COMPANY REVIEW

CORPORATE CONNECT

Immutep Limited

Efti a highly sort after compound for mono & combo Cancer treatment

Marc A, Sinatra, BSc (Hons), MBA

Immutep (IMM.AX) is one of the most promising drug developers listed on the ASX. A core competency is its unsurpassed understanding of the biology of the lymphocyte activation gene-3 (LAG-3) and the development of therapeutics based on that knowledge. In this report, we take a deep-dive into Immutep's project pipeline. We look at major factors in oncology drug development and the broader market and how Immutep are likely to support the value of its lead asset, eftilagimod alpha (efti), currently in mid-late-stage clinical trials. Finally, we look at the company's intellectual property and management, the latter being often overlooked by investors.

Pipeline: Immutep's pipeline is impressive. It features efti, which is being studied in several cancer indications. The main trials are in late-stage cancers of the breast, lung and head & neck cancer. **The latter two are in collaboration with pharmaceutical giant Merck & Co. (NYSE: MRK) and feature the combination of efti with the No. 1 selling cancer drug in the world right now, Keytruda®** (FY20 sales USD14.4b), a immune checkpoint inhibitors (ICIs). An extension of the collaboration with Merck, will see efti studied in combination with Keytruda® in the first-line treatment of advanced head and neck cancers. **A solid result in this trial could see efti on the market via a special route through the US Food and Drug Administration very quickly**.

LAG-3 biology also relates to autoimmune diseases and Immutep is likely to commence a phase-I trial of its LAG-3 agonist, IMP761, soon.

Immutep's outlicenced pipeline features LAG525, a LAG-3 inhibitor, fully outlicenced to **Novartis AG (NYSE: NVS)** for cancer indications, as well GSK'781 (IMP731), which is fully outlicenced to **GlaxoSmithKline (NYSE: GSK)** for autoimmune diseases. Both compounds are in the clinic and have been generating milestone payments.

Still, there is even more underneath the hood of Immutep.

Management: Immutep features **Dr Frédéric Triebel** who cloned the LAG-3 gene and is **the world's foremost expert in LAG-3 biology.** He is joined by CEO Marc Voight, who has truly proven himself at Immutep. The rest of the executive team is similarly talented and without a team with those traits no drug would ever get developed.

Oncology Drugs Market: The market for protected therapeutics is anything but a free and uniform one. Marketing exclusivities on products, large development costs, a high regulatory bar for entry and varied means of payment are just some of its peculiarities. Still, the market has evolved to support innovation and cope with rapidly rising costs when new medicines of significance are released.

The market for ICIs, such as Keytruda®, has grown from zero in 2011 to USD28.5 billion in 2020. Twelve of the 15 world's largest drug companies have a direct interest in an ICI. There are currently eight ICIs on the market. Seven of them are highly similar, as are many of those still to come. **The ICI market is likely to get very competitive very quickly.** ICIs do, however, combine well with certain other medicines and it seems almost certain that large companies will look to ICI + drug combinations to allow them to grow and defend market share. Given the competitive nature brewing in the ICI market and long leads times in therapeutic development, it is **unlikely to be long before these large companies start looking towards smaller ones with attractive compounds** that will give them an edge in the ICI and broader immuno-oncology market.

Efti is a compound that would combine well with ICIs, as the trial data in combination with Keytruda® is bearing out. It also has a unique mechanism of action and benign safety profile which means it will likely combine well with many drugs, not to mention that it is showing clinical activity in the absence of an ICI in breast cancer.

Whether it is a large licensing deal for efti or an acquisition of Immutep in the next two to five years, Immutep shareholders are likely to do very, very well.

Company Information

ASX Ticker	IMM
ASX Price	AUD$0.425
NASDAQ Ticker	IMMP
NASDAQ Price	USD$3.10
Shares on Issue	672 million
Fully Diluted Shares on Issue	748 million
Market Capitalisation	AUD$285 million
ASX Vol. (Shares/Day)*	3.9 million

* Shares per Day for the Last 20 Trading Days.

Cash Sufficiency

	AUD$ Million
A) Last Appendix 4C	April 2021
B) Cash & Equivalents at 4C	51.7
C) Burn[1]	3.1
D) Quarters Cash Remaining[2]	16.7
E) Estimated Current Q Burn[3]	1.0
F) Incoming Cash Post 4C[4]	1.6
G) Estimated Current Cash[5]	**52.3**
H) Significant Estimated New Commitment(s)[6]	

1 Burn = Net Cash from/used In Operating Activities; **2** Quarters Cash Remaining = G/C

3 Equals C *(# Days Since previous Q end Q4 / # Days in Current Q);

4 Equals Capital Raising(s) – Estimated Costs + Licencing /Milestones Receipts + Other Income; **5** Equals B – E + F

6 Equals estimated maximum new significant commitments that the company has or is likely to become contractually or ethically committed to.

Directors & Key Personnel

Dr Russell Howard	Chairman
Mr Marc Voight	Executive Director & CEO
Mr Grant Chamberlain	Non-Executive Director
Mr Pete Myers	Non-Exec. Director & Deputy Chair
Dr Frédéric Triebel	Chief Scientific & Medical Officers

Share Price Chart

The recommendations and opinions expressed in this research report accurately reflect the research analyst's personal, independent, and objective views about any and all the companies and securities that are the subject of this report discussed herein. **For important information, please see the Important Disclosures on page 34 of this document.**

Immutep Limited

Efti a highly sort after compound for mono & combo Cancer treatment

Background

Before getting into Immutep, below is some background on the science, therapeutics and events that are driving its drug development efforts. It is intended to lay a foundation for why we believe Immutep is highly likely to be purchased by a large pharmaceutical (as many have already been) or engage in a very large and lucrative licensing deal for its lead cancer program, eftilagimod alpha or efti.

However, that is not all that Immutep is, though;

- It has a fully outlicenced clinical-stage program with GlaxoSmithKline for autoimmune diseases
- A fully outlicenced clinical-stage program with Novartis for cancer
- Management has been and continues to be top-notch; and
- Immutep is one of the most well-round ASX-listed companies we have seen.

Immuno-oncology – bringing the fight to cancer

The human immune system has many roles. It does not exist simply to fight off diseases caused by viruses, bacteria and fungi. **Another key role is to scan and despatch cells that have undergone abnormal changes.** In doing so, the immune system prevents these cells from undergoing additional changes and, ultimately, forming cancers or tumours. Despite this preventative role, cancers still manage to develop, grow and metastasize (move around the body) and, ultimately, cause death. Evidence supports the view that cancers develop because their cells have undergone a change that allows them to escape this immune surveillance. This change(s) allows them to down-regulate the immune system around them and the response it might bring against them, providing them safe harbour to grow.

Immuno-oncology therapeutics are broad class of medicines and putative medicines that work to train the bodies immune system on cancers. Within that class of drugs are another class of drugs termed immune checkpoint inhibitors (ICIs). These drugs target specific regulators of the immune system which cancers use to hide. These drugs have been the cancer therapeutics discovery of the last decade, with sales of them growing from nil in 2011 to over USD28 billion in 2020.

During March 2011, the US Food and Drug Administration (FDA) approved ipilimumab (Yervoy®, Bristol Myers Squibb (BMS)) for the treatment of late-stage melanoma and, hence, it became the first therapeutic approved that acted by re-awakening the immune system. Ipilimumab, a monoclonal antibody-based therapeutic, binds a receptor termed CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4), which is found on certain immune cells. One of these immune cells is the cytotoxic T-cell (T_C). When ipilimumab binds CTLA-4 on T_Cs, it blocks the T_C from receiving inhibitory signals through the receptor. **This is important because T_Cs have another receptor, called the T-cell receptor, which is specifically designed to scan for abnormal cells.** When an abnormal cell is recognised by the T_C, the T_C dispatches it. This receptor varies considerably across T_Cs and groups of T_Cs allowing the group as a whole to recognise the huge number of abnormal signs that can develop on cells. A melanoma patient's T_Cs that recognise the tumour become activated toward it, but they start to express CTLA-4, as well. The melanoma, through an indirect mechanism, uses CTLA-4 to down-regulate the activated T-cells near it, such that they no longer pose a threat. **The study that the FDA based its approval decision on, found that advanced or metastatic (cancer that has spread) melanoma patients had a median overall survival (OS) of 10 months, which was significantly longer than the OS of 6.5 months in the control arm cohort of patients**.

Three years after ipilimumab's approval, in 2014, the FDA approved a pair of new ICIs, which targeted a different immune checkpoint and the transformative potential of these drugs become obvious. Pembrolizumab (Keytruda®, Merck & Co) and nivolumab (Opdivo®, Bristol Myers Squibb (BMS)) are monoclonal antibodies that **target the cell surface molecule PD-1 (programmed cell death protein 1). They bind PD-1, which is found on the surface of immune cells, in particular T_Cs, and prevent it from interacting with a protein that is often expressed on the surface of the cells that make up a cancer. This protein is PD-L1 (programmed death-ligand 1). When PD-1 expressing on immune cells interact with PDL-1 expressing tumour cells, the immune cells essentially stand down, leaving the cancer to grow as it pleases**. Preventing the interaction of PD-1 and PD-L1 reawakens the immune cells and their ability to act against the cancer.

Companies have, subsequently, developed therapeutics to PD-L1, as well. They appear to behave in a similar manner to those therapeutics that target PD-1. From here on, when referring to those drugs as a group, we will call them PD-1/L1 inhibitors.

There are now seven PD-1/1L targeting drugs on the market, with more coming, but pembrolizumab is the market leader, followed by nivolumab. **Pembrolizumab had FY20 sales of USD14.3 billion, while nivolumab had sales of USD7.0 billion**. Pembrolizumab was the second highest selling drug across all prescription drugs, regardless of the indication. Nivolumab was the fourth highest selling drug of 2019 but slipped out of the top 10 selling drugs in 2020, as pembrolizumab replaced nivolumab in the treatment of a key cancer.

It is thought tumours eventually escape the immune response an ICI allows by developing a change which, again, allows it to down regulate the immune response too it. **This led to the idea that by combining ICIs with other drugs that affect the immune**

system directly or indirectly you could have a longer more durable effect on the cancer, because the cancer would have more trouble developing two changes at the one time rather than just one. The first strong evidence that this was the case came when nivolumab was approved by the FDA in combination with ipilimumab for treating a distinct subset of metastatic melanoma patients (Ref).

The massive sales growth of the PD-1/L1 market and the strategic importance of having an approved PD-1/L1 inhibitor to offer customers, has spurred the search to find further drugs that can improve the performance of the PD-1/L1 drugs and help companies increase sales, while also defending territory won.

Immutep is one such company. **Its primary therapeutic efti, is believed to activate the immune system. The idea is essentially that the PD-1/L1 inhibitor allows the immune response against the cancer, while efti makes the immune response allowed larger**. This should increase the number of patients who respond to PD-1/L1 drugs and how durable (how long) the response lasts.

Investors should not, however, forget that efti appears to have clinical activity when used in combination with standard chemotherapy, so the drug is not tied to PD-1/L1 combination therapy. It is simply that the combination with PD-1/L1 therapies may be the stronger driver of value.

Autoimmune Diseases – fighting inflammation

The second area Immutep is active in, is autoimmune diseases. This activity is based upon the company's core-competency in the biology of LAG-3, a recently confirmed immune checkpoint (lymphocyte activation gene-3), which serves to negatively regulate or decrease immune responses.

In healthy humans, immune checkpoints serve an essential role in the complex act of balancing the body's immune responses between too strong and too weak. If the immune system is not sensitive enough, invaders or abnormal human cells will be allowed to grow. **If the immune system is too sensitive, it can recognise healthy human cells as aberrant and attack them.** This is what causes autoimmune diseases, such as type I diabetes, where the immune system destroys the insulin producing cells of the pancreas.

Immutep has developed a drug to LAG-3 which increases its activity or rather is designed to decrease immune responses. Through an elegant piece of science and development, the company believes this drug may be the first one which treats the heart of autoimmune diseases. **That heart is inflammation caused when then the immune system starts to target normal healthy tissues**.

Immutep

Efti targets the LAG-3 checkpoint pathway. LAG-3 was discovered by Dr Frédéric Triebel and colleagues in France in 1990 (Ref). Dr Triebel also founded Immutep in France in 2001. Immutep is a spin-off from Institut Gustave Roussy (the largest cancer centre in Europe) and Serono (now Merck Serono, the pharmaceutical company). It was founded to exclusively focus on LAG-3 research. Dr Triebel is Immutep's chief medical officer (CMO) and chief scientific officer (CSO). His presence gives Immutep a monopoly on the world's foremost expert in LAG-3 biology and therapeutic development.

