EDISON

Imugene

Clinical trial mid-2016

Anti-tumour vaccine trial to start mid-2016

Pharma & biotech

Imugene will test its reformulated therapeutic cancer vaccine, HER-Vaxx, in gastric cancer at trial sites in Asia. The Phase Ib/II trial is expected to start in mid-2016. HER-Vaxx aims to replicate or improve on the combination of two proven therapeutic antibodies, Herceptin and Perjeta (Roche). Imugene aims to gain a major pharma deal following Phase II data in the buoyant cancer immunotherapy area. A$3.0m raised in October gives it sufficient funds to undertake the Phase Ib component of the trial.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
06/15	0.6	(2.0)	(0.17)	0.0	N/A	N/A
06/16e	0.8	(2.4)	(0.15)	0.0	N/A	N/A
06/17e	0.8	(2.5)	(0.14)	0.0	N/A	N/A
06/18e	0.9	(2.5)	(0.15)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments.

Phase Ib/II gastric cancer trial to be based in Asia

Imugene is moving its upcoming Phase Ib/II study to trial sites in Asia. The previous strategy had been to do the trial in Australia and Eastern Europe, but government plans to subsidise Herceptin treatment for HER2 positive gastric cancer patients would have made recruitment in Australia difficult. Novotech has been appointed as the CRO to manage the trial at a number of leading cancer centres in Asia. The level of HER2 antibodies produced after treatment with HER-Vaxx will be measured in the Phase Ib trial, which will be an important pointer towards potential efficacy.

Improved HER-Vaxx formulation

Imugene's new HER-Vaxx formulation uses the vaccine carrier protein CRM_{197} plus an adjuvant, in place of the virosomes used in previous formulations. This new formulation is easier to manufacture and stimulates faster immune responses and greater antibody production than the original vaccine. A patent application filed in April based on the new formulation could extend IP protection by six years to 2036.

HER2 antibodies known to boost cancer survival

HER-Vaxx aims to stimulate a strong antibody response targeting normal HER-2 proteins, which are overexpressed in ~20% of breast and gastric cancer patients and are a proven cancer target. In a previous Phase I conducted with the original formulation in 10 breast cancer patients, eight developed antibodies against HER2. Global gastric cancer incidence is 952,000 cases with few therapeutic options and low survival. A potent vaccine would be a major advance in gastric cancer therapy.

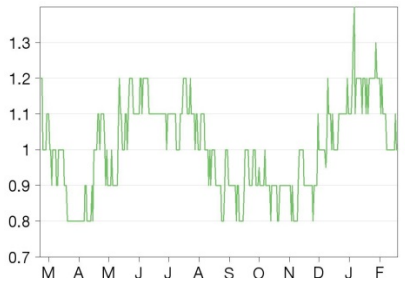
Valuation: Modest rise to A$56m

The additional cash from the recent capital raise sees our valuation increase slightly to A$56m (3.2c/share) from A$53m, with the impact on valuation of a 12-month later expected launch date offset by the likely extension of market exclusivity to 2036. The additional shares and options in issue following the capital raise and issue of loyalty options sees our diluted per share valuation fall to 2.9c per share (vs 4.1c). Pro forma cash is A$4.9m following the A$3m capital raise in October.

19 February 2016

Price	**A$0.01**
Market cap	**A$17m**
	US$0.72/A$
Net cash* (A$m) at 30 September 2015 *Pre-capital raise	1.3
Shares in issue	1,732.1m
Free float	69%
Code	IMU
Primary exchange	ASX
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(9.1)	11.1	11.1
Rel (local)	(11.5)	14.2	29.4
52-week high/low	A$0.01		A$0.01

Business description

Imugene is developing HER-Vaxx, a proprietary HER2 +ve cancer vaccine. A Phase Ib dose-finding study is planned in gastric cancer starting in mid-2016 with a randomised Phase II follow-on study in 68 patients.

Next events

File HER-Vaxx IND	Q116
Initiate HER-Vaxx Phase Ib trial	mid-2016
Phase Ib data	Mid 2017

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Edison profile page

Imugene is a research client of Edison Investment Research Limited

Investment summary: Immune therapy play

Company description: Anti-tumour vaccine effect

Imugene is an Australian biotechnology company developing HER-Vaxx, a gastric cancer vaccine. The company is currently a pure-play, one-product, one-trial-focused cancer opportunity in the highly valuable area of cancer immunotherapy. If the proposed Phase Ib/II study shows a strong efficacy signal, data possibly in H219, it might enable a major deal with a big pharma company. The global market for gastric cancer is over 900,000 patients annually.

Valuation: A Phase II deal is the goal

If its Phase II succeeds, HER-Vaxx could gain a big pharma partner. Assuming an A$25m upfront, a regulatory milestone of A$50m with potential royalties of 12% starting in 2025 and ending in 2036 (due to 12 years of data exclusivity for biologicals in the US and the likelihood of additional patents based on the new HER-Vaxx composition), Imugene has an indicative value on discounted cash flow of A$56m. This assumes a Phase Ib/II probability of reaching the market of 20% and a 30% probability of a 2020 licensing deal. Our standard 12.5% discount rate is used. Imugene is assumed to pay 18% royalties to Biolife, based on Imugene revenues, until 2030. Our valuation is equivalent to 2.9c per share, including dilution for 480m options on issue. Note that most of the options are currently out of the money.

