EDISON

Imugene

Initiation of coverage

Potent anti-tumour vaccine effect

Pharma & biotech

Imugene is progressing its gastric (stomach) cancer therapeutic vaccine, HER-Vaxx, into a Phase Ib/II. This aims to replicate and improve on the combination of two proven therapeutic antibodies, Herceptin and Perjeta (Roche), which significantly improves survival in breast cancer and may do so in gastric cancer. Global gastric cancer incidence is 934,000 cases with few current therapeutic options and low survival. In the HER-Vaxx Phase I, management observes that patient antibodies displayed potent anti-tumour activity with an immune response. Imugene has placed A$2.25m of shares and announced a share purchase plan to initiate Phase Ib/II, with the aim of progressing the study to gain a major pharma deal following Phase II data in the buoyant cancer immunotherapy area.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
06/14	511	(0.36)	(0.05)	0.0	N/A	N/A
06/15e	0	(1.30)	(0.12)	0.0	N/A	N/A
06/16e	0	(1.83)	(0.16)	0.0	N/A	N/A
06/17e	0	(1.84)	(0.16)	0.0	N/A	N/A

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

From breast to stomach

HER-Vaxx is based on science from the University of Vienna, a leading European cancer institute. HER-Vaxx comprises three linked peptides (protein fragments) delivered in a flu-based virosome. In the 10-patient safety Phase I in 10 breast cancer patients, eight developed antibodies against HER2, a proven cancer target. Management notes that patient antibodies displayed potent anti-tumour activity with an immune response. This potentially improves on the Herceptin and Perjeta combination that reduces the hazard ratio of death to 0.66 in breast cancer.

Gastric offers more opportunity and faster data

A potent vaccine would be a major advance in gastric cancer therapy. An 18-patient Phase Ib dose-finding study is planned from H215, followed by a Phase II in 68 patients. The data from this could create the basis for a deal. HER2 is overexpressed in up to 20% of gastric cancers and Herceptin is approved for use in combination with chemotherapy. Gastric cancer is poorly served by other therapeutic options; trials are faster to run than in breast cancer as median survival in metastatic gastric cancer is less than 12 months.

Valuation: Major market with Phase II deal potential

There are 934,000 new gastric cases globally each year; the US has 22,220 cases, the EU 80,600, with over 100,000 in Japan and about 400,000 in China. Edison estimates a DCF risk-adjusted indicative value of A$49.3m based on a 20% Phase II probability, including a A$25m deal upfront after Phase II (at a 30% probability) and a A$50m Phase III success milestone at a 20% probability. The immunotherapy area has recently seen sizeable overall deal values including large milestones. Cash was A$0.88m on 30 September 2014.

26 November 2014

Price	**A$0.01**
Market cap	**A$12m**
Cash (A$m) at 30 September 2014	0.88
Shares in issue (12 Nov 2014)	1,156m
Free float	50%
Code	IMU
Primary exchange	ASX
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(9.1)	(33.3)	(50.0)
Rel (local)	(7.8)	(29.4)	(49.8)
52-week high/low	A$0.02	A$0.01	

Business description

Imugene restructured into a cancer vaccine business with the acquisition of HER-Vaxx, a proprietary HER2 +ve cancer vaccine, in December 2013. A Phase Ib dose study is planned in gastric cancer starting in mid-2015 with a direct Phase II follow-on study in 68 patients.

Next events

Phase Ib start	Q215
Interim results	Q115
FY15 results	Q315

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Edison profile page

Investment summary: Potent anti-tumour vaccine effect

Company description: Pure immune therapy play

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 II study shows a strong efficacy signal, data possibly in H218, 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 thing

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 2022-23 and ending in 2032-34 (due to biological patent life extensions and data protection), Imugene has an indicative value on discounted cash flow of A$49.3m. This assumes a Phase Ib/II probability of reaching the market of 20% and a 30% probability of a 2019 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.

Financials: Fund-raising to initiate Phase Ib/II

Imugene raised A$2.6m in FY14 (to 30 June) to fund initial HER-Vaxx development and preparation for the clinical trial. In December 2013, Biolife was acquired for A$4.5m in equity (300m shares at A$0.015 each). The previous focus, a drug delivery technology (Linguet) has a A$0.3m carrying value and is not being developed further, although patents are being maintained. Overall intangible assets are A$6.9m, of which 96% is now attributed on a fair value basis to HER-Vaxx.

Cash was A$883k on 30 September 2014. The completed funding of A$£2.25m gross is presumed to be sufficient to initiate the Phase Ib/II study. A share purchase plan is underway, but will not be included in our estimates until completed. Further funding is likely to be needed to complete Phase II and gain a deal. An A$2m illustrative funding has been included in 2017 financial estimates to reflect this. Revenue in FY14 comprised an R&D tax rebate of A$0.5m and some interest income. As most Phase II costs will be outside Australia, no R&D tax rebates have been forecast.