In what was effectively a backdoor listing, ASX-listed Prima Biomed (Prima) acquired Immutep in October 2014. In November 2017, Prima changed its name to Immutep Limited. Prima's previous focus, CVac, the ovarian cancer immunotherapy, was out-licensed for a combination of shares and contingent revenues (milestone and royalty payments).

While a range of molecules have been tagged as putative ICIs in literature, activity in the clinic is largely focused on three: LAG-3, TIM-3 (T-cell immunoglobulin and mucin-domain containing-3) and TIGIT (T-cell immunoglobulin and ITIM domain) (Ref). Of those, **LAG-3 is clearly of dominant interest**.

LAG-3 – suppressing the cytokine storm that can come with up-regulating the immune response

This section has largely been adapted from two recent reviews in scientific literature. "The Next-Generation Immune Checkpoint LAG-3 and Its Therapeutic Potential" by Lecocq et al and "LAG-3: from molecular functions to clinical applications" by Maruhashi et al. These articles are here and here, respectively.

Like CTLA-4 and PD-1/PD-L1, LAG-3 is an inhibitory receptor, where it functions to limit immune cell activity. All four and further immune checkpoints are thought to have a role in **ensuring that immune system activity in a desired area does not spill over into areas of healthy tissue and that potentially self-reactive immune cells are not activated**. The use of CTLA-4 and PD-1/L1 inhibitors can cause autoimmune reactions, by making the immune system too sensitive. The severest reaction is called a cytokine release storm and can be lethal. Cytokine storms are severe autoimmune reactions and have been particularly problematic with ipilimumab, both during its clinical development and subsequent approved use. Ipilimumab's safety profile has definitely impacted

its sales. Cytokine storms are not as common with PD-1/L1 inhibitors. Still, the issue does exist. **Severe autoimmune reactions have not been observed with any compounds targeting the LAG-3 pathway compounds in animal studies or in the clinic, giving these compounds an advantage particularly over CTLA-4 inhibitors. Moreover, the general safety and tolerability profile of LAG-3 inhibitors in the clinic has been particularly good.**

LAG-3 can be expressed by a wide array of immune cells, particularly in the tumour micro-environment (TME). The TME consists of the area immediately around and within tumours and is the area where checkpoints hinder the immune system attacking a cancer. Like CTLA-4 and PD-1, LAG-3 is not found on a key naive subset of immune cells of particular interest, the T_C, but it is expressed following their stimulation by an antigen. Importantly, the inhibitory activity of LAG-3 strongly correlates with its expression at the cell surface of immune cells. Prolonged, continuous exposure to viral, bacterial or parasitic antigens leads to high and sustained levels of LAG-3 expression on the surface of T_C cells, as well as the expression of other co-immune-inhibitory molecules on T-cell surfaces. Eventually, continually stimulated T-cells lose their effector function and become exhausted and are of no use in combatting the tumour. **A significant observation supporting LAG-3's role as a key checkpoint is that its blockade causes the T-cells within the TME to increase their activity.**

The best description we have seen supporting the role of LAG-3 as a key checkpoint is: "consistently, the levels of LAG-3 expression and infiltration of LAG-3+ cells in tumours have been reported to be associated with tumour progression, poor prognosis and unfavourable clinical outcomes in various types of human tumours, such as colorectal cancer, renal cell carcinoma, follicular lymphoma, head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer, breast cancer and diffuse large B cell lymphoma. **These results strongly indicate that LAG-3 contributes to immune escape mechanisms in tumours similar to PD-1**" (Ref). To put it another way, as a cancer progresses, it is more and more likely to start to use LAG-3 in such a way as to shield itself from the immune system.

In relation to many pre-clinical studies, it has been observed that the effects of targeting LAG-3 alone lead to a "modest" therapeutic effect. **However, when LAG-3 is targeted on top of PD-1/L1 inhibition, the usual therapeutic effect of the anti-PD-1/L1 inhibitor is greatly enhanced**. This synergistic effect is put down to the molecules having different mechanistic pathways, but an end result that is largely the same: a cancer escaping from immune surveillance. The view that LAG-3 and PD-1 are different mechanistic pathways to immune escape has further enhanced LAG-3's role as an immune checkpoint. If the mechanistic pathways were the same, LAG-3 inhibition would likely have minimal effect as a therapeutic target because its inhibition would be redundant, while a semi-shared pathway would result in it being less effective. **When you close largely separate pathways, the cancer will find it significantly more difficult to escape. The underlying reason is that the available changes a cancer can develop to escape immune surveillance is reduced**.

The role of LAG-3 as an immune checkpoint was, essentially, settled recently. BMS announced that its LAG-3 inhibitor, relatlimab, when combined with nivolumab out performed nivolumab alone in a phase III trial in patients with previously untreated metastatic or unresectable melanoma. Unfortunately, no results were released as per usual practice and we will have to wait see them at an upcoming meeting.

LAG-3 is thought to act through MHCII (major histocompatibility complex class II) to exert its negative effect on the immune system, although some other molecules are in the mix. MHCII is found on immune system cells that present antigen and are termed antigen presenting cells (APCs) as a group. The macrophage, called the body's scavenger, is probably the most often mentioned APC, although monocytes, which also express MHCII, are the precursor APCs. The role of MHCII is to display antigen an APC has picked up to other immune cells. If other immune cells, such as T_Cs, recognise the antigen an immune response may commence. An antigen bound to MHCII is termed a peptide-MHC II complex (pMHCII). LAG-3 has been shown to prefer binding stable pMHCII. Stability being important in antigen presentation.

Immutep's Internal Pipeline

Immutep has a quality pipeline.

Many companies will add compounds to demonstrate what is ultimately a false sense of depth. Developing a drug is a complex task requiring significant expertise and large sums of money. Invariably, smaller companies with a number of compounds in their pipeline must focus on one. Otherwise, they struggle to move any of them forward to a point of significant value accretion. **Immutep has focused on quality. It is also studying efti in multiple clinical trials to build its understanding of how the drug works and, of course, move it closer to regulatory approval. Immutep's core competency is LAG-3 biology and developing compounds based on their knowledge thereof and it correctly sticks to its strengths.**

Given Immutep's core competency in LAG-3 biology and that LAG-3 biology is of relevance to both cancer therapeutics and autoimmune disease, it is not surprising to find the company has an internal program in each area. As stated, efti is the company's oncology asset and current core program, largely due to the market that is developing in the area discussed in the background section. Immutep's autoimmune disease program centres around a **compound termed IMP761. IMP761 is an antibody-based agonist of LAG-3 or, rather, it increases LAG-3's activity**. The idea being that by increasing LAG-3's activity, you can dial down or blunt the immune response causing the autoimmune disease.

Judging the quality of a company's pipeline can be a near impossible task. Generally, this is due to a lack of scientific publications on the area and the scientific approach being taken. Publications, including abstracts and conference presentations, demonstrate to investors (and other drug companies) that a compound has promise in a clinical trial, and why that compound has promise. Publications are also, in general, peer-reviewed by scientists unaffiliated with the company, providing some comfort that what the company is saying is true or, at least, a possibility. **This is not an issue with Immutep or its compounds**. Immutep has a true expert in LAG-3 biology as its CMO/CSO who has authored more than 100 peer-reviewed papers on LAG-3 biology and therapeutics leveraging that biology. Immutep also actively supports the presentation of its data at scientific conferences and the publication of its research in peer-reviewed journals. Plenty of other groups are engaged in, and publishing on, LAG-3, lending further support to the validity of Immutep's approach, as well as a reality check on it.

Further positive signals regarding a company and its compounds come when it forms partnerships, be it a collaboration or licencing deal, with a reputable drug company. The reason is that reputable companies are not into wasting money and closely scrutinize the merits of the partnerships they form. The size and scope of the partnership a small company strikes with a larger reputable one also needs to be considered when assessing the weight investors should give to the partnership. Not all partnerships are created equal. In this area, Immutep shines. **It currently has deals with Merck, Merck KaGaA, Pfizer, EOC Pharma, Novartis, and GlaxoSmithKline (GSK)**. We will cover the nature of these deals later in in this report. A number of highly thought of companies have done their due diligence on Immutep and compounds it has developed and have agreed to a partnership. **These are clear positive signals**.

Combined with its two internal candidates, Immutep's pipeline also consists of two fully out-licenced compounds it has previously developed. These are LAG525, an anti-LAG-3 antibody, out-licenced to Novartis for cancer and GSK2831781 (GSK'781), previously known as IMP731, out-licenced to GSK for autoimmune diseases.

Eftilagimod Alpha – "efti"

Efti is an interesting compound and a highly promising approach to leveraging LAG-3 biology. It comprises four domains of the LAG-3 protein expressed on the outside of cells attached to the Fc region of the antibody-type immunoglobulin G, IgG1. The Fc region is essentially the tail of IgG1. The Fc region of antibodies is commonly used in therapeutic recombinant proteins for many reasons. Essentially, the antigen binding domains normally associated with an antibody are more or less swapped out for a peptide (segment of protein) of interest that a company wants to explore as a therapeutic, providing stability to that segment.

Mechanism of Action

Given efti contains the outside regions of LAG-3 it is not surprising to find that it too is believed to bind to pMHCII. LAG-3 and efti also both show a preference for binding pMHCII.

Where it gets interesting, though, is that efti does not act by blocking LAG-3. Instead, efti activates the APCs to whose MHCII it binds (Ref, Ref). It may well activate other immune cells whose MHCII it binds, such as T_C. It is not fully understood how this activation is brought about, but seemingly the usual signalling is reverse transduced. Taking the process further, activated APCs will present more of the cancer cell's antigens to T_C cells, which naturally increases their activity. Essentially, the theory is that the chain reaction started by efti leads to a greater immune response to the cancer, without inducing the cytokine storm.

An observation that investors need to understand, if they are considering an investment in this area, is what are called hot and cold tumours. Hot tumours show immune cell infiltrates within the TME, while these infiltrates are lacking in cold tumours. Hot tumours generally show high response rates to ICIs, while cold tumours generally do not. It seems likely that the number and volume of antigens that are unique to the tumour (termed neoantigens) are higher in hot tumours than in cold tumours. Without enough neoantigens, the immune system may not mount a response, may mount only a low level one or there could be a "threshold" effect below which immune cells may move into the TME. The exciting thing is that if efti is causing increased activation of APCs, it is probably decreasing the volume and/or number of unique antigens a tumour needs to have for the immune system to detect it and mount an immune response. **In effect, efti could turn cold tumours hot, which would increase the number of tumours ICIs would be effective in.**

If Immutep and its collaborators continue to produce data that supports these hypothesis, efti could become a highly sought-after compound.

1) Oncology Clinical Trials of Eftilagimod Alpha

Efti is and has been studied in a number of different oncology programs. The immune system is highly complex and building up a strong body of clinical evidence to define how and where your drug works is almost as important as demonstrating its potential for clinical efficacy. Furthermore, you can never be certain of a clinical trial result. Pembrolizumab has failed a number of studies, including some in liver cancer and bladder cancer. Nivolumab has also failed a number of studies, one of which allowed pembrolizumab to take nivolumab's front runner position as the leading PD-1 inhibitor. **A trial failure does not mean the end of**

clinical development of a drug. Many reasons can cause a trial to fail or for a drug to appear ineffective, such as clinical trial design and the wrong study population.

Table 1. Oncology Clinical Trials Immutep Has or Is Studying Efti In.

Clinical Trial	Indications	Type of Study	Size	Estimated Date Data Collection for Primary Outcome Will Be Complete
TACTI-mel	Unresectable or Metastatic Melanoma	Single Arm	N=24	Study completed
AIPAC	HER2+ Metastatic Breast Cancer	RCT[1]	N=241	May 2021
TACTI-002	Group A: 1st-line in Untreated Unresectable or Metastatic Non-Small Cell Lung Cancer	Single Arm	N=17+19+74=110	May 2022
	Group B: 2nd-Line in Recurrent PD-1/L1 Refractory Non-Small Cell Lung Cancer		N=23+13=36	
	Group C: 2nd-Line in Recurrent or Metastatic Head & Neck Squamous Cell Cancer		N=18+19=37	
TACTI-003	1st-Line in Recurrent or Metastatic Head & Neck Squamous Cell Cancer	RCT	N=154	April 2023 (Not Yet Started)

1 RCT = Randomised Controlled Trial

Source: ClinicalTrials.gov, Immutep Website

The key oncology trials Immutep has or is studying efti are given in table 1.