Financials: Cash to initiate Phase Ib

Imugene reported an operating loss of A$2.4m in FY15. We forecast operating losses of A$2.6m in FY16 and FY17. In September 2015 the company announced an A$3.0m placement (400m shares issued at 0.75c per share with 200m attached options at 1.5c per share, expiring 31 March 2017). The cash balance at 30 September 2015 (the end of Q116) was A$1.3m. End-September pro forma cash was ~A$4.9m including net capital raise proceeds and a A$0.8m R&D incentive payment received in October 2015. Operating and investing cash outflow for the first quarter of FY16 was A$0.7m. Current funding is sufficient to initiate the Phase Ib/II trial, but further funding will be needed to complete it. Additional illustrative long-term debt of A$3m in each of 2017e and 2018e is included to represent this. If instead of debt the A$6m was raised as equity at a 10% discount to the current share price, our diluted valuation would decline to 2.5c per share.

Sensitivities

The major potential value inflection point for investors would come if the Phase II trial produces strong data to enable a big pharma licensing deal (with an upfront fee) that covers Phase III costs. Before such time, it may be of interest to potential partners if the Phase Ib shows evidence of potential efficacy (cellular plus humoral immune response, generation of anti-HER2 antibodies). In October 2014 BMS paid US$50m for an option to acquire Austrian biotech F-star Alpha, and its Phase I-ready bi-specific antibody drug targeting HER2-positive cancers; total deal value could reach US$475m if the drug is approved in the US and Europe. However, there is no guarantee that Imugene will succeed in partnering, and the company would require additional funds to complete the Phase II trial, as outlined above.

Uncertainties arise as any survival gain in gastric cancer is not known, but may be smaller than that achieved in breast cancer as the Herceptin gain was smaller. It is unclear how effectively HER-Vaxx can be combined with chemotherapy in Phase II as vaccine responses take time to develop. Royalties are hard to forecast accurately since most gastric cancer patients are in Asia and therapeutic options may broaden over the next eight years as other trials report data.

Company description: Gastric cancer vaccine focus

Imugene is an Australian biotechnology company developing HER-Vaxx, a gastric cancer vaccine that aims to stimulate production of high levels of polyclonal antibodies against HER2. HER2 is a well understood cancer target that is expressed at high levels in about 15-25% of breast and gastric[1] cancers; it is targeted by the approved monoclonal therapeutics Herceptin (trastuzumab, Roche) and Perjeta (pertuzumab, 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. HER-Vaxx aims to replicate and improve on the Perjeta-Herceptin combination for patients with HER2-positive cancers. Management sees gastric cancer as a faster indication to develop, relative to breast, with a large potential gastric cancer market and high unmet medical need. Global gastric cancer incidence is 952,000 cases with few therapeutic options and low survival.

Imugene acquired the HER-Vaxx technology in December 2013 through the purchase of 100% of Biolife Science Qld for 300m issued shares valued at A$4.5m (A$0.015/share). The technology originated from the Medical University of Vienna, one of Europe's leading cancer institutes. Imugene has raised ~A$9m since late 2013 at prices ranging from 0.75-1.0c per share to fund the HER-Vaxx strategy.

Herceptin reimbursement and market opportunity prompted switch to Asian trial sites

Australia's Pharmaceutical Benefits Advisory committee (PBAC) recommended at its July 2015 meeting that the treatment of HER2-positive gastric cancer should be subsidised under the Pharmaceutical Benefits Scheme (PBS). Widespread access to an approved targeted therapy such as Herceptin would have made it difficult to recruit HER2-positive patients for the HER-Vaxx trial in that country, as previously planned.

Asia represents the largest target market for gastric cancer therapies. Of the 952,000[2] 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.

In addition to the high incidence of gastric cancer in Asia, many patients in Asian countries do not have ready access to Herceptin. The combination of these factors means that it makes sense to conduct the Phase Ib/II trial in Asia, where there is a large pool of suitable patients from which to recruit subjects for the trial.

The clinical research organisation (CRO) Novotech was appointed in December to manage the trial, which will recruit patients at a number of leading cancer centres in Asia. Novotech is based in Sydney, Australia, and has a particular focus on the Asia-Pacific region.

Final preparations for Phase Ib gastric cancer trial

Imugene is putting in place the finishing touches as it prepares to initiate the Phase Ib trial of HER-Vaxx in patients with gastric cancer in mid-2016. The trial design is largely complete and an Investigational New Drug (IND) application will be submitted to the US FDA in early 2016. Manufacture of the reformulated vaccine is on track to produce clinical doses of HER-Vaxx well ahead of trial commencement.

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

2 http://globocan.iarc.fr

The Phase Ib lead-in trial will test three different doses of the reformulated HER-Vaxx in 18 patients (three groups of six) in combination with 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;
- monitor immune responses to the vaccine; and
- compare booster vaccination every four weeks vs every eight weeks.

The Phase Ib trial 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 progression-free survival and overall survival.