Sensitivities: Antibodies to replicate proven activity

The nearest major value inflection point for investors is if Phase II produces strong data to enable a big pharma licensing deal (with an upfront fee) that covers Phase III costs. In 2013, AstraZeneca paid US$225m plus milestones of US$275m for Amplimmune's Phase I PD-1 antibody. This shows the potential value of a proven immune approach, although in the very dynamic T-cell therapy area. The double antibody action that HER-Vaxx aims to replicate and improve on is proven in breast cancer. In Phase I, in a non-target population, HER-Vaxx generated antibody responses against all three peptides. These are strong positive indicators. The Phase Ib study may provide valuable additional data and insight into HER-Vaxx; as it is open label, data will become available as they emerge.

Uncertainties arise as any survival gain in gastric cancer is not known, but will probably 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.

For information, Edison notes that the chairman, Mr Hopper, received 68.3m Imugene shares (A$1m at A$0.015/share) in connection with the Biolife acquisition. This was approved by shareholders on 20 December 2013.

Company description: Gastric cancer vaccine focus

Imugene is an Australian biotechnology company developing HER-Vaxx, a gastric cancer vaccine. In December 2013, Imugene refocused with the acquisition of 100% of Biolife Science Qld for 300m issued shares valued at A$4.5m (A$0.015/share).[a] This and a royalty-free deal with the Swiss company Pevion Biotech secured the intellectual property on HER-Vaxx (see below). Imugene was a drug delivery company, but has mostly written down the value of those IP assets. Imugene raised A$2.5m in late 2013 to fund the new strategy. A further A$2.25m placing was announced on 6 November 2014 and a share purchase plan at A$0.01/share is open until 28 November.

HER-Vaxx began as an innovative academic concept from the University of Vienna. The HER-Vaxx vaccine targets HER-positive patients; HER is a well understood cancer target found at high levels in about 15-25% of breast and gastric 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. Management sees gastric cancer as a faster indication to develop, relative to breast, with a large potential market and high unmet medical need.

HER-Vaxx and HER2 biology

HER-Vaxx is designed to produce antibodies against the HER2 receptor, a growth signal sensing receptors protein found on the cell surface, Exhibit 1.

Exhibit 1: Biological aspects

Key biological feature	Detailed comments
HER receptor family	HER2 (also called Her-2 /neu or ErbB-2) is a member of the epidermal growth factor receptor (EGFR) family. There are four family members: HER1, HER2, HER3 and HER4. The main family member is HER1, also called epidermal growth factor receptor (EGFR, also called ErbB-1).
What does HER do?	The HER receptors activate a major growth pathway known as the mitogen activated protein kinase system (MAPK). This is an amplified internal cell signalling chemical cascade, which creates a very strong cell growth signal. Cancer cells with more than normal HER2 (called over expressing) are strongly stimulated to grow and divide.
How does it function?	Until HER1, HER3 and HER4 bind to a molecule of growth factor, they remain in an inactive, closed shape. Growth factor binding opens the HER structure to expose a dimerization site. Another active receptor then needs to bind to give an active complex (see http://www.biooncology.com/research-education/hdis/her2-breast-cancer for an animation).
Why is HER2 different?	HER2 is the odd one out member of the EGFR family because it does not bind to any growth factors and exists permanently in an active, open state. Its role is to be the fast partner for activated ligands like HER1 (this binds most growth factors) and HER3.
What does HER3 do?	HER3 is stated in the literature to be an important in cancer as it activates two pathways – the growth MAPK and the survival PI3K pathways. HER1 only activates MAPK. HER3 binds a specialised set of growth factors, like neuregulins, normally associated with growth and repair of the heart and nervous system. When both MAPK and PI3K are activated, cancer cells grow and are less likely to be killed by therapy. However, breast cancer studies have been ambivalent about HER3 as a prognostic marker.
Which are the most important receptors?	Most signalling is from HER1-HER2 dimers activated by growth factors like EGF with a relative potency of 5 (1 is low, 10 is high). The most potent dimers are HER2-HER3 complexes with the highest potency of 10.5. HER1-HER1 homodimers have a relative activity of 3.2. This emphasises the importance of HER2 as it gives the strongest growth signal at low concentrations of growth factors.
Immune response to HER2+ cancer.	Many breast cancer patients develop antibodies against HER2. One 311 patient study found 18% of breast cancer patients had detectable levels HER2 autoantibodies.[1] These can block dimerization of HER2.
How is HER2 measured?	Only patients with high levels of HER2 get good results with Herceptin therapy. HERs 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 molecules per cell. This is more useful as it relates to the number of targets on a cancer cell.