In all of the trials Immutep has studied, or is studying efti in, efti is always paired with another therapy. We have already explained the reason for studying it with other ICIs - to reduce the chances of the tumour escaping the immune system. Efti is also being studied with chemotherapy. The reason is that chemotherapy can cause a rapid and substantial amount of tumour cell death. This releases large boluses of neoantigens into the body**. These neoantigens are more readily picked up by the activated immune system. In theory, the net result is that the immune response against the tumour is more amplified, overcoming the negative influence on the immune system by the tumour.** The question is whether the chemotherapy will affect the immune system as well. Chemotherapies work on the basis of being more toxic to quickly dividing cells than ones that divide slowly. A lot of cell division happens in a stimulated immune system. This could blunt or counteract efti's effect. Immutep's AIPAC study will help to answer that question.

TACTI-002 is another key study being undertaken by Immutep with efti. Two trials are listed with the name TACTI-002, which can create some confusion. The trial is being undertaken under one protocol and looks at two different cancer types: non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC). In fact, the trial is even more complex with two cohorts of NSCLC patients. One group of NSCLC patients will be receiving their first-line treatment, while the other group comprises patients who are PD-1/L1 refractory, meaning they have been given a PD-1/L1 therapy in the past and either failed to respond or stopped responding. Just for completeness, a naive patient is one who has never seen a particular treatment before (e.g., a PD-1/L1 naive patient).

We are going to look at the studies of efti in a semi-chronological order rather than the usual latest results first manner. We feel this gives a better view of efti's development and leads to a better understanding of the drug and is more appropriate for a review of the company. To fast track to the conclusion press here

First we will look at a completed phase I study of efti + pembrolizumab undertaken in unresectable or metastatic melanoma patients called TACTI-mel.

A) TACTI-mel: 1st Line in Advanced Melanoma

TACTI-mel (**t**wo active **i**mmunotherapeutics in **mel**anoma) was a phase I trial completed in 2019. The ClinicalsTrials.gov entry for the trial is: NCT02676869. Additionally, the study has been published in the Journal for Immunotherapy of Cancer. The paper for that study is here: Atkinson et al (2020) J Immunother Cancer.

This was a multicentre, open label study of two parts. Part A of the study was a dose escalation study to determine a recommended dose for phase II studies (RPD2). Part B was an expansion cohort treated at the RPD2. The patients in the study comprised those with unresectable or metastatic melanoma.

In part A of the study, three cohorts of six patients received escalating doses of efti, with each cohort receiving either of 1mg, 3mg and 30mg once every 14 days for nine cycles. Efti dosing commenced at week five of pembrolizumab therapy to allow patients to settle on pembrolizumab first and to enable the effect of adding efti on top of pembrolizumab to be studied. In part B of the study, a further six patients were dosed at the RPD2 for an extended period of 19 cycles. Dosing these patients with efti commenced at the

same time as pembrolizumab. In both parts of the study pembrolizumab was given to all patients at its recommended dosage and dosing schedule. As in all studies of this nature, the primary endpoint was to determine the safety and tolerability of the study drug. Data relevant to clinical activity are also be collected.

Table 2. Final Results From the TACTI-mel Study Announced 15 October 2019.

Measured according to irRC	Part A* N=18	Part B** N=6	Part A + B C1D1 analysis*** N=24
Overall Response Rate (ORR)	6 (33%)	3 (50%)	14 (58%)
Patients with tumour shrinkage	10 (56%)	4 (66%)	17 (71%)
Disease Control Rate (DCR)	12 (66%)	4 (66%)	Not reported
Progression free at 6 months	Not reported	4 (66 %)	14 (58%)

* Part A: Combination treatment began at cycle 5 of pembrolizumab treatment with patients having suboptimal response to pembrolizumab monotherapy and included a dose escalation of efti.
**Part B: Combination treatment started from cycle 1 day 1 of pembrolizumab.
*** Part A+B C1D1 analysis: Performed exploratory analysis starting from cycle 1 day 1 of pembrolizumab, including the 4 cycles pembrolizumab monotherapy ("C1/D1 Analysis") and includes patients from part B.

Source: Immutep Limited, ASX announcement, 15 October 2019; irRC refers to immune-related response criteria and is essentially the standard RECIST criteria modified to better reflect the activity of immunotherapies.

No safety concerns were observed at any dose level and a dose of 30mg of efti every two weeks was determined to be the RPD2.

Table 2 provides a summary of the final response-based results from TACTI-mel.

Part A of the study produced two complete responses (CR, 11.1%) and four partial responses (PR, 22.2%) for an objective response rate (ORR) of 33.3% (6/18). The disease control rate (DCR) was 55.6% (10/18). Response was measured using standard RECIST criteria, such that a CR was defined as no measurable disease and a PR was a decrease of 30% or greater relative to a target lesion. Calculation of the disease control rate control rate included patients with a best response of stable disease (less than a 30% decrease and no more than a 20% increase in the size of the target lesion) added to the ORR. The median progression-free survival (PFS, the time from when a treatment is first given until the cancer starts to grow again) was 4.7 months and the probability of the patient being alive at 12 months was 35.7%.

In studies such as these, assessment of response may also be based on immune-related response criteria (irRC). The RECIST criteria were developed around chemotherapies and radiotherapies, where the effect of the treatment happens quickly and is really only to kill tumour cells, reducing the tumour's size. Immunotherapies, however, do not work that way. They often take time to start to have an effect on a tumour's cells and you can also get immune cells moving into the tumour, increasing its size and giving the false impression that the tumour has progressed (grown). According to the researchers, when irRC was used to measure response in this trial, the results were similar to those produced by RECIST.

Three of the six patients (50%) whose tumours continued to grow on pembrolizumab monotherapy benefited from the addition of efti to the treatment regimen at week five, which is obviously an important point to notice. In part B of the study, the ORR was 50% (3/6) and the DCR 83% (5/6). All responses were ongoing such that a median PFS or duration of response could not be calculated. The probability of a patient being alive at 12 months was 67% and, again, the results were similar if irRC was used.

Figure 1 provides a swimmer plot of the best overall response by irRC for each patient. The irORR was 54% and the irDCR was 75% when all 24 patients were grouped together.

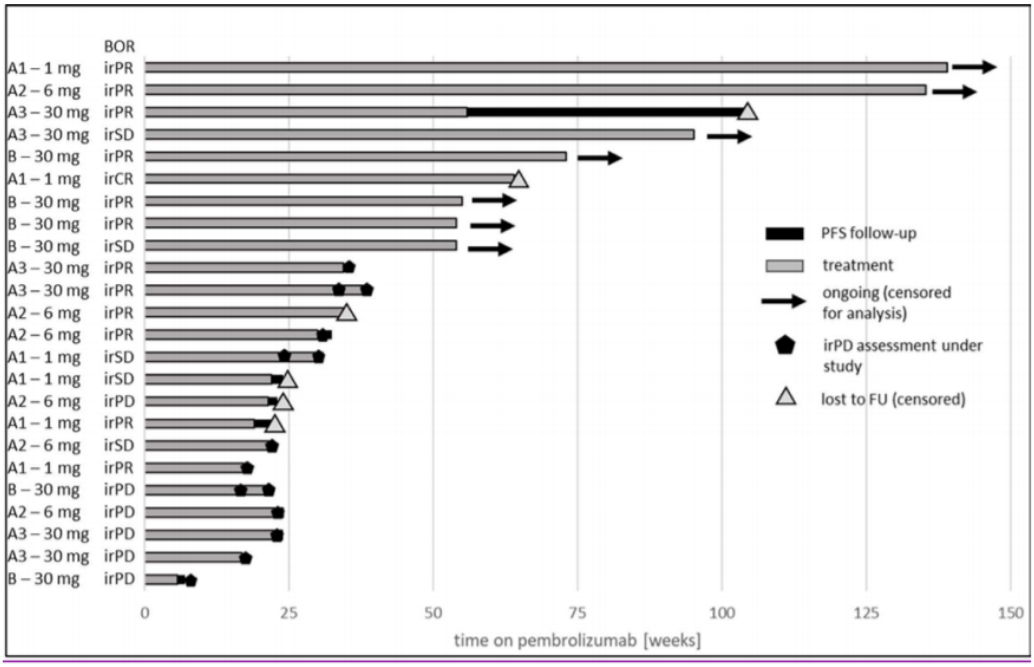
KEYNOTE-004, the pivotal trial of pembrolizumab in advanced melanoma that led to its approval by the FDA reported an ORR of 36% and a PFS of 4.1 months (Ref). For TACTI-mel, we were able to calculate the ORR of the combined groups, which yielded a result of 37.5%, The data was not provided in the paper to allow us to calculate a traditional PFS from Part B patients. PFS in part A of the study, however, was 4.7 months and the inclusion of the data from part B of the study would have only increased that number.

It is always difficult to make assessments across different studies and **it needs to be remembered that only those six patients in part B of the study would have been considered optimally treated with efti, since 75% (18/25) of the patients started efti later than pembrolizumab and 50% (12/24) of patients received dosages of efti that were no more than a tenth of that of 30mg which was defined as optimal.** Finally, the authors felt the patients were very much at the sicker end of the usual metastatic melanoma patient population that would be receiving their first-line of therapy. Having sicker patients in these sort of studies is not uncommon, since the doctors and patients often feel they do not have much to lose by going into the study. Nonetheless, it is possible to say that the data from TACTI-mel compares favourably to that of KEYNOTE-004.

Importantly, efti treatment induced an increase in activated T_C, as would be hoped based on the proposed MOA of efti.

The only complaint you could make about TACTI-mel is that it would have been nice to see a larger expansion cohort than six patients.

Figure 1. Swimmer plot with best overall response according to irRC for all patients of parts A and B. Each patient is displayed from the start of pembrolizumab therapy. All four groups are shown with A1=part A, 1 mg EA; A2=part A, 6 mg EA, A3=part A, 30 mg EA and B=part B, 30 mg EA. BOR, best overall response; irPD, immune-related progressive disease; irPR, immune-related partial response; irSD, immune related stable disease; PFS, progression-free survival.



Source: Atkinson et al (2020) J Immunother Cancer

The first indications ipilimumab, nivolumab and pembrolizumab received were in advanced melanoma patients and that is probably why efti was first studied in this patient population. The reason melanoma is a popular disease to study ICIs and combination immunotherapies in is that it was thought, and rightly so, that the disease would respond well to immunotherapy treatments. Sun exposure causes a high level of mutations in the DNA of skin cells. This, in turn, means they have a high number of abnormal proteins or neoantigens the immune system can attack.

While melanoma may have been an attractive cancer for immunotherapies to be studied in, it is not a big market and it is already becoming crowded. That may well be the reason the expansion study in this cohort was small and that Immutep has not announced further plans for studying efti in melanoma patients. **Essentially, they got what they wanted from this study: a read on safety and tolerability of efti + pembrolizumab, an RP2D of 30mg and reasonable signal of activity. Let us move on.**

B) The AIPAC Trial: efti & Chemo in the Treatment of Metastatic Breast Cancer Patients

The AIPAC trial (**A**ctive **I**mmunotherapy **PAC**litaxel) is a phase IIb multi-centre, **randomised, double-blind, controlled trial** comparing efti + paclitaxel to paclitaxel + placebo in the treatment of hormone receptor positive, HER2 negative, metastatic breast cancer (HR+ mBC) patients who have progressed after hormone therapy. The trial had two stages. The first, or run-in, stage examined the safety of combining efti with the chemotherapy paclitaxel and confirmed the dose of efti to be used in the second phase of the trial. Once the therapy was assessed as safe, the second stage commenced. Overall, 227 patients were enrolled. The ClinicalTrials.gov entry for the trial is here: NCT02614833.

The latest interim analysis of the AIPAC trial was released on the 10th of December 2020. **The key overall survival (OS) results from this study are given in Table 3**. The Total Population results and those of subgroups were all done on an intention-to-treat

(ITT) basis and refers to all patients in the trial being included in the analysis of results regardless of their level of participation in the trial post-enrolment (e.g., the number of doses of efti received, etc). Those and other key results key results were as follows:

- A 2.7-month benefit in OS in the intention-to-treat population overall, with a hazard ratio (HR, a relative measure of death in the treatment arm versus control arm at data cut-off, lower is better) of 0.83 and a p-value = 0.14. In other words, a trend towards improved OS in the gold standard endpoint for cancer trials favouring the combination of efti + paclitaxel.
- A statistically significant 9.4-month benefit in OS was demonstrated in patients who had low baseline monocyte counts at the beginning of the study, with an extraordinarily strong HR of 0.47. This result is important because monocytes are precursor APCs

Table 3. Overall Survival Data in Key Groups in AIPAC.