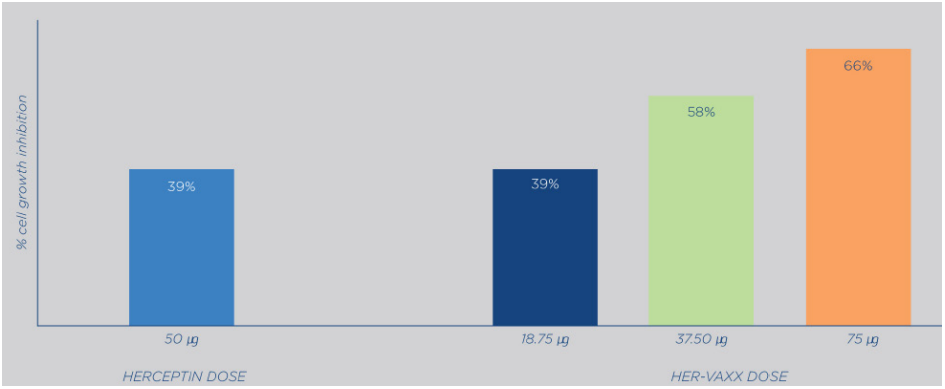
Monitoring patient immune responses will give an indication of potential efficacy

Imugene will closely monitor the immune responses that patients generate following administration of HER-Vaxx in the Phase Ib trial, to determine whether the patient's immune system is being 'turned on' to produce the desired anti-HER2 polyclonal antibodies. The level of anti-HER2 antibodies that patients produce following vaccination will be an important indicator of the potential for the treatment to be an effective anti-cancer therapy.

Data from previous preclinical studies showed that polyclonal antibodies produced following vaccination with HER-Vaxx were more potent than the marketed monoclonal antibody (mAb) Herceptin at inhibiting the growth of breast cancer cells. Exhibit 1 shows that less than half the dose of HER-Vaxx-stimulated antibodies was required to inhibit cancer cell growth to the same degree as Herceptin; 18.75µg of polyclonal antibodies isolated from the serum of rabbits that had been immunised with HER-Vaxx inhibited the growth of breast cancer cells to the same degree (39%) as 50µg of the monoclonal antibody Herceptin.

While immune responses are not direct evidence of efficacy, they will be important early data to provide to potential pharma partners because we can infer that if HER-Vaxx can stimulate high levels of antibody production, it could potentially match or exceed the efficacy of Herceptin.

Exhibit 1: HER-Vaxx antibodies are more potent than Herceptin at inhibiting breast cancer cell growth in vitro



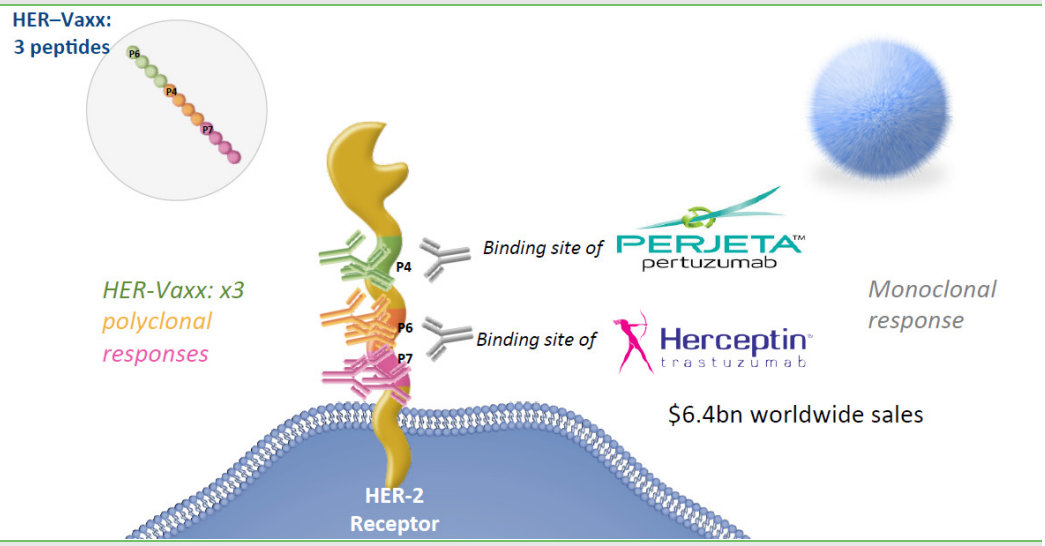
Source: Company announcement. Note: Chart reproduced by Imugene from patent EP 1 844 788 A1, fig 7&8. Data previously published in Wagner et al, Breast Cancer Res Treat (2007) 106:29-38.

New formulation stimulates stronger immune responses

HER-Vaxx is designed to produce antibodies against the HER2 receptor, a growth signal receptor protein found on the cell surface that is overexpressed in many cancers. 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. These peptides cover the Herceptin (P6 and P7) and Perjeta (P4) binding sites, as shown in Exhibit 2. 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 HER-Vaxx and binding to the P4, P6 and P7 sites on the HER2 molecule would act in the same way. They may also trigger an immune response against the HER2-expressing cells, so called antibody-directed cell cytotoxicity (ADCC).