Source: Edison Investment Research

HER-Vaxx contains three peptides that stimulate the patient's immune system to produce antibodies against the P4, P6 and P7 sites on HER molecule (see diagram). These peptides cover

[a] Acuvax Ltd tried to acquire Biolife in Q213. Mr Hopper, now a director of Imugene, was associated with this proposed transaction and was a director and COO of Biolife at that time. This lapsed transaction is separate from the successful acquisition of Biolife by Imugene and the terms of the Imugene acquisition differ.

the Herceptin and Perjeta binding sites. This antibody combination has shown synergistic effects in gastric cancer preclinical studies.[2]

Peptide 4 (P4) is from the region responsible for dimer formation. This is in the area bound by the therapeutic antibody Perjeta. If an antibody binds here, HER2 cannot link to activated HER1 or HER3 so the growth signals are not triggered.

Peptides P6 and P7 are from the area where Herceptin binds. Herceptin does not prevent dimerization, but it does prevent the activation of the receptor.

If HER-Vaxx can create a strong polyclonal antibody response against these sites, it ought to have similar effects to the clinical combination of Perjeta and Herceptin. A further mode of action is that the antibodies mark HER2+ cells for destruction by the white cells of the immune system, so called antibody-directed cell cytotoxicity (ADCC).

Current HER2 antibody products

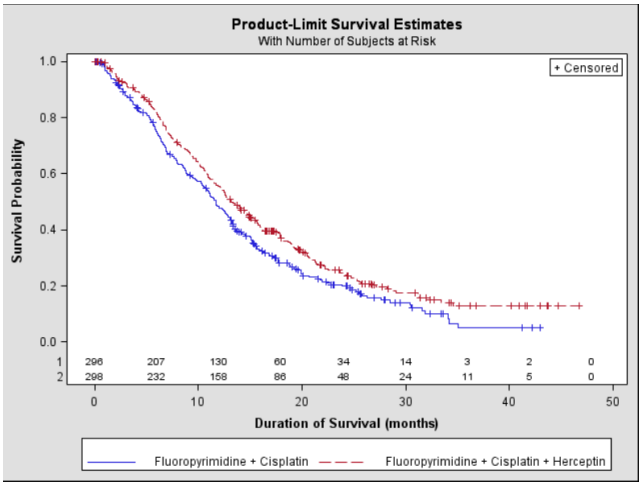
The clinical performance of current anti-HER2 monoclonal antibodies is given in Exhibit 2 and gives a benchmark for potential HER-Vaxx responses. Herceptin is a well-established therapeutic monoclonal antibody approved for use in IHC3+ patients, Exhibits 2, 3 and 4. In clinical trials, the HER2 status of patients is very important (see Exhibit 1 for IHC and FISH definitions).

Exhibit 2: 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 only chemotherapy. The patients who had the best responses were IHC3+. Patients with both IHC3+ and FISH+ responded best to Herceptin. The chemotherapy regimen was important: the TTP for doxorubicin/epirubicin and cyclophosphamide being superior (7.6 months with Herceptin vs 5.7 months without) to paclitaxel (6.7 months with Herceptin vs 2.5 months without). 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 study was open label in 594 patients randomised 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine like 5-fluorouracil (FC+H) or chemotherapy alone (FC). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC3+). Herceptin was given every 3 weeks until disease progression. The main outcome measure was overall survival (OS). The trial analysis used for approval had 351 deaths and a 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. The hazard ratio was 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 survival 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 as against. 25.1 months.
Cardiotoxicity – a known risk factor	
Herceptin therapy carries an FDA Black Box warning due to the risk of cardiomyopathy and Congestive Heart failure (CHF) where the heart becomes distended.	The biochemical reasons for this are still debated in the literature.[4] The rates of cardiotoxicty for Herceptin as a single agent are low: up to 7% if aggregated across several studies. In combination with doxorubicin, the rate jumps to 28%. Doxorubicin has very well characterised cardiotoxicity. It is possible that Herceptin blocks cardiac regeneration after chemotherapy damage. Herceptin might also affect cardiac regeneration by cardiac stem cells.