Group	% of patients in efti group	Efti group / Comparator group	Median OS (months)	Absolute OS benefit from efti
Total Population	100%	Efti + paclitaxel	20.2	**+2.7 months** HR = 0.83 p = 0.14
		Placebo + paclitaxel	17.5	
< 65 years	66.7%	Efti + paclitaxel	21.9	**+7.1 months** HR = 0.62 p = 0.012
		Placebo + paclitaxel	14.8	
Low monocytes < 0.25/nl	21.9%	Efti + paclitaxel	22.4	**+9.4 months** HR = 0.47 p = 0.02
		Placebo + paclitaxel	12.9	
Luminal B	48.8%	Efti + paclitaxel	16.3	**+3.8 months** HR = 0.69 p = 0.077
		Placebo + paclitaxel	12.6	

Note: A lower HR, means a reduced risk of death, e.g. by 53% in the low monocyte group.

Source: Immutep Limited, ASX announcement, 10 December 2020

- and the precursor cells of the mature APCs found at the site of the tumour. Therefore, this is a strong signal that efti is acting as APC activator expected, underscoring eftie's MOA.
- A statistically significant 7.1-month benefit in OS was shown in patients aged under 65 compared to those who were older, again, with a strong HR of 0.62. This is an interesting result and can likely be traced back to the fact that those of a younger age generally have a stronger immune system than those of an older age.
- A strong trend (p=0.077) toward increased OS for patients with luminal B-type cancers, with a HR of 0.69. These cancers are more immunogenic than other forms of HR+ mBC and if you are activating APCs, again, you would expect a stronger immune response to more immunogenic cancers.
- A statistically significant increase in the number of T_Cs (n=70), the cells that directly attack cancer cells, was found in patients treated in the efti arm compared to the control arm. Since APCs activate T_Cs and these T_Cs multiply and address the cancer, this, again, exactly what we want to see if efti is working as intended.

It can be easy to show differences in clinical trials simply by doing enough analyses. Eventually you will find a difference that is simply due to chance. **However, when the analyses fit with the proposed MOA of the drug, as these do, they are much more powerful as a predictor of future success.**

The ability to show a statistically significant increase in the number of T_C is pretty impressive. Since T_Cs are the effector cells that are directly responsible for addressing the tumours, the result underscores that efti is acting to stimulate the immune system, make it more receptive to responding to antigen and increasing the magnitude of the immune response to it. The immune system is designed such that the T-cells that recognise an antigen displayed by APCs divide and increase in number. The evolutionary reason for this is that (a) it increases the response to an antigen and (b) if the immune system has seen the invader once, it may see it, again. A subset of the T_Cs act as memory T-cells and should the invader come back, they will be ready.

Overall, this interim analysis of the AIPAC trial results provides strong evidence that efti is activating the immune system, as intended, and that this activation is allowing the immune system to overcome any immunosuppressive activity the tumour has developed. **Once you tick that box off, any clinical response can probably be attributed to efti's immune-stimulating activity.**

EOC Pharma (EOC), Immutep's partner for China (discussed below) gave several positive signals regarding efti's AIPAC December 2020 interim results when it announced it would commence a phase II trial in 152 mBC patients that would run under the same protocol as the AIPAC trial. In March 2020, Immutep announced that EOC had completed recruitment in a phase I trial (trial name: EOC202A1101) of HER+ mBC patients. At the time, EOC reported that its phase I trial was producing results in line with Immutep's work on efti, which had indicated a twice weekly 30mg dosing of efti was optimal.

The positive signals from this announcement are:

- Immutep got the design and population of AIPAC right.
- EOC would have had access to more data from AIPAC than Immutep has released and, hence, we can conclude the underlying data is sound.
- EOC is appropriately progressing efti toward the Chinese market

The final results from AIPAC should be available soon, with the ClinicalTrials.gov entry for the study having an estimated study completion date of May 2021. **The principal investigator of the study said in the 10th of December ASX announcement that the data will continue to mature between the time of this interim analysis and study completion. So, the result from the total population is still definitely in play.**

This interim analysis has provided Immutep with:

- A strong signal of a clinical effect of efti on the OS in HR+ mBC patients in combination with chemotherapy.
- Strong evidence efti boosts the immune response to HR+ mBC.
- If the chemotherapy is having a negative effect on the immune cells, it is not enough to dampen the immune response into insignificance.
- Enough data to indicate the efti has a role to play in treating HR+ mBC, although it remains unclear as to exactly what groups of HR+ mBC efti will be applicable to.

In a presentation released to the market the day after the second interim results were released, Immutep provided two recent cases to which the efti results could be compared.

One was based on the HER2 targeting margetuximab (Margenza®, MacroGenics). It demonstrated a 1.8-month non-significant improvement OS in combination with chemotherapy when compared to trastuzumab (Herceptin®, Roche) and chemotherapy in a 536-patient phase III trial in mBC patients who had already received two lines of anti-HER2 therapy (21.6 months [95% C.I.:18.9 - 24.1] vs 19.8 months [17.5 – 22.3], respectively; HR=0.89, p=0.326). The FDA approved the drug on 17 December 2020. That approval was based more on PFS and HR observations, rather than OS. Median PFS in the margetuximab arm was 5.8 months (95% CI: 5.5, 7.0) compared with 4.9 months (95% CI: 4.2, 5.6) in the control arm. The HR was 0.76 [95% CI: 0.59, 0.98]; p=0.033) in terms of disease progression or death. **The overall point Immutep was making with this example was that: In cases of high unmet need, a small difference in the right endpoint maybe sufficient for approval**.

The second example Immutep gave was atezolizumab (Tecentriq®, Roche Holding AG), a PD-L1 inhibitor. It gained accelerated approval in March 2019 for metastatic triple negative breast cancer (mTNBC), in combination with the chemotherapy, Nab-paclitaxel (Abraxane®, BMS). In the phase III IMpassion130 study, the atezolizumab combination produced an OS of 25.0 months (C.I.: 22.6 months – not estimated) compared to Nab-paclitaxel alone of 15.5 months (95% C.I.: 13.1 months – 19.4), a difference of 9.5 months, in mTNBC patients with PD-L1 expressing tumours. The HR was an impressive 0.62 (95% C.I.: 0.45 – 0.86). **Importantly, however, this was a retrospective subgroup analysis. Despite that, the FDA still granted atezolizumab accelerated approval**. While this is an accelerated approval only and Roche will have to undertake a prospective study demonstrating the out-performance of atezolizumab in mTNBC patients whose tumours express PD-L1. mTNBC is traditionally the hardest to treat of the breast cancers and what this demonstrates is that the agency will still grant an accelerated approval based on retrospective subgroup data, provided that data is strong enough**. The point is that subgroups are important in high need groups**. The HR of 0.62 the accelerated approval was granted to atezolizumab based on is similar to the HR's found in the AIPAC trial subgroups.

The next step toward achieving registration for a HR+ mBC indication is a short, one-year (n=24) trial found here: NCT04252768. In the AIPAC trial, efti was given the day after paclitaxel, on days 1 and 15. Since these patients are not in hospital, this creates a burden, because it adds another trip to the hospital to receive the efti injection, which is not ideal. While the aim of the trial is safety and efficacy, whether the trial is a success or not will depend on a range of secondary endpoints aimed at determining whether the effect of giving efti on the same day, but still after paclitaxel, is likely to affect the overall efficacy of efti in HR+ mBC. A positive result will be one that shows efti will perform equivalent to, or better than, it is in AIPAC and a negative one will be if its efficacy is likely to decline. **This is low risk trial and being able to give efti on the same day as paclitaxel will be a subtle, but important, simplification of incorporating efti into treatment regimens.**

We are unlikely to know much about what Immutep is contemplating in terms of a potential HR+ mBC indication until it is known whether efti can be given on the same day as the chemotherapy or not. **The risk that efti cannot be dosed that way is low in our estimation, but you can never be sure**. If it can, they would certainly want to incorporate the new dosing schedule into any pivotal trial(s) they run.

From the data coming out of AIPAC, **we are near certain that Immutep will be able to select from a few groups of HR+ mBC patients in which it could be highly confident that further trialling would prove successful.** We will see where that bar is at when the final AIPAC results are released likely in Q3 this year. Referring back to Table 3, it can be seen that two out of three subgroups for which Immutep produced data still represent around 50% of the HR+ mBC market. **The HR+ mBC market is a big market and a subgroup alone can generate highly significant revenue.**

Metastatic Breast Cancer Partner Trial: EOC Pharma

In May 2013, Immutep licensed the Chinese rights for efti to Eddingpharm, a Chinese pharmaceutical company. Eddingpharm, with the blessing of Immutep, on-licenced the rights to EOC Pharma, a spin-out company that it created in 2015 (which stands for Eddingpharm oncology).

In line with standard practice for two unlisted companies, which Immutep was at the time, the financial details of Immutep's licencing of efti to Eddingpharm in 2013 were not announced. This was very early in efti's development for oncology indications, so the numbers are unlikely to be headline grabbling. An investor should expect no more. **In January 2018, Immutep announced that it had received a USD1 million milestone payment from EOC.** This payment occurred just after EOC was granted an Investigational New Drug Application by the Chinese Food and Drug Administration (CFDA), which would allow clinical trialling of efti in China. Every licencing deal is different, so even with this data in hand it is still hard to make any strong conclusions about the value of the milestones remaining in the deal, their timing or the royalty attached to it. **Overall, a USD1 million payment to mark the granting of a Chinese IND is at the higher end of our expectations, albeit in a qualified manner.** The next milestone payment, when it occurs, will enable us to make a more accurate determination of what the remaining value of the licensing agreement might be worth to Immutep.

C) TACTI-002: 1st and 2nd Line in Non-Small Cell Lung and 2nd Line in Head and Neck Squamous Cell Carcinomas

The TACTI-002 (**T**wo **A**ctive **I**mmunotherapeutics, NCT03625323) trial is a three-arm, open label, international, multi-centre clinical study designed to evaluate the safety and potential efficacy of efti when combined with pembrolizumab in three separate groups of patients with advanced or metastatic cancer. These groups are:

A) First-line previously untreated or unresectable, PD-1/L1 naïve, non-small cell lung cancer (NSCLC) patients.
B) Recurrent PD-1/L1 refractory NSCLC patients (refractory: patients have not responded/become resistant to PD-1/L1 inhibitors).
C) 2nd-Line PD-1/L-1 naïve recurrent head and neck squamous cell carcinoma (HNSCC).

Patients are being treated for 12 months and up to 183 patients are expected to be enrolled.

Recruitment for this study began in August 2018 and the latest significant update on its progress was announced to the market on 10th November 2020.

Pembrolizumab has often been approved for patients whose tumours express a certain level of PDL-1 (e.g., ≥ 1%, 20%, 50%), because they are more likely to respond to the drug. **There were no PD-L1 expression criteria for entry into this study**.

Importantly, this study is being undertaken in collaboration with Merck, a positive signal on its own. The study design of TACTI-002 has the hallmarks of a large pharmaceutical company and Immutep will benefit from Merck's involvement. It is important to recognise that **Merck has not taken a licence to efti and that this trial in no way encumbers efti.**

An unusual feature of this study is its adaptive design, which allows for changes to be made to a trial while in progress, based on predefined criteria. Adaptive trials increase the efficiency of a clinical trial and, for that reason, are becoming more popular. In this study, a certain number of each group of patients were to be treated in the first stage of the study. If a group's results met a predefined threshold, a second set of patients would be recruited for that group, referred to as stage 2 of the trial.

There are two things to note about the nature of the results:

1. They are from a single arm study, meaning there is no other group, like a control group, to compare them to. This makes them difficult to interpret conclusively. The reason is that no matter how hard you try, even studies conducted under the same protocol, but with different trial sites or at different times, nearly always have some bias or difference in the patients recruited and/or the way the patients are treated during the trial. To highlight this issue, group A of TACTI-002 contains an apparent bias in the patients recruited into it between stages one and two. Patients in stage 1 of the trial were nearly 10 years younger than those in stage 2, while based on patients' ECOG status, those in stage 1 were healthier than those in stage 2. ECOG status is a physician-answered, questionnaire-based calculated score on a scale of 0 (fully active) to 5 (dead), designed to assess the impact a patient's disease is having on their daily activities. A likely reason for this bias is that after a good set of results in stage 1, investigators became more willing to recruit older, less healthy, patients into the trial on the basis that patients may see some benefit from the study drug. With biases like that, where everything remained exactly the same between the two stages, one can just imagine the magnitude of the differences between totally separate trials. This does not make the results invalid, the vast majority of studies done at this stage of a drug's development are single arm. **It does mean, however, that care must be taken not to write a compound off or declare it a certain winner based on the results of such trials**.