Exhibit 2: HER-Vaxx peptide contains Herceptin and Perjeta binding sites



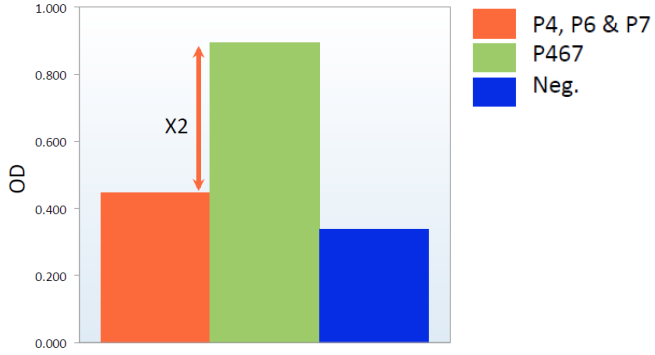
Source: Imugene investor presentation

The HER2 receptors that are expressed at abnormally high levels in many cancers are normal or 'wild-type' proteins that do not typically contain any mutations. These wild-type HER2 proteins would normally be tolerated as 'self' antigens and would not trigger an immune response. A key attribute for a successful HER-Vaxx vaccine will be its capacity to stimulate the production of enough antibodies to block the growth-promoting activity of the HER2 receptors. Imugene has made two important improvements to HER-Vaxx that would be expected to stimulate anti-HER2 antibody levels that were at least four times higher than seen in the Phase Ia breast cancer trial.

Fusing the three peptides doubles antibody responses

The original formulation of HER-Vaxx that was tested in a Phase I breast cancer trial contained the three separate P4, P6 and P7 peptides incorporated into a virosome, an artificial virus. Imugene has shown that synthesising all three peptides together as one long, straight peptide strand doubles the production of antibodies that bind to the target HER2 native protein, as shown in Exhibit 3. The company refers to the fusion peptide as P467.

Exhibit 3: Reactivity against native HER2 protein twice as great for fused P467 peptide

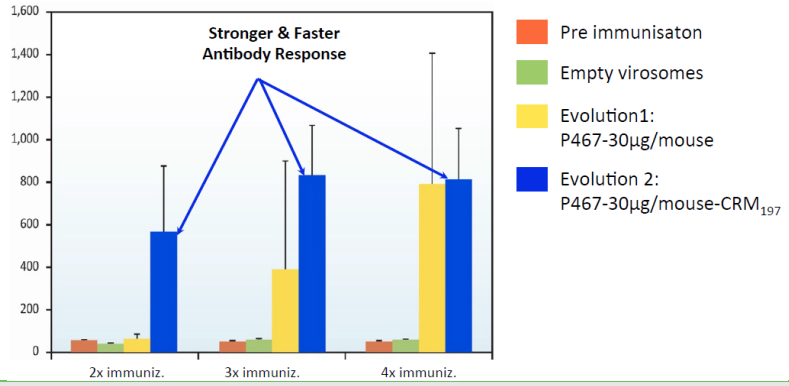


Source: Company presentation, 20 April 2015

New HER-Vaxx formulation stimulates faster and stronger immune responses

Imugene has made a second enhancement by replacing the virosomes used in previous formulations of HER-Vaxx with an existing, clinically and commercially validated vaccine carrier protein called CRM_{197} together with an adjuvant.

Exhibit 4: Early onset of response with new formulation – antibody levels against HER2 from P467 virosomes and P467 CRM_{197} conjugates



Source: Company presentation, 20 April 2015

Exhibit 4 shows that immunisation with the P467 fusion peptide conjugated with CRM_{197} leads to earlier HER2 antibody production (significant after two immunisations), with a peak response after three immunisations, compared with an earlier P467 virosome-based formulation of HER-Vaxx. After four vaccinations, the antibody levels stimulated by the CRM_{197} and virosome formulations were similar.

Advantages of the new CRM_{197} formulation include a notably faster and stronger immune response, a new patent filed that will extend IP coverage to 2036 vs 2030 at present, if granted, and a cheaper, simpler and more reliable manufacturing process.

HER2 biology

HER-Vaxx is designed to produce antibodies against the HER2 receptor, which is a member of the epidermal growth factor receptor (EGFR) family of growth signal receptors found on the cell surface. Only patients with high levels of HER2 achieve good results with Herceptin therapy. HER2 is quantified in cancer in in two ways.

- Fluorescence in-situ hybridisation (FISH) directly measures the number of copies of the HER2 gene. A 'normal' cell will have two copies, but HER2+ cancer cells often have multiple copies, so are FISH+.
- Immunohistochemical analysis (IHC) uses antibodies to detect the level of HER2 protein on the surface of the cells. This is expressed as normal (level 0) up to level 3. High levels correspond to over 1 million molecules per cell. Low or normal levels are less than 50,000 per cell.

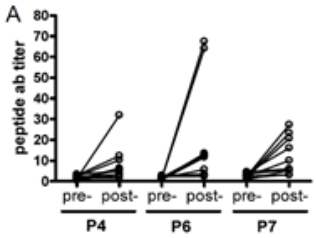
Previous HER-Vaxx clinical development

The previous Phase I trial of HERR-Vaxx was conducted in 10 patients with metastatic breast cancer. Results have been published and a detailed summary is in Exhibit 5. 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.