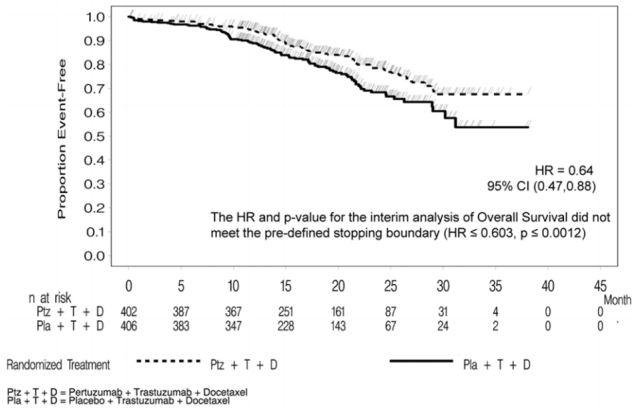
Source: FDA Herceptin label, FDA Perjeta label, FDA Kadcyla label

Exhibit 3: Herceptin overall survival in metastatic gastric cancer



Source: Herceptin FDA label

Exhibit 4: Perjeta overall survival analysis in breast cancer combined with Herceptin



Source: Perjeta FDA label

The use of Herceptin for gastric cancer creates potential trial design problems for HER-Vaxx development in the US. Herceptin is believed to be less used in the EU for gastric cancer but, for example, it is recommended in the UK for IHC3 patients as being cost effective. Consequently, gastric cancer patients eligible for Herceptin therapy in the US and Western Europe should receive the therapy as standard of care. This would make it hard to see any therapeutic response to HER-Vaxx without a Herceptin-only arm.

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. Cells can shift to other growth factors, like HER3 and HER4 or to other mechanisms entirely.[3] In patients resistant to Herceptin, Kadcyla (trastuzumab emtansine, Roche) is approved for use in metastatic breast cancer; a gastric trial is underway.

HER-Vaxx development

HER-Vaxx aims to generate an antibody and perhaps T-cell immune response against cancer cells. Natural antibody responses are polyclonal and might have higher potency. For clinical use, all three peptide sequences (P4, P6 and P7) are synthesised as one long, straight peptide strand. To get an immunogenic response, this long peptide is incorporated into a virosome, an artificial virus. This is not infective, but it carries haemagglutinin H1, a protein found on the surface of influenza virus that enables the virus to enter cells. The virosome is attacked as a virus by the immune system.

Preclinical models indicate that successful reduction of HER2 tumours by vaccination requires both antibody and T-cell responses.[b] As the authors of the HER-Vaxx paper observe, “Several studies in experimental models including our own preclinical data have demonstrated that successful reduction of Her2/neu overexpressing tumours after vaccination requires both humoral and cellular

[b] A cellular response requires T-cells to learn to recognise cancer cells as “non-self”. T-cells detect specific short peptides presented on the surfaces of cells. The HER-Vaxx peptides appear to be optimised for antibody rather than T-cell use. The NeuVax candidate from Galena (Phase III) is designed as a T-cell peptide has shown that T-cell activation can happen.[12 5] Note that the immune system is strongly controlled by regulatory T-cells to prevent attacks on “self” cells. Because of the success of Yervoy (ipilimumab, BMS) in melanoma and the clinical trial results with the new generation of checkpoint inhibitors, immune strategies against cancer have become valuable. In gastric cancer, Ono Pharmaceuticals is running a Phase III study with nivolumab, a promising anti PD-1 checkpoint inhibitor being developed in other indications by BMS. These therapeutics relax the tight regulatory T-cell control so the immune system ceases to tolerate the cancer as “self” and so attacks it.

immune responses".[6] Economically, a vaccine might require fewer injections and be cheaper to produce, offering greater pricing flexibility.

Gastric cancer has been selected since a breast cancer trial would be prolonged (4-5 years at least) and need more patients, costing more, to see an effect as the disease is less aggressive and mortality lower. In addition, Herceptin is now the standard of care for HER2 positive patients and it will be very difficult to get a clear HER-Vaxx outcome if monoclonal antibody therapy is also offered.

Gastric cancer is a more aggressive and difficult disease with better treatment options urgently needed. It also offers a substantial market and HER2 is a major risk factor.[7] It is theoretically possible that the combined Herceptin-Perjeta combination vaccine effect offered by HER-Vaxx will be superior to Herceptin. As yet, the Herceptin-Perjeta combination is not proven in gastric cancer. Roche is now running a large Phase III to test the hypothesis following an unpublished Phase II.

It is not possible to know yet if HER-Vaxx has any chronic toxicity. Herceptin and Perjeta have been given for over a year to patients in clinical trials and Herceptin has low toxicity in the absence of chemotherapeutic agents. A small HER2 vaccine trial with a five-year follow up found no toxicity.[5]

HER-Vaxx Phase II progression

Phase I was in 10 patients. Results have been published and a detailed summary is in Exhibit 5. The main conclusion identified by the lead investigator[c] 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. Management notes that antibodies induced potent anti-tumour activity. [d]

To produce HER-Vaxx for the new clinical trials, Imugene has retained two specialist companies: Bachem, a specialist in clinical grade peptides, will synthesise the triple peptide, and Mymetics, the Swiss-based virosome specialist, will produce the final virosome -based vaccine.