2. The results presented by Immutep have been calculated on an intention-to-treat or ITT basis. That means as soon as a patient is recruited into the study, their results count and are used in the analysis. This is so even if they never receive any study drug. Quite often companies exclude patients who did not receive the study drug or did not receive all of it. Analyses like these are said to be done on a per protocol basis and they are innately advantageous to study drugs in single arm trials. The reason for this is that patients who do not receive the study drug will not benefit from it and those who do not receive all of the study drug are likely to benefit less (analyses done on intermediate populations who received only a certain number of doses of study drug are often said to have been done on a modified intention to treat basis but are still innately biased toward the study drug and should be avoided). Removing the patients from the analysis means you will invariably be removing patients who had poorer

outcomes. Consequently, the results end up looking better than they will down the track in later stage trials. **There are good reasons why analyses should be performed on an intention to treat basis. That is what the FDA requires of studies submitted as part of a drug's approval application. Many companies have deluded themselves and their shareholders with per protocol analyses that, generally, end in tears**.

One reason for pointing out these issues is to ensure investors understand the numbers. The other reason is that Immutep noted the bias we gave as an example, above. **The point is, investors can be confident they are looking at results produced in an appropriate fashion and, for this reason, they can give them more weight.**

Table 4. Interim Study Results From Tacti-002, Group A, Stages 1 & 2 Released on 10 November 2020.

Tumour response (iRECIST)	Stage 1 (N=17) N (%)	Stage 2 (N=19) N (%)	Stage 1+2 (N=36) N (%)
Complete Response	1 (5.9)	1 (5.3)	2 (5.6)
Partial Response	8 (47.1)	3 (15.8)	11 (30.6)
Stable Disease	4 (23.5)	7 (36.8)	11 (30.6)
Progressive Disease	4 (23.5)	5 (26.3)	9 (25.0)
Not Evaluable	0 (0)	3 (15.8)	3 (8.3)
Overall Response Rate ITT [95% CI interval]			**13 (36.1) [20.8-53.8]**
Overall Response Rate (evaluable patients only)			**13/33 (39.4)**
Disease Control Rate			**24 (66.7)**

Source: Immutep Limited, ASX announcement, 10 November 2020

Group A: Previously Untreated or Unresectable PD-1/L1 Naïve Non-Small Cell Lung Cancer Patients

The data from an interim analysis of this group of TACTI-002 is provided in Table 4.

Despite the lack of a control arm, overall, the data looks solid. A CR was recorded in each stage of the trial and the ORR was 36.1%. The fact that stage 2 patients were older and likely not as healthy as those in stage 1 may be showing its effects in the number of partial responses in stage 1 (47.1%) compared to stage 2 (15.8%), particularly if the immune systems of stage 2 patients are generally weaker as a result of the more severe disease (as opposed to the cancers suppressing the immune system).

Merck sought approval for pembrolizumab in patients whose cancers expressed high levels of PD-L1 (≥50%), so there is not a lot of data on pembrolizumab that the results of this trial can be directly compared to. That is not the case for nivolumab, who did not restrict the entry of NSCLC patients on the basis of PD-L1 expression into their trials. A meta-analysis of the published studies of nivolumab in NSCLC patients, involving 3,404 patients, found that the use of nivolumab in NSCLC patients returned an ORR of 18% (95% CI: 15-20%) (Ref). **Obviously, the ORR of 36.1% (95% CI: 20.8-53%) from this interim analysis compares favourably to that determined for nivolumab in the meta-analysis. Although, again, we are not comparing like for like here.**

In the announcement on the results of the interim analysis of TACTI-002, Immutep pointed out that there was data on a comparable group of NSCLC patients with pembrolizumab who had a PD-L1 expression level of ≥1%. That population yielded an ORR for pembrolizumab on its own of ~27%, which was lower than the 44% (11/25) found for efti + pembrolizumab in the comparable adjusted interim analysis population from this study. **It also needs to be remembered that even restricting the study population to patients with a PD-L1 expression level of ≥1% biases this comparison against efti since efti is potentially active in all patients.** Moreover, based on the TACTI-002 population, 30% of the interim analysis population would be left without a potential treatment (i.e., 30% of patients in this study had PD-L1 expression of below 1%). That is also a big slice of the market to give up.

One of the big signals about this trial group was made public on 19 November 2020. Immutep announced that an additional 74 patients would be recruited for this group. To be able to do this, Merck had to agree to extend its clinical trial supply collaboration beyond the original agreement, announced in March 2018. Increasing the study by this number suggests **Immutep and Merck see something in the data and want to be sure**.

Ultimately, out of this group of NSCLC patients, Immutep wants to see an increase in the durability of the responses for those patient's with PDL-1 expression levels ≥50%. This group of patients is right in pembrolizumab's wheelhouse. Below that level of PD-L1 expression, both the response rate and durability will be equally important. If efti increases in the number of responses seen in ≥50% PD-L1 expression group, that will be an added bonus.

Advanced NSCLC was the first big group of patients that pembrolizumab gained FDA approval for and was its second approval overall in October 2015. Nivolumab did not gain first-line approval for the indication until October 2016. This meant Merck came from well behind BMS in developing the first significant ICI to take the leading position. Analysts predicted Merck would dominate the NSCLC market from that point forward and, so far, they have been right.

BMS did gain two approvals with the combination of nivolumab and ipilimumab in 2020, one as a first-line treatment for NSCLC patients whose tumours express ≥1% PD-L1 and, two, as first-line treatment of metastatic or recurrent NSCLC in general. The combination was found to have an ORR of 35.9% (Ref) . As a reminder, in group A, the efti + pembrolizumab combination in this patient population had an ORR of 36.3% and an ORR of 44%, respectively, when the 30% of patients with PDL-L1 expression <1% tumour expression were excluded. **When you consider that ipilimumab has real safety issues, as indicated by its boxed warning, an efti + pembrolizumab would be a good chance to capture the whole first-line NSCLC market.** Nivolumab's sales were flat in 2020, indicating that what would normally be considered as two nice approvals did not excite doctors, given the

Table 5. Interim Study Results From TACTI-002, Part C, Stages 1 & 2 Released on 10 November 2020.

	Part C 2nd line HNSCC
Tumour response - iBOR per iRECIST	**Stage 1 & 2 N (%) Total (N=28)**
Complete Response (iCR)	3 (10.7)
Partial Response (iPR)	7 (25.0)
Stable Disease (iSD)	3 (10.7)
Progressive Disease (iPD)	10 (35.7)
Not evaluable	5 (17.9)
Disease Control Rate (DCR)	**13 (46.4)**
Objective Response Rate (iORR) ITT*	**10 (35.7)**
Objective Response Rate in eval. pts	**10 (43.5)**

Source: Immutep Limited, ASX announcement, 10 November 2020

approvals occurred in May and would have enough time to make an impact on revenues. It is likely that ipilimumab's safety profile had a lot to do with doctors not wanting to use the combined the nivolumab + ipilimumab combination.

An efti-pembrolizumab combination, which could treat all first-line NSCLC patients, not just those with a certain level of PD-L1 expression, would simplify the treatment of all NSCLC patients, assuming that the data works out it in efti's favour.

Everything from this interim analysis is heading in the right way for efti.

Group B: Recurrent PD-1/L1 Refractory NSCLC Patients.

This is the hardest group of patients in the trial for efti to perform in because the cancer has already developed a way to escape PD-1/L1 inhibition and, consequently, the immune system, so you would not expect pembrolizumab to add too much to efti's benefit in this group of the study.

The data that came out on the 23 patients in the first stage of this group underlined the fact that this was a hard population to treat. One patient had a strong partial response and was still under therapy at six months, this response meant an ORR of 4.3% for group B patients. Four patients (17.4%) had stable disease for six months and a further two have had stable disease for more than two months and were still stable at the time of this analysis. **More than 50% of patients were alive at 12 months, which according to a reference provided in the announcement, compares favourably to chemotherapy, where 50% of patients are expected to survive only six months (Ref).**

On the basis of this data, the data monitoring committee recommended opening the second stage of this study, which will comprise recruiting an additional 13 patients, which is clearly a positive signal.

As with the first-line data, this data looks as good as could be expected.

Group C: 2nd Line PD-1/L-1 Naïve Recurrent Head and Neck Carcinoma.

This is probably the best set of data generated using efti, so far.

In this setting, patients will have received and their cancer will have progressed on a first-line platinum-based chemotherapy. Additionally, they will not have received any prior treatment with a PD-/L1 inhibitor as occurred in group B of the study

The results from the interim analysis of group C are provided in Table 5. At the time the data was prepared, a further two patients were recruited into the study.

The ORR attributable to efti + pembrolizumab was 35.7% (10/28). A reasonably large number of patients, five or almost 20% were not evaluable. As per our explanation above, the ITT numbers are important, so those five patients are automatically considered fails and, potentially, dilute the ORR considerably, because the study drugs would not have been a benefit to them. To have 20% of patients automatically considered fails puts the efti + pembrolizumab combination at a disadvantage. If those five patients had been evaluable, the ORR could have been as high as 64%. If those patients are excluded from the analysis altogether, it yields a per-protocol ORR of 43.5%, not nearly 64%, but still higher than 35.7%. **It will be interesting to see if Immutep finds a way to get the number of evaluable patients up, because it will help efti's results**.

As it stands, however, the efti + pembrolizumab ORR is nearly double that of ~15% found for pembrolizumab alone in its phase III trials (Ref, Ref) and even slightly better when compared to the ~13% found for nivolumab in its pivotal trial (Ref) for the indication.

Both pembrolizumab and nivolumab have gone on to gain first-line approvals in HNSCC. Again, caution needs to be taken when comparing across trials, especially from a single-arm study. **A response rate considerably more than double to that of the PD-1/L1 inhibitors, even in a single arm, cross-study, comparison, does tend to make you feel there is a true difference, which Immutep should be able to demonstrate in future randomised trials.**

Immutep recently announced a new clinical trial collaboration and supply agreement with Merck for a multicentre-centre (AU, US, Europe), randomised, actively controlled (pembrolizumab) phase IIb trial of efti + pembrolizumab in the first-line treatment of HNSCC.

One would expect the efti + pembrolizumab combination to report better results in the first-line setting than in the second-line setting, because patients generally get harder to treat as their cancer progresses.

This is a serious trial and one that could lead to the granting of Breakthrough Therapy Designation (BTD) by the FDA and quick approval of efti if the results fall the right way. BTD is an FDA program aimed at decreasing the time to market for drugs that look especially promising for treating a life-threatening disease. Unlike orphan drug designation and fast track status (two other FDA programs to aid the development of therapeutics for certain indications, largely granted based on the nature of the indication the company is seeking), the granting of BTD is based on an FDA assessment of likely efficacy and has been shown to bring truly tangible benefits to therapeutics it has been granted to. Ultimately, this study could even bring an accelerated approval if the data continues to show an ORR of twice that of pembrolizumab and nivolumab. An accelerated approval would see efti on the market much, much sooner than would normally be expected.

It would be interesting to know whether Immutep talked with any companies with their own PD-1/L1 inhibitor, other than Merck, to collaborate on a trial of this nature. Convincing another company to jump into Merck's place would not be easy. Perhaps other potential collaborators would have thought, "Well, if we do get good results by combining our drug with efti, **Merck will come in with their bigger cheque book and push us aside." And they would almost certainly be right.**

According to the ClinicalTrial.gov entry for the study, (NCT04811027), it will include 154 patients who will be randomised 1:1 to either efti + pembrolizumab or pembrolizumab + placebo.

Inclusion criteria will be:

- Available tissue for the assessment of PD-L1, as well as other exploratory markers.
- ECOG status of between 0 and 1 (healthy individuals to those whose cancer impairs their daily activities by a small amount).
- Adequate organ function.

The endpoints for the study are likely to be:

- **Primary Endpoint**: ORR.
- **Secondary Endpoints**: PFS, OS, drug pharmacokinetics, pharmacodynamics, biomarker analyses (PD-L1, LAG-3, etc) and the safety and tolerability of the drug combination.

Immutep had stated in a presentation earlier this year that a trial of such nature was on the way.

The trial is expected to report results a bit after April 2023.

