,507)	(4,431)	(5,925)	(7,992)
Tax benefit	0	0	0	0	0
Profit After Tax (norm)	(2,731)	(2,507)	(4,431)	(5,925)	(7,992)
Profit After Tax (reported)	(2,731)	(2,507)	(4,431)	(5,925)	(7,992)
Average Number of Shares Outstanding (m)	1,449.0	2,069.0	2,610.1	3,207.4	3,559.8
EPS - normalised (c)	(0.19)	(0.12)	(0.17)	(0.18)	(0.22)
EPS - diluted (c)	(0.19)	(0.12)	(0.17)	(0.18)	(0.22)
Dividend per share (A$)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	6,623	6,623	6,836	6,587	6,347
Intangible Assets	6,600	6,600	6,336	6,082	5,839
Tangible Assets	3	3	480	484	487
Investments	20	20	20	20	20
Current Assets	2,913	6,054	9,328	22,748	14,996
Stocks	0	0	0	0	0
Debtors	1,313	1,220	1,486	2,456	3,336
Cash	1,583	4,814	7,821	20,272	11,640
Other	18	20	20	20	20
Current Liabilities	(694)	(297)	(297)	(297)	(297)
Creditors	(657)	(232)	(232)	(232)	(232)
Short term borrowings	0	0	0	0	0
Other	(36)	(65)	(65)	(65)	(65)
Long Term Liabilities	(985)	(985)	(985)	(985)	(985)
Long term borrowings	0	0	0	0	0
Other long term liabilities	(985)	(985)	(985)	(985)	(985)
Net Assets	7,857	11,395	14,882	28,052	20,059
CASH FLOW					
Operating Cash Flow	(3,089)	(2,708)	(4,482)	(6,623)	(8,735)
Net Interest	39	35	48	78	203
Tax	0	0	0	0	0
Capex	(71)	(2)	(477)	(100)	(100)
Acquisitions/disposals	0	0	0	0	0
Equity Financing	2,735	5,928	7,918	19,095	0
Dividends	0	0	0	0	0
Other	(20)	(0)	0	0	0
Net Cash Flow	(385)	3,253	3,007	12,451	(8,632)
Opening net debt/(cash)	(1,957)	(1,583)	(4,814)	(7,821)	(20,272)
HP finance leases initiated	0	0	0	0	0
Other	11	(21)	0	0	0
Closing net debt/(cash)	(1,583)	(4,814)	(7,821)	(20,272)	(11,640)

Source: Edison Investment Research, Imugene accounts

Contact details	Revenue by geography
Level 3 62 Lygon St Carlton VIC 3053 Australia +61 3 9824 5254 www.imugene.com	N/A

Board and Management	
MD and CEO: Leslie Chong	**Executive chairman: Paul Hopper**
MS Chong has over 20 years of oncology experience in Phase I – III of clinical program development, including leadership role involvement in two marketed oncology products. She was previously Senior Clinical Program Lead at Genentech, Inc., in San Francisco. Genentech is widely regarded as one of the world's most successful biotech companies with a strong oncology franchise including the best-selling breast cancer drug Herceptin.	Mr Hopper has international & ASX biotech capital markets experience, particularly in immuno-oncology & vaccines. He is former Chairman of Viralytics (sold to Merck for $500m), Founder & Director of Prescient, Founder of Imugene & Polynoma LLC, former Director pSivida, Somnomed & Fibrocell Science.
Chief technology officer: Dr Nick Ede	**Non-executive director: Dr Axel Hoos**
Dr Ede has over 25 years' peptide vaccine and drug development. He was formerly CEO of Adistem and CEO of Mimotopes. Prior to that he was VP Chemistry at Chiron (now Novartis), and has been a Research Fellow at the CRC for Vaccine Technology.	Dr Axel Hoos is Senior Vice President and Head of Oncology at GSK. Before his current role, he was at Bristol-Myers Squibb where he was Medical Lead for the development of the Yervoy, the first survival-improving medicine in immuno-oncology. He is Chairman of the Board of the Sabin Vaccine Institute and Co-Chair of the Cancer Immunotherapy Consortium Think-Tank.
Vice President of Clinical Research: Dr Anthony Good	**Non-executive director: Charles Walker**
Dr Good has over 20 years global clinical development experience. He was integral to the development of significant new medicines including Viagra, Revatio, Lipitor, and Somavert. He formerly held roles with Pfizer Global Research and Development, and with Covance Clinical Services.	Mr Walker is an experienced listed biotech CEO and CFO, He is experienced in financial markets including executing 55 international tech corporate transactions. His clinical experience includes managing pipeline of drugs in all stages from discovery, through to Phase III and to launched products.

Principal shareholders	(%)
Private portfolio managers	7.1
Platinum Asset Management (Australia)	5.6
Paul Hopper	2.1

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