Phase I did not test dosing. The initial Phase Ib open-label study being planned will recruit three cohorts of six patients each to test three undisclosed doses. If this starts in H215, results should be available in early 2016. The trial will then move to a placebo-controlled, double-blind randomised Phase II study with 68 patients, 34 in each arm.

The Phase II trial is likely to take two to three years depending on recruitment and mortality. Assuming a H116 start, data could be available in H218. That could lead to partnering in 2019 and Phase III development from 2020. We have assumed a three-year period to complete Phase III studies and a year to gain regulatory approval with a possible 2023-24 launch. The endpoints will be progression-free survival and overall survival. It is likely that it will recruit IHC3+ patients with metastatic disease. Centres will be in Eastern Europe and Australia. The trial will offer "standard of care" to all patients.[e] In the ongoing Phase III Perjeta-Herceptin gastric study, patients receive 5-FU, capecitabine and cisplatin chemotherapy, as standard of care.

Gastric cancer: Where and how many cases?

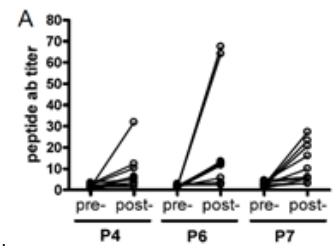
989,600 new stomach cancer cases and 738,000 deaths are estimated to have occurred globally in 2008.[8]

[c] Conference call with Professor Ursula Wiedermann, October 2014.

[d] Investor presentation, 5 November 2014, on ASX website (ASX link).

[e] According to the US National Cancer Institute (gastric cancer) the usual treatment is an epirubicin, cisplatin and 5-FU (ECF) combination. In ECF, oxaliplatin and capecitabine are often substituted for cisplatin and 5-FU. ECF treatment gave a significantly longer median survival (8.9 vs 5.7 months, p = .0009) than the alternative FAMTX (5-FU, doxorubicin, and methotrexate).
Against MCF (mitomycin, cisplatin, and 5-FU), there was no statistically significant difference in median survival (9.4 vs. 8.7 months, p = 0.315).

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. These were all IHC1 or IHC2 HER2 patients and all were hormone responsive. None of them were eligible to receive Herceptin.
HER2 status	To avoid giving Herceptin, patients with IHC1 or IHC2 were selected. One patient had autoantibodies against HER2 on enrolment.
Dose	10µg of peptide in virosome injected intramuscularly on day 1, 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.
Response to the virosome	Of the 10, seven had a measurable antibody response to the flu protein on enrolment. This should mean that their immune systems were primed to respond. Two did not respond to the flu protein incorporated into the vaccine and showed no antibody response.
Antibody responses	The seven responding patients with no prior HER2 antibodies all generated antibodies against each peptide. The patient with pre-existing auto anti HER2 levels also responded. The antibody affinities were not measured.
Immune responses	Patient levels of Interleukin -2, Tumour Necrosis NF and Interferon gamma were variable. All are powerful signalling molecules involved in the anti-viral response.
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 that a normal donor, who will have, probably, under 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 below 48 µg/ml was observed in gastric cancer). Prejeta has a trough level of 62.7 µg 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.
Dosing with chemotherapy	There are no data on the immune response when HER-Vaxx is given with intensive chemotherapy. Chemotherapy is strongly immune suppressive and generation of an immune response against a stimulus requires the immune cells to be able to growth and divide.
Survival and progression	This was not a survival study and there was no matched control group. Every patient received either an aromatase inhibitor (anastrozol or exemestan) or an oestrogen receptor agonist (fulvestrant). The authors report that one patient died one month after the last vaccination. After six months, one showed a partial remission and three developed progressive disease. After a year, five patients still had stable disease. The authors noted that it is more probable to attribute any clinical effects to the endocrine therapy.[6]

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

Of these cases, 15-20% are found to have high levels of HER2 expression, although estimates vary up to 30%.[9] Data show 36% of US cases are metastatic with 4.7% five-year survival. Localised disease is 26% of cases with 65% five-year survival.

Europe, including Russia, has about 140,000 new cases with 80,600 in the EU. In the EU, Germany and Austria, Italy, Spain the UK and Ireland and France are 86% of cases.[10] The Eastern European EU members plus Greece are 23%, but unlikely to sustain a major market. The US has about 22,220 cases per year. Japan is a big potential market with over 100,000 cases per year.[11] Over 70% of new cases and deaths occur in developing countries.

The highest incidence rates are in Eastern Asia, Eastern Europe and South America and the lowest rates are in North America and most parts of Africa. China accounts for 41% of cases. Regional variations probably reflect differences in diet and the prevalence of the *Helicobacter pylori* infection, a major risk factor linked to economic development.