In further recent news (April 8th, 2021), **efti has been granted Fast Track Designation by the FDA in the first-line treatment of recurrent or metastatic HNSCC**. Fast Track Designation can be granted by the FDA in cases where a drug fills an unmet medical need (defined as providing a therapy where none exists) or providing a therapy which may be potentially better than available therapy. It is designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill unmet medical needs. It offers benefits like:

- More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval.
- More frequent written communication from FDA about such things as the design of proposed clinical trials and use of biomarkers.
- If certain criteria are met, Accelerated Approval: This allows a compound on to the market on the basis of a surrogate endpoint, rather than a clinical endpoint, such as OS. The company will still need to run a trial showing the compound has an effect on a clinical endpoint, but this can be done while the drug is on the market at selling. Granting of accelerated can get a drug on the market years before it might otherwise reach it.
- If certain criteria are met, Priority Review: Where priority review is granted, the FDA has 6-months to review a compound's marketing application, rather than the standard 10-months.
- If certain criteria are met, Rolling Review: Normally, the FDA will only accept fully completed marketing applications, which are very large and complicated to prepare. Under a Rolling Review, the FDA will accept sections of the document overtime, which allows the FDA to get started reviewing a marketing application well before it normally would.

The more frequent meetings and more frequent written communication from the FDA are particularly useful to small companies and makes it much easier to keep the development of their compound on track.

D) INSIGHT: Administration Method in Solid Tumours Including With the ICI Avelumab (004)

Table 6. Interim Study Results From Patients in the Insight-004 Study who Received one of two Doses of efti in Combination With the PD-L1 Inhibitor Avelumab Released on 18 September 2020.

Tumor response – according to RECIST 1.1	Total N (%) Total (N=12)
Complete Response (CR)	0 (0)
Partial Response (PR)	5 (41.7%)
Stable Disease (SD)	1 (8.3%)
Progressive Disease (PD)*	5 (41.7%)
Not Evaluable (NE)**	1 (8.3%)
Objective Response Rate (ORR)	**5 (41.7%)**
Disease Control Rate (DCR)	**6 (50%)**

*Includes 2 patients with clinical progression
**Response assessment not yet performed

Source: Immutep Limited, ASX announcement, 10 November 2020

Unlike the PD-1/L1 inhibitors on the market, efti is given by a subcutaneous (SC) injection. Most immuno-oncology drugs on the market or in development are given as an intravenous (IV) infusions. SC injections are preferred by patients by a ratio of 9:1. Key reasons are pain, time and the need to travel to a medical facility with trained professionals to have an IV infusion administered. The medical community prefers SC injections because there is less chance of an injection site infection, and payers prefer SC injections because they cost less to deliver.

All else being equal, the route of administration can also influence how well a drug performs. The INSIGHT trial was an investigator-led study designed to assess the feasibility and potential benefits of administering efti as an intratumoral injection. The theory being that since tumours supress the immune system within the TME, direct injection of efti into the tumour could improve response rates. Additionally, intra-peritoneal therapy was examined for patients with tumours within that space, because of the unique anatomical barriers drugs face in accessing that site.

A major benefit of this study was that it is allowing Immutep to collect some data on how efti might perform in combination with a PD-L1 inhibitor, in this case avelumab (Bavencio®, Pfizer Inc. & Merck KGaA). Avelumab was first approved by the FDA in 2017 for metastatic Merkel cell carcinoma, a particular type of skin cancer. **It is likely this arm of the study, undertaken in collaboration with Pfizer Inc. & Merck KGaA, was the main driver behind Immutep's willingness to provide efti for the study.** There is no reason to believe that efti would not function with a PD-L1 inhibitor as it does with pembrolizumab, but, if it failed to work or did not work as well, it is better safe than sorry.

Overall, INSIGHT is an explorative, single center, open-label, phase I study. It aims to evaluate the feasibility and safety of intra-tumoral, intra-peritoneal and SC administration of efti in patients with advanced solid tumours. The ClinicalTrial.gov entry for the study is: NCT03252938. The study is due to have just concluded primary data collection. The study had the following four arms where patients with particular cancer states and being given particular treatments were given efti via various routes:

1) Solid tumour patients received bi-weekly intratumoral injections of efti as a monotherapy in increasing doses.
2) Solid tumour patients with peritoneal carcinomatosis (many tumours) received bi-weekly intra-peritoneal injections of efti as a monotherapy in increasing doses.
3) Solid tumour patients undergoing chemotherapy received efti SC at the optimal dose of efti, as defined in the AIPAC trial, for a maximum of 24-weeks.
4) Solid tumour patients receiving avelumab every two weeks by IV infusion for a maximum of 24 cycles were also given one of two doses (6mg or 30mg) of efti every two weeks SC for a maximum of 12 cycles.

Interim results from the study were first reported at the American Society for Clinical Oncology in June 2020. The results of a second interim analysis was reported at the European Society for Medical Oncology (ESMO) Annual Congress in September 2020.

Immutep's announcement on 18 September 2020 on the trial focused on arm 4 of the study, which is where we will focus. Twelve patients have been recruited into this arm group, and results from the interim analysis are in Table 6.

As can be seen, an ORR of 41.7% had been recorded at data cut-off for the analysis. Based on what we have presented so far, an ORR of that magnitude, in general, is a good result. Again, this a single-arm study with a small number of patients, so saying much more than that is hard. **The trial investigator did point out correctly that several of the patients in the study who responded had tumours in which strong response rates to ICIs are not normally seen, such as in the colon and rectum.** Moreover, the study population had been reasonably heavily pre-treated, with participation in the study representing the third or fourth lines of treatment for half of the study population. One of the 12 patients had not had their response assessment performed at data cut-off. It is worthwhile noting that only six patients received efti at its optimal dose of 30mg. The poster presented on the study does not appear to provide the data linking response to dose.

The conclusion from the study was that the low dose of efti + avelumab was safe, while the higher dose appeared safe, suggesting they had not seen enough data yet to make a firm conclusion. Efti's safety data has been fine in all of its studies to data, so we see little risk that will not be the case in this study. **Probably the main thing to come out of this study for Immutep, so far, is that efti can be safely dosed with a PD-L1 inhibitor and that the signs of efficacy were not dramatically lower and may even have been higher than expected**.

The method of efti administration in arms 1 and 2 was also safe and tolerated according to another poster presented at the conference, which is here. The authors also indicated that both intratumoral and intra-peritoneal delivery of efti was technically challenging, although it is reasonable to conclude that this observation was independent of the study drug.

E) Cancer Vaccine – CYTLIMIC INC

The idea of a therapeutic cancer vaccine has been around for at least 30-40 years, maybe longer. It is also fairly simple. The theory behind it is closely related to the theory that has allowed us to produce preventative vaccines for all sorts of bugs for decades. The idea of a cancer vaccine is to inject an antigen that is common to a particular type of cancer into a patient with that cancer and allow the immune system to do what it is supposed to do. That is, develop an immune response to the antigen and target the tumour cells bearing it. There have been, literally, hundreds of attempts at developing a cancer vaccine, but only one has ever been approved by the FDA. There are probably several reasons cancer vaccines have almost uniformly been a bust. One is that common antigens seen across the tumours of different patients tend not to be very immunogenic. They are also probably only a small amount of the unique antigens any particular tumours has, with researchers these days believing that the bulk of antigens a cancer produces are unique not only to that tumour type, but to the patient, as well. The other, of course, is that we now know that tumours can defend themselves from the immune system by suppressing it.

Provenge® (sipuleucel-T) was developed by Dendreon LLC and approved by the FDA for prostate cancer in April 2010. To develop an immune response strong enough to have an effect on prostate cancer, the product goes to extraordinary lengths. Quite simply, the patient's T-cells are isolated from their blood, pulsed with the antigen in a laboratory and then infused back into the patient's body. Unlike a normal drug, where the cost of goods sold is often immaterial, in Provenge®'s case it was/is about 50%. Provenge® is still around today but not a player in the prostate cancer market (Ref).

To a certain extent, the development of ICI's has led to renewed interest in cancer vaccines, based on the belief that removing a tumour's ability to suppress the immune system with an ICI would leave the door open for the immune system to respond to the vaccine's antigen and target the tumour. CYTLIMIC Inc, a Japanese immunotherapy company, was established in 2016 by NEC Corporation (TSE: 6701) to advance the development of therapeutic peptide vaccines.

In June 2019, Immutep entered into a clinical trial collaboration, service and supply agreement with CYTLIMIC to enable CYTLIMIC to use efti as part of a cancer vaccine. Under the agreement, Immutep received USD500 000 upfront and is eligible for up to a further USD4.5m in milestones. A royalty rate on sales was not mentioned.

CYTLIMIC has been conducting two studies of CYT001, its lead cancer vaccine, YNP01 and YCP02. CYT001 comprises peptides designed using artificial intelligence from the HSP30 and GCP-3 proteins, plus two adjuvants, efti and Hiltonol (Poly ICLC). In this setting, the term adjuvant describes agents within the vaccine that are intended to boost the immune response to the antigens within it.

In addition to publishing a paper on study YNPO1 in 2020, which is here. CYTLIMIC presented a poster at the AACR Annual Conference, mentioned below.

CYTLIMIC has made some progress in its trials of CYT001. **If CYT001 is successful and/or cancer vaccines do come back into vogue, Immutep will be in a good position to benefit given all of the data that has been collected on it and how it can be leveraged as an adjuvant in these vaccines.**

Immutep's relationship with NEC and then CYTLIMIC developed as follows:

- May 2015: Immutep enters into a collaboration agreement with Japan's NEC Corporation and Yamaguchi University, for the two to use efti as an adjuvant in a cancer vaccine.
- May 2017: Post-CYTLIMIC's spinout, Immutep entered into a material transfer agreement to allow CYTLIMIC to use efti in a test of a cancer vaccine peptide.

- June 2017: CYTLIMIC presents a poster at the American Society of Clinical Oncology (ASCO) Annual Meeting, which identifies multi-epitope peptides derived from HSP70 (heat shock induced protein 70, a stress-induced protein) and GPC3 (Glypican-3 protein, a developmental regulatory protein) for development of a novel immunotherapy. A novel cancer vaccine comprising efti and Poly-ICLC (a toll-like receptor-3 agonist and further adjuvant) and the identified peptides were tested in a phase I trial (YNP01) in 12 solid tumour patients. The vaccine was found to be safe and effective, although effective here is defined as being able to invoke an immune response, as opposed to having an effect on the cancer.
- November 2018: CYTLIMIC presents a poster at the Society for Immunotherapy of Cancer (SITC) Annual Meeting which showed that a dual peptide vaccine for HSP70/Glypican-3, which was designed using artificial intelligence and combined with efti and Poly-ICLC, produced strong induction of antigen-specific T_C cells and disease stabilisation in the last-line treatment of gastrointestinal cancers (further results from the YNP01 phase I study).
- June 2020: A poster was presented at the American Association for Cancer Research (AACR) Annual Meeting, which looked at further results from study YNP01, as well as a new study, YCP02, in patients with resectable hepatocellular carcinoma (HCC). The study concluded that the cancer vaccine CYT001 was responsible for tumour cell death in six HCC patients who had "hot" tumours, whereas there was no tumour cell death or T-cell infiltration caused by CYT001 in three patients with "cold" tumours.

Overall, it is too early to judge whether CYT001 has a good chance of being successful. More comprehensive studies are needed.

2) Eftilagimod Alpha – Infectious Diseases

Dr Triebel, Immutep's CMO/CSO, has consistently shown interest in LAG-3 and how it could be targeted to increase immune reactions in oncology, and also in infectious diseases. In fact, efti was first trialled as IMP321 in a study that examined its ability to act as an adjuvant in a hepatitis B vaccine in 2006. While Immutep's focus for efti has been firmly drawn to oncology, the theory still exists for the drug's use in the treatment of infectious diseases.

EAT COVID – Efti in the Treatment of COVID-19

On 23 October 2020, Immutep announced that efti would be looked at in an investigator lead study to determine whether the drug was capable of slowing the progression of COVID-19, the disease caused in some patients by SARS-CoV-2 infection. Immutep's only role in the study is to provide the study drug and, likely, some informal advice as it relates to efti.

The study, "**Efti**lagimod **A**lpha **T**reatment by Immune Modulation in **COVID-19** Disease", is a phase 2, 1:1 randomised, double-blind, placebo-controlled trial in 110 COVID-19 patients and is being undertaken at the University Hospital Pilsen in the Czech Republic. 10mg of efti is to be given on days 1, 3 and 7, along with the standard of care, after the patient's admission to hospital. A short lead-in stage of six patients was carried out to assess the safety of the study protocol and that lead-in stage is now complete and the randomised portion of the trial has commenced, as announced by Immutep on 27 January 2021. The European Union Clinical Trials Register (EudraCT) entry for the trial is here under the EudraCT number: 2020-002009-25.