With the Phase Ib open-label gastric cancer study to start in mid-2016, results should be available in 2017. The Phase II trial is likely to take two to three years depending on recruitment and mortality. Assuming a H217 start, data could be available in H120. This could lead to partnering in

2020 and Phase III development from 2021. We have assumed it will take three years to complete Phase III studies and a year to gain regulatory approval with a possible 2025 launch.

Exhibit 5: HER-Vaxx Phase I data summary

Aspect	Outcome
Design	The Phase I open-label study was run in 10 HER2 IHC1 or IHC2 metastatic breast cancer patients. Patients were followed for 84 days in total. To avoid giving Herceptin, patients with IHC1 or IHC2 were selected and all were hormone responsive.
Dose	10µg of peptide in virosome injected intramuscularly on days one, 28 and 56. The last blood sample was taken on day 84.
Safety	There were no cardiovascular events reported. There were some minor localised injection site reactions. These are common in vaccines.
Antibody responses	Eight of the 10 patients developed anti HER2 antibodies (including one patient who already had low levels of auto anti HER2 antibodies. The seven responding patients with no prior HER2 antibodies all generated antibodies against each of the three peptides.
Responses to specific peptides	Each of the three peptides generated an antibody response, but longitudinal data across the cohort was not disclosed. There were some higher responders in each group, particularly two high P6 responses. This is a relative measurement so, for example, a level of 10 means that a patient has 10 times more HER2 antibody than a normal donor, who will probably have less than 1µg/ml. These values are not a guide to possible efficacy and they cannot be related to therapeutic monoclonal levels (Herceptin has a trough level of 63µg/ml in breast cancer and less than 48µg/ml was observed in gastric cancer). Perjeta has a trough level of 62.7µg ml. 
Regulatory T-Cells	Overall, there was a statistically significant drop in regulatory T-cells seen relative to normal donors (who also declined). Levels of other immune system cells were unaltered. The picture is complicated by the use of a virosome since this should activate the immune system.

Source: Edison Investment Research, based on Wiedermann U, et al 2010 [6]

Current HER2 antibody products

The clinical performance of current anti-HER2 monoclonal antibodies is given in Exhibit 6 and gives a benchmark for potential HER-Vaxx responses. Herceptin is a well-established therapeutic monoclonal antibody approved for use in IHC3+ patients. In clinical trials, the HER2 status of patients is very important.

Gastric cancer patients eligible for Herceptin therapy in the US and Western Europe should receive the therapy as standard of care.

Exhibit 6: Clinical data on approved HER2 antibodies

Cancer	Evidence
Herceptin in breast cancer	
Adjuvant therapy: early-stage IHC3+ or FISH+ node negative patients	Herceptin given after chemotherapy to patients in whom the cancer was still localised to the breast improved disease free survival, hazard ratio 0.54.
Advanced cancer: FISH+ and with 71% node positive	Herceptin was given alongside chemotherapy in patients where the cancer had reached the lymph nodes, but was not metastatic. The progression hazard ratio was either 0.67 or 0.60, depending on the chemotherapy regimen used.
Metastatic breast cancer	Overall time to progression was 7.2 months with Herceptin plus chemotherapy and 4.5 months with chemotherapy alone. IHC3+ patients had the best responses. The median overall survival secondary endpoint was positive, p=0.05.
Herceptin in gastric cancer	
Patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma.	The open-label study in 594 patients randomised 1:1 to Herceptin in combination with chemotherapy or chemotherapy alone. All patients were either HER2 overexpressing (IHC3+) or HER2 gene amplified (FISH+). The main outcome measure was overall survival (OS) – hazard ratio of 0.73 based on median OS of 13.5 vs 11.0 months, which was statistically significant. The final OS analysis (a year after the final trial analysis with 448 deaths) showed median overall survival of 13.1 months with Herceptin as against 11.7 months on only chemotherapy (HR 0.8).
Perjeta	
Patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.	Progression-free survival (PFS) increased with a median PFS of 18.6 months for the Herceptin with Perjeta combination as against 12.6 months for Herceptin alone. The hazard ratio of 0.62 was statistically significant. Final OS results showed that median OS was 40.8 months on placebo plus Herceptin arm and 56.5 months if patients received Perjeta plus Herceptin. The median difference was 15.7 months and statistically significant.
Perjeta in gastric cancer (Phase III)	In June 2013, Roche started a 780-patient Phase III overall survival study (NCT01774786) in HER2 positive gastric cancer. Patients receive 5-FU, capecitabine and cisplatin chemotherapy plus either the antibody combination or just Herceptin until disease progression. Target completion in March 2022. Preclinical data is supportive[2].
Kadcyla (trastuzumab emtansine)	
Herceptin resistant HER2+ patients after other therapy and if the disease reoccurs.	This is Herceptin coupled to a cytotoxic agent, mertansine. It improved median progression-free survival to 9.6 months from. 6.4 months. Median overall survival increased to 30.9 months vs 25.1 months.