Competition

Gastric cancer is currently a major unmet medical need with ineffective chemotherapy and little additional gain from Herceptin use. Exhibit 6 shows that a number of trials in HER2 are underway. Various oral 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.[f] The major threats to HER-Vaxx are nearer term: the Kadcyla study due to report in 2016 and the Perjeta-Herceptin trial due in 2022. MM-111 might also be a

[f] 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.

strong product and Nivolumab could be well established in the Japanese market by 2023, with possible extension onto the US and EMA labels.

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. Genentech estimates the combination cost at approximately US$188,000 for an 18-month course of the combination therapy. The cost of Kadcyla therapy is high: US$9,800 a month, or US$94,000 for a typical course, which is about twice the price of Herceptin alone.

In H114, Roche reported Herceptin sales of CHF3.1bn, up 6%. At current rates, this is US$3.2bn or A$ 3.7bn, annualised about US$6.6bn. Prejeta H1 sales were 276% up at CHF388m after the 2012 launch. Kadcyla, launched in 2013, had sales of CHF277m. Herceptin is threatened by the launch of biosimilars. The European patent expired in July 2014 and the US patent expires in 2019. Price falls are less aggressive than small molecule generics, but there will be a fall in market value and possibly wider use of the therapeutic.

Exhibit 6: HER2 targeting or related gastric therapies in clinical development

Company	Product	Phase and NCT	Patients	Data	Action mode and notes
Lilly	LY2875358	Ph II (multiple indications) NCT01874938	15	August 2014	LY2875358 is a bivalent monoclonal antibody to hepatocyte growth factor receptor signalling.
Galena with Genentech	NeuVax plus Herceptin	Ph II, NCT01570036	300	Jan 2015	T-cell vaccine. Early stage node positive breast cancer low HER2. Disease-free survival endpoints.
Merrimack	MM-111	Ph II (multiple indications) NCT01774851	120	July 2015	Bispecific antibody targeting HER2 and HER3 to prevent HER3 resistance.
Roche	Kadcyla	Ph II/II NCT01641939	412	August 2016	Two doses compared to taxane therapy in three-arm adaptive open study.
Galena	NeuVax (nelipepimut-S)	Ph III NCT01479244	700	January 2017	T-cell vaccine. Early-stage node positive breast cancer low HER2. Disease-free survival endpoints.
Ono /BMS	Nivolumab	Ph III (Japan) NCT02267343	480	August 2017	Anti-PD-1, in trials for multiple indications.
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.

Source: www.clinicaltrials.gov, Edison Investment Research

Patents

Biolife[g] has acquired the intellectual property (IP) from BSFE on HER2.[h] A separate patent acquisition agreement and licence with Pevion Biotech covers the virosome technology used to deliver the vaccine.[i] No Japanese patents appear to be in progress. As a biological agent, HER-Vaxx will enjoy extended protection post-approval of 12 years in the US and 10-year data exclusivity in the EU. Biolife receives royalties of 18% of Imugene revenues.

[g] Biolife Science incorporated on 27 April 2012. Biolife executed a deed of assignment with Biolife Science Forschungs-und Entwicklungsges mbHH (BSFE, a company incorporated in Austria), to acquire ownership rights of two families of granted and pending patents (specified IP). BSFE was founded in 2000 by scientists from the University of Vienna and Euro Capital Partners. The specified IP forms the basis of HER-Vaxx, as originally developed by scientists at the Medical University of Vienna. BSFE transferred to Biolife rights to the specified IP once Biolife, having completed due diligence, was acquired by Imugene. BSFE gains an 18% royalty, based on Imugene sales, in exchange for the IP. Note that patents are only granted by national authorities so a world patent application number does not mean that a patent is in force world-wide. Even European patent has to be confirmed by each country within the treaty.

[h] The world patent application WO02068474 includes the granted US patent US7348010 expiring on 27 February 2022. World patent application WO2007118660 includes the granted European patent EP1844788 expiring on 13 April 2026. The status in Japan and China is not clear.

[i]. The world patent application acquired by Biolife from Pevion is WO2011020604, expiring on 18 August 2030. This covers the HER-Vaxx peptide with a virosome carrier. It is granted in the US (US 8,852,604). The European patent is published as an application EP2467155. Biolife has a non-exclusive licence to WO2006/069719, which covers the virosome construct. This is granted in EP, US, CN, AU, Eurasia and SA and expires on 21 December 2025.

Sensitivities

The nearest value inflection point for investors is that the Phase II produces strong data to enable a big pharma licensing deal (with an upfront fee) that covers Phase III costs. In 2013, AstraZeneca paid US$225m plus milestones of US$275m for Amplimmune's Phase I PD-1 antibody, although this is in the active T-cell therapy area and was not an antibody vaccine. 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. These are strong positive indicators.