The rationale behind the study is that efti, as an APC activator, will stimulate APCs to more robustly present antigens associated with SARS-CoV-2 to the rest of the immune system. The idea is that the response to efti will, result in a stronger immune response to the virus-infected cells of the patient, via both cell-mediated (T_C) and antibody-mediated responses (helper T-cells). Efti may also cause the T-cells and their response to develop more rapidly.

The primary endpoint of the study is clinical status at day 15, as per the World Health Organisation recommended evaluation scale. The scale is as follows:

5) Not hospitalised.
6) Hospitalised, not requiring supplemental oxygen.
7) Hospitalised, requiring supplemental oxygen.
8) Hospitalised, on high flow oxygen device.
9) Hospitalised in ICU, on non-invasive ventilation.
10) Hospitalised in ICU, on invasive mechanical ventilation or ECMO.
11) Death.

There are numerous secondary outcome measures, including how many days the patient does not require supplemental oxygen in the first 28 days, ventilator free days over the same period and mortality at days 28 and 90.

All six patients (four men, two women, age range: 50 to 83 years) in the lead-in stage of the study received all three efti injections and have since been discharged from hospital.

Regardless of what the medium to long term holds for the world with SARS-CoV-2, the short-term cause of death in COVID-19 patients is acute respiratory distress syndrome (ARDS). ARDS can be caused by a range of infectious diseases, most commonly influenza A or B. **This is an indication for which there are no approved drugs, although headway is being made in trials of some drugs currently.**

In the pre-pandemic period, the mortality rate in hospitalised patients from ARDS has been found to be between 35% and 46% (Ref), with 40% being a commonly quoted number. Finding a worldwide or even a reliable US-specific number for incidence is difficult and the literature varies heavily. One of the larger studies found the incidence of ARDS had dropped from 82.4 to 38.9 cases per 100,000 person-years between 2001 and 2008 (Ref). Given the population of the United States presently, this would be consistent with a fall in the number of cases per year from 270,000 to 128,000. The corresponding mortality figures would be 108,000 and 51,000 persons, respectively. This incidence data comes from a single county in the northern US and will not be representative of everywhere. **At the end of the day, whether it is one number or the other, it is an extremely large number for an unmet medical need and one that would represent a significant market for an approved therapeutic.**

Every shareholder would want Immutep management's time focused on the oncology applications of efti, given the quality of the data the trials are producing. However, there is little downside in Immutep providing study drug for the trial. It will take little time and cost little to do so. The upside is a positive result and the opening up of a large market opportunity. Should the market open up, there are a number of ways to handle the situation, such as out-licensing the infectious disease applications of efti to another company, which would still not take management's attention away from its required oncology focus.

The EAT-COVID trial appears to have a risk-benefit profile that strongly favours Immutep and it could pay off handsomely for shareholders.

3) IMP761 – Autoimmune Diseases

As mentioned, the immune system has to maintain a fine balance, such that threats are detected with a high level of sensitivity, but not so high that it starts to see self-proteins as foreign and mounts an attack on them. While LAG-3 has received considerable attention for its potential oncology applications, potential autoimmune applications have not received the same level of focus.

Immutep has previously out-licenced a putative LAG-3 therapeutic for autoimmune diseases, which we will discuss below. Immutep's internal program focused on autoimmune diseases is based on IMP761, an antibody toward LAG-3. **IMP761 is designed to bind LAG-3 and increase its activity.**

More specifically, the theory around using a LAG-3 agonist to treat autoimmune diseases is this. During an immune response, memory T-cells form. They are specific to the antigens that caused the immune response and their role is to remain in the body long-term, well after the antigens causing their formation have gone. In autoimmune diseases, self-reactive memory T-cells accumulate at the sites of inflammation and are thought to be the cause of the inflammation. When these cells are continually stimulated by self-antigens, they become exhausted and start to express LAG-3 (activated T-cells in the blood do not normally express LAG-3). The idea behind IMP761 is that when it binds LAG-3 on these self-reactive memory T-cells, their activity should be down regulated, hopefully by enough to decrease or stop the self-reactive memory T-cells from causing the inflammation. Thus, decreasing or eliminating the activity of the particular autoimmune disease.

Immutep reported in September 2018 that it had conducted preclinical studies with IMP761 in non-human primates (NHPs) which confirmed the antibody's ability to suppress immune responses in the animal's tissues. Having done that, Immutep was ready to engage a partner to develop a cell line under Good Manufacturing Practice (GMP) from which a clinical trial quality drug (antibody) could be produced.

In March 2019, Immutep presented the results from the *in vitro* studies and the NHP studies of IMP761 at the 14th Congress of European Crohn's and Colitis Organisation (ECCO). The study involved injecting doses of an antigen into the NHPs SC to create a delayed-type hypersensitivity reaction (DTH). A DTH is one that takes days to develop, whereas the other type of hypersensitivity reactions occur in minutes. The reason for the delay in this type of reaction is thought to be that it requires cell to cell interactions to occur, rather than just the detection of a foreign compound by immune cells, which then release chemical stimulators within minutes of exposure. The abstract for the presentation can be found here. Ultimately, the study was published in full and the article can be found here.

In the NHP study, the monkeys were vaccinated with Bacillus Calmette–Guérin or a BCG vaccine, which protect humans against tuberculosis. The vaccine comprises live attenuated (no-longer harmful) *Mycobacterium bovis*, which shares enough similarity with *M. tuberculosis* to create immunity to it. Two weeks after vaccination was complete, the 12 vaccinated NHPs were challenged with tuberculin to demonstrate all had been vaccinated and that they would develop a DTH reaction upon tuberculin challenge. Six to seven weeks after vaccination completion, three NHPs were given IMP761 at one dose, three at a higher dose and six were given phosphate buffered saline as a control. One day after IMP761 dosing, the NHPs were, again, challenged with tuberculin. Skin biopsies of the animals demonstrated that both doses of IMP761 were capable of decreasing T_C cell infiltration at the injection site, as well as T_H cells. The study concluded that IMP761 was capable of ameliorating a DTH reaction in NHPs and should be able to do the same in humans and may have utility as a therapeutic in autoimmune diseases. **Essentially, this study provides animal proof of concept for IMP761.**

In April 2020, Immutep announced that Batavia Biosciences, the group Immutep engaged to create the cell line for IMP761, had made significant progress toward that aim. Importantly, the yield of IMP761 produced by the Chinese hamster ovary (CHO) cell line would be sufficiently high to support IMP761 development requirements going forward.

Common autoimmune diseases include multiple sclerosis, rheumatoid arthritis, coeliac disease, ankylosing spondylitis and type 1 diabetes. A drug capable of stimulating LAG-3, especially selectively, could reduce the severity of these diseases by bringing the immune system back into its normal balance, where those self-antigens are no longer attacked. That is, IMP761 would play a disease-modifying role, whereas existing therapies only treat the symptoms of autoimmune diseases. Although we do not yet know the indications for which IMP761 will be developed, the market for autoimmune diseases is thought to be bigger than that for cancer or heart disease. Its value was estimated at ~110 billion in 2018, with an expectation that it will grow to USD153 billion in 2026 (Ref). According to the US National Institutes of Health, 24 million Americans are believed to have an autoimmune disease of which there are 80 known types (Ref). Humira (adalimumab, AbbVie Inc), which is indicated for rheumatoid arthritis, as well as several other autoimmune diseases, was the world's top revenue-generating drug last year. Its sales were just shy of USD20 billion in 2020. **Five (25%) of the world's top-20 revenue generating drugs are for autoimmune diseases and account for USD42.9 billion in revenues (M. Sinatra Research).**

Immutep says that further updates on the development of IMP321 are expected throughout 2021.

While it is early days for IMP761, given the expertise of Dr Triebel, the man behind the program, investors should treat it seriously and not as a potential source of unaccounted upside.

Immutep's External Pipeline

Two clinical-stage therapeutics form the base of Immutep's external pipeline. The drugs were fully out-licenced at the pre-clinical stage of development, nine and 10 years ago. If either or both of these drugs are a success, they could generate very substantial revenues via sales royalties, not to mention the milestones payable along the way. Overall, a royalty could be in the mid-single digits or provide USD50 million to Immutep for every billion dollars of sales generated by the out-licenced drugs collectively. The main game at the moment, though, is efti, such that if one of these programs is not successful, it would not be the end of the world. Still, for the potential value that these deals may create, it is worth understanding them and following the progress of the development candidates.

One of the downsides of out-licencing a therapeutic to another company is that the compound essentially becomes the property of that company. The licencee determines what can and cannot be said publicly about the development of the candidate. Moreover, when compounds are licensed to large companies, as Immutep's have been, listed or not, information regarding their development slows to a trickle. These large companies do not have to provide a steady stream of news about their developmental candidates to keep their shareholders engaged and attract new ones. Moreover, rarely does an event with one developmental candidate rise to the level of materiality for such companies, given they are so large. What to disclose and what not to disclose in these situations comes down to simple competitive dynamics. The less your competitors know about what you are doing, the better. Investors considering Immutep should not invest on the basis that they will be told about everything happening with either of the two following compounds. Thus, you have to kind of guess what a what a big licensee is doing with a partnered compound.

A) LAG525 – Licenced to Novartis

LAG525 or, as it was then known, IMP701 was licenced by Immutep to CoStim Pharmaceuticals in 2012. Novartis International AG (SWX: NOVN) bought CoStim in 2014 and with the purchase it gained IMP701, which it later renamed LAG525. The terms on which Immutep licenced LAG525 to CoStim are not in the public domain, nor is the purchase price that Novartis paid for CoStim, although it is known that CoStim had several late-stage development programs, one aimed at a PD-1 inhibitor. While Novartis' main interest in CoStim may have been its PD-1 inhibitor, spartalizumab is the PD-1 inhibitor the company has been moving forward with in the clinic and they do not appear to be one and the same.

LAG525 is a much simpler concept than efti. It is a blocking antibody, such that its MOA is to prevent LAG-3 from interacting with pMHCII and downregulating the cell's activity. The studies that Novartis has LAG525 in, and their stage of development, are given in Table 7. **To be clear, LAG525 does not have any APC activating characteristics**. In fact, you could probably combine efti and LAG525 to activate APCs and as well as block LAG-3 and a route of immune escape.

The first thing to note is that Novartis has paired LAG525 with spartalizumab in every trial. The second is that all of these studies are single arm, open-label trials such that Novartis has been able to watch the data as it comes in. The 490-patient solid tumour study was the first that Novartis commenced. In 2018 and early 2019, it started the other four studies. The solid tumour and haematological malignancy trial may have been to take a closer look at a few interesting things they saw in the main solid tumour trial. The main focus now seems to be the melanoma trial, which just completed, and the triple negative BC trial that has a little less than a year to run. In both of these trials, the focus is on what further drugs Novartis can pair with LAG525 + spartalizumab to increase response rates,

Unfortunately, the trials do not seem to be building and the issue seems to be spartalizumab, not LAG525. Spartalizumab failed a phase III trial in melanoma in August 2020 when paired with two targeted therapies. In January 2021, Novartis paid BeiGene USD650 million upfront, USD1.5 billion in milestones and royalties on sales for ex-China co-development, and commercial rights for tislelizumab, BeiGene's PD-1 inhibitor. Tislelizumab already has approvals in non-Hodgkin's lymphoma and metastatic urothelial carcinoma in China.

The question is whether or not Novartis will seek to pair LAG525 in any trials with tislelizumab. There is, in fact, some crossover between the patients recruited in the completed 76-patient solid tumour and haematological cancers study and some of the indications Novartis said it will be seeking approval of tislelizumab for (Ref). Moreover, Novartis does appear to be getting ready to take a combination therapy route with tislelizumab, which would work in LAG525's favour. The next few months will tell us a lot about LAG525's future at Novartis.

Novartis is a cancer drug powerhouse. If it does get serious about pairing LAG525 with tislelizumab, things could happen quickly and a 5% royalty on LAG525's sales could turn out to be a reasonably large cash flow.

B) GSK'781 – Licenced to GlaxoSmithKline

GSK'781 (also known as GSK2831781 and previously, IMP731) was licenced from Immutep in January 2011. For the rights to the antibody, GSK paid an unknown upfront fee and agreed to pay aggregated milestones of £64m (or around USD100m, at the time). They also agreed to pay tiered single-digit royalties on sales if all objectives are achieved. In September 2019, GSK paid Immutep a £4.0m milestone on first patient dosing in a phase II trial GSK'781 in the treatment of ulcerative colitis.