Source: FDA Herceptin label, FDA Perjeta label, FDA Kadcyla label

The majority of metastatic breast cancer patients who respond to Herceptin develop resistance within one year of treatment. In the adjuvant setting, 15% of patients relapse despite Herceptin. In

patients resistant to Herceptin, Kadcyla (trastuzumab linked to the cytotoxic agent emtansine, Roche) is approved for use in metastatic breast cancer; a gastric trial is underway.

Competition

Gastric cancer is a major unmet medical need with ineffective chemotherapy and modest additional gain from Herceptin use. Exhibit 7 shows that a number of trials in HER2 are underway. Various tyrosine kinase inhibitors have been tried (dacomitinib, afatinib, lapatinib) but with limited results (not shown). NeuVax is a T-cell vaccine aimed at low HER2 patients, but with no gastric studies currently underway.[3] The major threat to HER-Vaxx is the Perjeta-Herceptin trial due in 2021.

The immune checkpoint inhibitor Opdivo (nivolumab, BMS) could be launched in the Japanese market by 2019, with possible later extension into the US and EU. Separately, Merck partnered with MacroGenics in November 2015 to conduct a Phase Ib/II trial of MacroGenics' margetuximab and Merck's Keytruda (pembrolizumab) for gastric cancer. Margetuximab is a mAb against HER2 (ie comparable to Herceptin and Perjeta) that has been optimised to increase killing of cancer cells by ADCC.

Herceptin costs US$4,500 a month, or US$54,000 a year. Perjeta costs US$5,900 a month, or about US$71,000 a year, and combination therapy with the two drugs costs US$125,000 per year. In the first nine months of 2015, Roche reported Herceptin sales of CHF4.9bn, up 10%. At current exchange rates, this is US$4.8bn for the period, annualised about US$6.4bn. Perjeta sales were up 66% at CHF1.0bn after the 2012 launch. This demonstrates that there is a large potential market for HER-Vaxx if it can match the efficacy of Herceptin and Perjeta.

Herceptin is threatened by the launch of biosimilars, with Biocon/Mylan and Celltrion/Hospira having already launched biosimilars in India and Korea, respectively. The European patent expired in July 2014 and the US patent expires in 2019. While this suggests that there may be a decline in Herceptin pricing and market value by the time HER-Vaxx enters the market (if successful) price falls are less aggressive for biologicals such as Herceptin than small molecule generics.

Exhibit 7: HER2 targeting or related gastric therapies in clinical development

Company	Product	Phase and NCT	Patients	Data	Action mode and notes
Galena with Genentech	NeuVax plus Herceptin	Ph II, NCT01570036	300	Dec 2016	T-cell vaccine. Early-stage node positive breast cancer low HER2. Disease-free survival endpoints.
Roche	Kadcyla	Ph II/II NCT01641939	412	Failed October 2015	Two doses compared to taxane therapy in three-arm adaptive open study. Failed OS primary endpoint.
Galena	NeuVax (nelipepimut-S)	Ph III NCT01479244	758	Apr 2018	T-cell vaccine. Early-stage node positive breast cancer low to intermediate HER2. Disease-free survival endpoints.
Ono /BMS	Nivolumab	Ph III (Japan) NCT02267343	480	August 2017	Anti-PD-1. Unresectable advanced or recurrent gastric cancer. FDA approved in melanoma and lung cancer.
Roche	Perjeta	Ph III NCT01774786	780	March 2022	In trial with Herceptin to see if combination extends survival as in breast cancer known Herceptin action.
Boston Biotech	BB1608	Ph III NCT02178956	680	Aug 2017	Oral small molecule blocking cancer stem cell – renewal and inducing tumour death cell.
MacroGenics with Merck		Ph I/II	N/A	Initiation Q116	Anti-PD-1 + anti HER2. Phase Ib/II trial of margetuximab and pembrolizumab for gastric cancer is planned to start Q116.

Source: www.clinicaltrials.gov, BioCentury, Edison Investment Research

Two potential competitors failed in clinical development in gastric cancer in 2015. Merrimack terminated developing its MM-111 bispecific antibody targeting HER2 and HER3 after a failed Phase II trial. Roche revealed in October that the Phase III trial of Kadcyla in gastric cancer failed to meet its primary endpoint to improve overall survival.

[3] NeuVax has one HER2 epitope designed to fit a particular HLA molecule: HLA-A2/A3. It is given with GM-CSF. This aims to trigger a CD8+ T-cell response in a genetically specific patient population, about 50-60% of cases. The trial design targets low HER2 patients so avoiding any direct competition with Herceptin.

Valuation

The additional cash from the recent capital raise sees our valuation increase slightly to A$56m (3.2c per share) from A$53m, with the impact on valuation of a 12-month later expected launch date offset by the likely extension of market exclusivity to 2036 (Exhibit 8). The additional shares and options in issue following the capital raise and issue of loyalty options see our diluted per share valuation fall to 2.9c per share (vs 4.1c). Note that most of the options are currently out of the money. The main changes to assumptions since our previous report are:

- updated global gastric cancer incidence from 2008 data (934,000) to 2012 estimate (952,000);
- deferred market launch by 12 months to FY25;
- deferred upfront and milestone payments by 12 months to FY20 and FY24 respectively;
- extended cash flow forecasts out to FY36 (vs FY32) due to 10 and 12 years' market exclusivity in the US and EU, respectively, and the potential for a patent on the P467/CRM_{197} formulation to extend IP protection to 2036;
- adjusted exchange rate to US$0.76 per A$ (was US$0.80); and
- dilution due to the A$3m placement in September and loyalty option issue.