Uncertainties arise as any survival gain in gastric cancer is not known, but will probably be smaller than 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 since most gastric cancer patients are in Asia and therapeutic options may broaden over the next eight years as other candidate trials report data. Mr Hopper received 68.3m Imugene shares (A$1m at A$0.015/share) in connection with the Biolife acquisition though connected parties. This was approved by shareholders on 20 December 2013.

Valuation

To calculate a discounted, risk-adjusted cash flow valuation, Edison has used the key assumptions in Exhibit 7. These are then applied to the market data in Exhibit 8 to give a potential market value of about A$827m. Note 2030 is shown as it is the last year of assumed BSFE royalties.

Exhibit 7: Valuation parameters

Key model assumptions	Value
HER2+ percentage of diagnosed patients[9]	20%
Percentage eligible for therapy	75%
US Price (US$) per year	75,000
Royalty percentage from Partner	12%
Royalty to BSFE until 2030 (based on royalties received from partners)	18%
Upfront payment in 2019 (A$m)	25

Source: Edison Investment Research

Exhibit 8: Market data and non-adjusted cash flow in 2030

Market (US$ unless otherwise stated)	Cases	Eligible	Share	Price (US$)	Value (m)
US	22,200	3,330	25%	75	62
Western EU	62,240	9,336	40%	60	224
Eastern EU	18,360	2,754	25%	37.5	26
Eastern Europe and Russia	59,000	8,850	25%	37.5	83
Japan	102,740	15,411	15%	112.5	260
China	382,940	57,441	5%	18.75	54
E Asia	37,360	5,604	2%	18.75	2
RoW (S America and Africa)	249,160	37,374	2%	18.75	14
Total	**934,000**	**140,100**			**725**
Sales in A$	Rate A$/US$	1.14			A$827
Royalty from Partner to Imugene	Rate	12%			A$99
Royalty paid to BSFE (18%)					(A$18)
Potential Imugene profit after A$2m admin costs and 30% tax in 2030					A$56

Source: Market data references[8] [10], Edison Investment Research

Pricing and market share will vary according to patent strength, competition and the level of healthcare funding and infrastructure at that time. A US price of $75,000 per year is assumed, with patients taking therapy for a year on average. Prices are usually lower in Europe, higher in Japan and reduced elsewhere. There seems to be no Japanese patent so a lower share is used there. The upfront of A$25m is generally comparable with Phase II deals, although no specific antibody-

based vaccine benchmarks can be ascertained. An approval milestone of A$50m is assumed at the technical probability of 20%. Phase II projects generally have 20-30% probability of reaching the market. There is a higher general probability, about 30-40%, of a completed Phase III project progressing to Phase III. However, deal and risk data on cancer vaccines are limited so these probability estimates have a high level of uncertainty. Milestones paid on and after approval are much higher than upfront payments as the project is then technically lower risk. Upfront and milestone payments are assumed to be shared with BSFE. A 30% Australian tax rate is applied from 2026. This gives an indicative value (Exhibit 9) of A$49.3m; this is not a price target.

Exhibit 9: Valuation table (based on Exhibits 7 and 8)

Discounted cash flow stream	Probability	Present value (A$m)
Value of net cash flow until 2032 (excluding upfront payments)	20%	43.2
Value of 2019 upfront and 2023 milestone (net of royalties)	30%	6.1
Total value		**49.3**

Source: Edison Investment Research

Financials: Cash to fund Phase II

In December 2013, Biolife Science was acquired for A$4.5m in equity (300m shares at A$0.015 each). The previous focus, a drug delivery technology (Linguet) now has a carrying value of A$0.3m and is not being developed further. Total intangible assets as of 30 June balance sheet were A$6.9m, of which 96% is HER-Vaxx. The cost of HER-Vaxx IP acquired in FY14 was A$600k in total between BSFE and Pevion. A$525k of this was unpaid on 30 June, of which A$450k was a current liability with A$75k as a non-current liability. These are expected to be settled in cash. There is a non-current fair value liability of A$1.12m for future royalty payments (calculated by Imugene using a 25% discount rate) mostly on HER-Vaxx.

Imugene raised A$2.6m in FY14 (to 30 June 2014) to fund initial HER-Vaxx development and in preparation for the clinical trial. Cash was A$883k on 30 September 2014. Revenue in FY14 comprised an R&D tax rebate of A$0.5m and some interest income. As most Phase II costs will be outside Australia, no further R&D tax rebates have been assumed. In November 2014, a A$2.25m November funding was announced (225m shares placed at A$0.01/share; no estimate of the proceeds of the share purchase plan also announced at that time has been made). The current funding is sufficient to initiate the Phase Ib/II trial but further funding will be needed. An illustrative long-term debt of A$2m is included in 2017 to represent this. Financial projections are in Exhibit 10.