Our valuation assumes a 20% likelihood of success and includes a A$25m deal upfront after Phase II (at a 30% probability) and a A$50m Phase III success milestone at a 20% probability.

Exhibit 8: Valuation table (based on Exhibits 9 and 10)

Discounted cash flow stream	Probability	Present value (A$m)
Value of net cash flow until 2036 (excluding upfront payments)	20%	44.9
Value of 2020 upfront and 2024 milestone (net of royalties)	30%	6.1
Pro forma cash at 30 June 2015		4.9
Total value		55.9

Source: Edison Investment Research

Exhibit 9: Valuation parameters

Key model assumptions	Value
HER2+ percentage of diagnosed patients[4]	20%
Percentage eligible for therapy	75%
US price (US$) per year	75,000
Royalty percentage from partner	12%
Share of IMU revenue payable to BSFE until 2030 (based on royalties and milestones received from partners)	18%
Upfront payment in 2020 (A$m)	25

Source: Edison Investment Research

Exhibit 10: Market data and non-adjusted cash flow in 2030

Market (US$ unless otherwise stated)	Cases	Eligible	Uptake (%)	Number treated	Price (US$000s)	Value ($m)
US	21,200	3,180	25	795	75.0	60
Western EU	62,240	9,336	40	3,734	60.0	224
Eastern EU	18,360	2,754	25	689	37.5	26
Eastern Europe and Russia	59,000	8,850	25	2,213	37.5	83
Japan	107,900	16,185	15	2,428	112.5	273
China	405,000	60,750	5	3,038	18.8	57
E Asia	40,000	6,000	2	120	18.8	2
other	238,300	35,745	2	715	18.8	13
Total	**952,000**	**142,800**				**738**
Sales in A$	Rate	US$0.76/A$				A$971
Royalty from partner to Imugene	Rate	12%				A$117
Share of Imugene income paid to BSFE (18%)						(A$21)
Potential Imugene profit after A$2m admin costs and 30% tax in 2030						A$66

Source: Market data references,[5,6] Edison Investment Research

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

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

We assume that peak sales of HER-Vaxx will reach US$740m in 2029, following market launch in FY25, and that the company receives a 12% royalty on net sales (Exhibits 8 and 9). We assume that sales peak in 2029, plateau for three years and decline by 5% pa after 2032, and that 18% of HER-Vaxx revenue received by Imugene up until 2030 (including upfront, milestone and royalty payments) is paid to BSFE,[7] the original owners of the HER-Vaxx IP. We have applied the key assumptions in Exhibit 9 to the market data in Exhibit 10 to give potential peak sales of ~US$740m.

Financials: Cash to initiate Phase Ib

Imugene reported an operating loss of A$2.4m in FY15. We forecast operating losses of A$2.6m in FY16 and A$2.7m FY17. In September and October 2015 the company raised A$3.0m (gross) in a placement (400m shares issued at A$0.0075/share plus 200m options expiring on 31 March 2017 with an exercise price of A$0.015 per share). In addition, 177m bonus loyalty options with the same terms were issued to existing Australia and New Zealand-based shareholders. The cash balance at 30 September 2015 (the end of Q116) was A$1.3m. Pro forma cash was ~A$4.9m including net capital raise proceeds and a A$0.8m R&D incentive payment received in October 2015. Operating and investing cash outflow for the first quarter of FY16 was A$0.7m. Current funding is sufficient to initiate the Phase Ib/II trial, but further funding will be needed to complete it. Illustrative additional long-term debt of A$3m in both 2017e and 2018e is included to represent this. If the A$6m was raised as equity at a 10% discount to the current share price, our diluted valuation would fall to 2.5c/share.

Sensitivities

The major potential value inflection point for investors would come if the Phase II trial produces strong data to enable a big pharma licensing deal (with an upfront fee) that covers Phase III costs. Before such time, possible partners may also take notice if Phase Ib shows evidence of potential efficacy (cellular plus humoral immune response, generation of anti-HER2 antibodies). In October 2014 BMS paid US$50m for an option to acquire Austrian biotech F-star Alpha, and its Phase I-ready bi-specific antibody drug targeting HER2-positive cancers; the total deal value could reach US$475m if the drug is approved in the US and Europe. This example highlights that potential partners may seek to acquire the company rather than enter a licensing deal. The double antibody action that HER-Vaxx aims to replicate, and perhaps improve on, is proven in breast cancer. In Phase I, in a non-target population, HER-Vaxx generated antibody responses against all three peptides. While these are strong positive indicators, there is no guarantee that Imugene will succeed in attracting a partner or additional funding at acceptable terms.