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Exhibit 10: Financial summary

A$000s	2014	2015e	2016e	2017e
Year end 31 June	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	511	0	0	0
Cost of Sales	0	0	0	0
Gross Profit	511	0	0	0
EBITDA	(386)	(1,350)	(1,850)	(1,850)
Operating Profit (before GW and except.)	(386)	(1,350)	(1,850)	(1,850)
Intangible Amortisation	(1,691)	0	0	0
Exceptionals	(66)	(75)	(75)	(75)
Other	0	0	0	0
Operating Profit	(2,143)	(1,425)	(1,925)	(1,925)
Net Interest	27	50	25	10
Profit Before Tax (norm)	(359)	(1,300)	(1,825)	(1,840)
Profit Before Tax (FRS 3)	(2,116)	(1,375)	(1,900)	(1,915)
Tax	0	0	0	0
Profit After Tax (norm)	(359)	(1,300)	(1,825)	(1,840)
Profit After Tax (FRS 3)	(2,116)	(1,375)	(1,900)	(1,915)
Average Number of Shares Outstanding (m)	689.2	1,059.1	1,171.6	1,171.6
EPS - normalised (c)	(0.05)	(0.12)	(0.16)	(0.16)
EPS - FRS 3 (c)	(0.31)	(0.13)	(0.16)	(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	6,874	6,874	6,874	6,874
Intangible Assets	6,874	6,874	6,874	6,874
Tangible Assets	0	0	0	0
Other	0	0	0	0
Current Assets	1,758	2,014	114	274
Stocks	0	0	0	0
Debtors	15	15	15	15
Cash	1,223	1,988	88	248
Other	520	11	11	11
Current Liabilities	(697)	(322)	(247)	(247)
Creditors	(247)	(247)	(247)	(247)
Current loans	0	0	0	0
Other inc HER-Vaxx IP creditor	(450)	(75)	0	0
Long Term Liabilities	(1,202)	(1,127)	(1,127)	(3,127)
Long term debt	0	0	0	(2,000)
HER-Vaxx IP Creditor	(75)	0	0	0
Other long term liabilities	(1,127)	(1,127)	(1,127)	(1,127)
Net Assets	6,732	7,438	5,613	3,773
CASH FLOW				
Operating Cash Flow	(1,171)	(1,366)	(1,925)	(1,850)
Net Interest	27	50	25	10
Tax	0	0	0	0
Capex	(600)	0	0	0
Acquisitions/disposals	6	0	0	0
Financing	2,396	2,250	0	0
Dividends	0	0	0	0
Other funding	0	(169)	0	0
Net Cash Flow (ex debt movements)	657	765	(1,900)	(1,840)
Opening net debt/(cash)	(566)	(1,223)	(1,988)	(88)
HP finance leases initiated	0	0	0	0
Other	0	0	0	0
Closing net debt/(cash)	(1,223)	(1,988)	(88)	1,752

Source: Imugene reports, Edison Investment Research. Note: FY13 is omitted as it is not relevant to the current business.

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

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2012-16e	N/A	ROCE 15e	N/A	Gearing 15e	N/A	Litigation/regulatory	●
EPS 2014-16e	N/A	Avg ROCE 2012-16e	N/A	Interest cover 15e	N/A	Pensions	○
EBITDA 2012-16e	N/A	ROE 15e	N/A	CA/CL 15e	N/A	Currency	○
EBITDA 2014-16e	N/A	Gross margin 15e	N/A	Stock days 15e	N/A	Stock overhang	○
Sales 2012-16e	N/A	Operating margin 15e	N/A	Debtor days 15e	N/A	Interest rates	◖
Sales 2014-16e	N/A	Gr mgn / Op mgn 15e	N/A	Creditor days 15e	N/A	Oil/commodity prices	○

Management team

Executive chairman: Mr Paul Hopper	CEO: Mr Charles Walker
Mr Hopper has served as managing director of Cappello Group, Inc, 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.	Mr Walker joined Imugene in August 2014. He was previously CEO of Alchemia, before which he spent over 10 years in corporate finance. He has an MBA from Warwick Business School (UK) and a pharmacology degree from the University of Bristol (UK).
Non-executive director: Dr Axel Hoos	**Non-executive director: Mr Otto Buttula**
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.	An active and substantial investor in the biotechnology sector, Mr Buttula has an extensive background in equity research. He was CEO of IWL, an online financial services company acquired in 2007 for $373m. He was until recently non-executive chairman of Investorfirst, now HUB24.

Principal shareholders	(%)
Mr P Hopper (chairman) (held via Kilinwata; Moreglade; Deborah Coleman)	6
Mr O Buttula (Non-executive director)	5
Webinvest Pty	5
JK Nominees Pty	5
Tisia Nominees Pty	5

Companies named in this report

Viralytics, Roche, BMS, Ono, Merimack, Boston Biotech, Galena

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