Uncertainties arise as it is unclear how effectively HER-Vaxx can be combined with chemotherapy in Phase II as chemotherapy could potentially inhibit the immune response to the vaccine. On the other hand, some chemotherapy agents, including cisplatin, have been shown to stimulate the immune system.[8] We note that patients in the upcoming Phase Ib/II trial of HER-Vaxx will be treated with cisplatin in combination with either capecitabine or 5-fluorouracil chemotherapy. The Phase I trial showed that patients treated with HER-Vaxx produced antibodies against HER2, but we do not yet know how the concentration of antibodies produced compares with the levels seen in patients treated with Herceptin or Perjeta. As the vaccine aims to stimulate an immune response against the normal HER2 protein that the immune system usually tolerates as 'self', the amount,

6 Ferlay, J. et al. Cancer incidence and mortality patterns in Europe. Eur. J. Cancer 49, 1374–403 (2013).
7 Bio Life Science Forschungs und Entwicklungsges mbH (BSFE, a company incorporated in Austria).
8 Biasi et al. Cisplatin induced antitumor immunomodulation. Clin Cancer Res; 20(21); 5384–91 (2014).

potency and duration of anti-HER2 antibody production will be an important indicator of likely efficacy.

Exhibit 11: Financial summary

A$000s	2015	2016e	2017e	2018e
Year-end 30 June	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	600	800	840	880
Cost of Sales	0	0	0	0
Gross Profit	600	800	840	880
EBITDA	(2,006)	(2,400)	(2,460)	(2,520)
Operating Profit (before GW and except.)	(2,006)	(2,400)	(2,460)	(2,520)
Intangible Amortisation	(274)	0	0	0
Exceptionals, share based payments	(199)	(200)	(200)	(200)
Other	0	0	0	0
Operating Profit	(2,479)	(2,600)	(2,660)	(2,720)
Net Interest	38	0	0	0
Profit Before Tax (norm)	(1,967)	(2,400)	(2,460)	(2,520)
Profit Before Tax (FRS 3)	(2,441)	(2,600)	(2,660)	(2,720)
Tax	0	0	0	0
Profit After Tax (norm)	(1,967)	(2,400)	(2,460)	(2,520)
Profit After Tax (FRS 3)	(2,441)	(2,600)	(2,660)	(2,720)
Average Number of Shares Outstanding (m)	1,176.5	1,611.5	1,732.1	1,732.1
EPS - normalised (c)	(0.17)	(0.15)	(0.14)	(0.15)
EPS - FRS 3 (c)	(0.21)	(0.16)	(0.15)	(0.16)
Dividend per share (c)	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	6,600	6,600	6,600	6,600
Intangible Assets	6,600	6,600	6,600	6,600
Tangible Assets	0	0	0	0
Other	0	0	0	0
Current Assets	2,515	2,743	3,158	3,513
Stocks	0	0	0	0
Debtors	541	541	541	541
Cash	1,957	2,185	2,600	2,955
Other	17	17	17	17
Current Liabilities	(397)	(331)	(331)	(331)
Creditors	(331)	(331)	(331)	(331)
Current loans	0	0	0	0
Other inc HER-Vaxx IP creditor	(67)	0	0	0
Long Term Liabilities	(985)	(985)	(3,985)	(6,985)
Long term debt	0	0	(3,000)	(6,000)
HER-Vaxx IP Creditor	0	0	0	0
Other long term liabilities	(985)	(985)	(985)	(985)
Net Assets	7,732	8,027	5,442	2,797
CASH FLOW				
Operating Cash Flow	(2,082)	(2,592)	(2,585)	(2,645)
Net Interest	38	0	0	0
Tax	0	0	0	0
Capex	(464)	0	0	0
Acquisitions/disposals	0	0	0	0
Financing	3,584	2,820	0	0
Dividends	0	0	0	0
Other funding	(342)	0	0	0
Net Cash Flow (ex-debt movements)	734	228	(2,585)	(2,645)
Opening net debt/(cash)	(1,223)	(1,957)	(2,185)	400
HP finance leases initiated	0	0	0	0
Other	0	(0)	0	0
Closing net debt/(cash)	(1,957)	(2,185)	400	3,045

Source: Edison Investment Research, company financial statements

Contact details	Revenue by geography
Suite 1, 1233 High Street Armadale VIC 3143 Australia +61 3 9824 5254 www.imugene.com	N/A

Management team

Executive chairman: Mr Paul Hopper	Chief Operating Officer: Ms Leslie Chong
Mr Hopper has served as managing director of Cappello Group, an investment bank, since November 2005, where he is both head of the Life Science/Biotech Group and the Australia desk. He is also the non-executive chairman of Viralytics.	MS Chong was appointed COO in September 2015. Previously, Ms Chong was a senior clinical program leader at Genentech 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.
Non-executive director: Dr Axel Hoos	
Dr Axel Hoos is vice president, oncology R&D at Glaxo Smith Kline Pharmaceuticals (GSK). Before his current role, he was at Bristol-Myers Squibb (BMS) where he developed the Yervoy monoclonal antibody in melanoma and other indications.	

Principal shareholders	(%)
Mr O Buttula	6.2
Mr P Hopper (chairman) (held via Kilinwata; Moreglade; Deborah Coleman)	4.1

Companies named in this report

Merck, Roche, BMS, Ono, Merimack, Boston Biotech, Galena, Merrimack

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