GSK'781 and IMP761 are different. GSK'781 is a depleting antibody**. It does not bind to LAG-3 expressing cells to suppress their activity, but to kill them.** Upon binding LAG-3 on a target on a cell, LAG525 can theoretically cause the cell's death in one of two ways. One is called antibody-dependent cellular cytotoxicity (ADCC), which occurs when another immune cell (known as a natural killer or NK cell) comes across it and recognises the tail end or Fc region of an antigen-bound antibody. When that occurs, the NK cell sets in motion a chain of events to see the target cell's membrane lysed (broken down) resulting in its death. Other cells, such as macrophages, can also cause ADCC. The second mechanism is known as complement-dependent cytotoxicity and is a chemical reaction the bound antibody starts, which also results in the bound cell's death. The aim of GSK'781 is to target the memory T-cells causing the inflammation resulting in the autoimmune disease and kill them. An ideal outcome of the use of

Table 7. Recent Clinical Trials of LAG525 and Various Parameters.

Broad Indication	Combination Agent(s)	Trial Size – # Patients	Trial Completion Date (Estimated)	Stage of Development
Solid Tumours & Blood Cancers	spartalizumab	76	February 2019	Phase II - Complete
Triple Negative Beast Cancer	spartalizumab, carboplatin	88	February 2020	Phase II - Ongoing
Melanoma	spartalizumab, capmatinib, canakinumab, ribociclib	195	December 2021	Phase II - Ongoing
Solid Tumours	spartalizumab	490	December 2020	Phase II - Complete
Triple Negative Beast Cancer	spartalizumab, capmatinib, lacnotuzumab, canakinumab, taminadenant	220	January 2022	Phase I - Ongoing

Source: ClinicalTrials.gov, M. Sinatra Research

GSK'781 would be to reduce the severity of the autoimmune disease over time to the point where the patient was cured or functionally cured.

GSK has studied GSK'781 in a phase I study where healthy Japanese and Caucasian subjects were given single IV infusions of the drug. In the same study, a cohort of healthy Caucasian patients were given single administrations of two different doses of the drug by SC injection. GSK has also studied the drug in a phase I dose escalation study in Caucasians with psoriasis where the drug was given by IV administration. The results of the latter trial have been published (Ref). The study found that adverse events were evenly spread across the various groups in the study and that no safety or tolerability concerns were identified. Importantly, **Psoriasis disease activity improved up to day 43 at all dose levels tested compared to placebo in a dose-related manner. This was reflected in reductions of LAG-3+ T-cells in the blood and psoriatic plaques**.

A phase II trial of GSK'781 was commenced in May 2019 in patients with ulcerative colitis, an inflammatory disease of the colon and rectum. Patients experience a variety of symptoms, including rectal bleeding, blood in their faeces and abdominal pain, due to inflammation and ulcers caused by the disease. Most patients will have part or all of their large bowel removed at some point in their life. The primary endpoints of the study were both safety and efficacy-based and the ClinicalTrials.gov entry for the study can be found here: NCT03893565.

The trial design was somewhat complex and was as follows:

Cohort A – Double Blind: Patients were given GSK'781 intravenously in a 10-week induction phase at different dose levels. Patients identified as responders at week 10 received the study drug via SC injection during a 12-week extended treatment phase.

Cohort B – Open Label: Patients received GSK'781 in a 10-week induction phase. Participants who were identified as non-responders at week 10 were given GSK'781 from week 12 to week 22. Patients identified as responders at week 22, then entered an open label extended treatment phase for 12 weeks. Non-responders at week 22 discontinued treatment.

Cohort C – Double Blind: Patients received a placebo in the induction phase. Those that responded at week 10 continued to receive placebo SC during the extended treatment phase from weeks 14 until week 26.

Unfortunately, the trial was stopped by the data review committee on 22 January 2021. The precise reason was not stated in the announcement to the market, though there are only two reasons why trials are stopped at this stage of a study. A serious adverse event, or futility. Futility means the study results, although not complete, had reached a point where the study drug would almost certainly not show a benefit over the control arm. **When we checked the pipeline section of GSK's website, it said the trial was stopped for futility**.

It is not overly surprising that GSK would run a trial in one autoimmune condition, psoriasis, and get a positive readout and then run another one in a different condition, ulcerative colitis, and get a different result. **Autoimmune diseases are highly complex and do vary considerably from one to another, such that disparate trial results are not unexpected**.

GSK will undoubtedly have a very close look at the ulcerative colitis data. What they do in the end will probably depend a reasonable amount on the need to give the drug by IV infusion. In some forms of autoimmune disease, such a drug delivery method would be acceptable to patients, in others, like psoriasis, it is not an ideal offering.

Whatever GSK decides to do, the most unlikely outcome will be to discontinue development of GSK'781 in our view. A therapy for autoimmune diseases that stops them from occurring, rather than just treating the symptoms, is too tantalizing a prospect. They also already have proof of concept for the compound in a different autoimmune indication**. Most likely, GSK will pick a different autoimmune disease and take another shot.**

Importantly, there will be learnings that Immutep can apply to IMP761 and its development. In the NHP studies of IMP761, the drug did not need to be given as an IV infusion like GSK'781. If that holds true in the clinical setting, Immutep will have a wider range of autoimmune diseases to choose from than GSK. More importantly, **Immutep already knows of one indication in which IMP761 is likely to work, psoriasis.**

Major Forces That Will Influence and Support Eftilagimod Alpha's Value

Efti and its application in oncology clearly forms the core value of Immutep. As a result, the remainder of this document will focus largely on that topic. It will look at the nature of therapeutic markets, the ICI market as it stands, other drugs looking to activate the immune system in development and the end-game for Immutep and efti. Where appropriate, reference may be made to other assets and the final section of the document will look at management. Management is never focused on enough. Technologies do not invent themselves or commercialise themselves. Moreover, the drug industry, in particular, is one that is reliant on several key areas where you must have the right level of knowledge and experience.

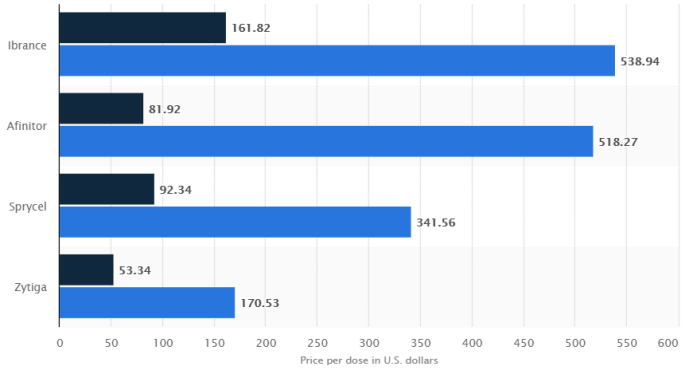
The Nature of the Oncology Market

The market for oncology therapeutics is complex and far-removed from standard free supply and demand-driven markets. We will focus on a few peculiarities of this market, with an emphasis on oncology, giving reasons why the market is the way it is.

One of the first things investors must understand about the protected prescription drug market is it is not a free market. Each of the products in the market are protected, to varying degrees, from direct competition. The degree of protection can vary from complete, almost monopolistic protection to more subtle protection where highly similar products may exist, but exact copies are not allowed. These protections come about because of patents and are legislationally-mandated in other cases. The latter are usually seen in therapeutic areas where a government wants to further stimulate innovation, such as the development of therapeutics for rare, life-threatening conditions, where the market size alone is not enough to stimulate product development. These protections, in general, fall into two categories. One is market exclusivity, where copies of a drug cannot be marketed. The other is data exclusivity, where those who wish to develop a copy of a drug are not allowed to use the originator's (the company who developed the protected drug) data to support the use of their copy in approval applications. Companies wishing to develop a copy in the circumstance where an originator's therapeutic has data exclusivity must largely start from scratch. They must do all of the studies, such as clinical trials, to build a full data package to support the approval of their product. Needless to say, such a requirement almost always results in a situation where it is not commercially appealing to develop a drug only to be second to market. Primarily, it is just too expensive.

It is also highly regulated. The FDA employed 17,686 full-time equivalents and had a budget of USD5.9 billion in 2019 to enable the agency to regulate the areas that fall under its purview (Ref). The FDA does a lot more than regulate the development of therapeutics. For example, it also regulates medical devices, certain foods, veterinary products, and conducts a range of post-marketing surveillance activities over the areas it regulates. However, 33.0% of the agency's budget is dedicated to drugs and 7.1% to biologics, the two areas in which are responsible for new therapeutics. **For nearly every step of the development of a therapeutic, there is an FDA document stating how something needs to be or should be done**. In Europe, the European Medicines Agency (EMA) acts as an over-arching regulator, with country-specific regulators as well.

Figure 2. 2018 Prices per Dose of Four Common Branded Oncology Drugs in the US Compared to the Rest of the World.



Source: Statista 2021

The main payers for protected therapeutics are also not the end user in the vast majority of cases. The main payers in the US are, in fact, employers, insurance companies and the US government through its Medicare and Medicaid programs. In the UK, it is a government body, the National Health Service (NHS) who provides funding for most medicines. Another body, called the National Institute of Health and Care Excellence (NICE), determines what the NHS will pay for a particular medicine.

Pharmaceutical companies seeking NHS funding for their medicines must justify the price they intend to charge the NHS. NICE's job is largely to ensure that the price the NHS pays for a therapeutic accurately reflects the benefit it brings, relative to existing therapeutic options. One of the major differences between the US and UK therapeutics markets is that Medicare and Medicaid are forbidden from getting involved in negotiating individual drug prices, while NICE in the UK essentially has a formula for what it is willing to pay. If a therapeutics company is not willing to sell at that price, the NHS will not be buying. A significant outcome of the two different systems is that the cost of protected medicines in the US is roughly twice that compared to the UK, according to an analysis done by the research firm IHS Markit (Ref).

The prices of oncology drugs in the US are particularly high, as figure 2 illustrates.

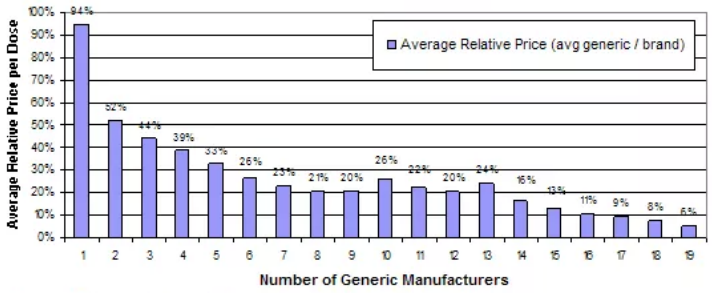
The point is, the value of the market for protected medicines overall, and per disease, does not reflect a pure supply and demand-driven market. They do not reflect a monopolistic pricing market, either. Instead, they reflect variables unique to each geographic market in which they are sold.

The market for therapeutics is not a zero-sum game, as it is with many other products. This is important for investors/potential investors to understand. The market for medicines to treat a disease, or stage of disease, can expand and contract almost instantaneously. How and why, it happens is, to a large extent, due to the magnitude of the need of the patient, the politics surrounding that patient group and the level of attention the size of the market demands from payers (largely other than the patients that comprise the market). At the end of the day, though, the structure of the therapeutic market and sub-markets within it has evolved to meet the requirement that rapid expansion and contraction needs to occur. This enables new protected therapeutics that command a premium price, for the various reasons they do, to come on to the market without causing much of a ripple. The same is true for therapeutic spaces like immuno-oncology drugs over longer periods. The size of the market for these medicines has expanded at an extraordinary rate from zero in 2011 to over USD28 billion and growing today. Still, the money to pay for them has been found.

Market sizes, however, can fall away just as quickly, when protected medicines lose their protected status, generics enter the market and prices quickly start to head toward the marginal cost of production. In fact, the US and others have actually legislated to speed the contraction of therapeutics markets. For example, the US has incentives that encourage companies to challenge the patent protection of protected therapeutics. Moreover, the US also has incentives for those companies who would seek to bring a generic copy of a protected therapeutic on to the market, once the therapeutic loses protection. That incentive is a period of six months for small molecules and between 12-months and 42 months for biologics, of market exclusivity as the only generic allowed on to the market. Immutep's therapeutics are considered biologics. It may not sound like all that much of an incentive, but for generics companies that compete in the volume game of that part of the market, it is a windfall. Generics companies are relatively simple businesses, which, over many decades, have honed their ability to compete based on price. They can make a lot of money in a short period of time, when they do not have the normal competition to deal with.

A good basis for visualising the entry of small molecules into a market comes from a study conducted by IMS Health in 2005. When there is only one generic in competition with a branded drug, the average price for the compound the therapeutics are based on declines by only 6%. Once a second generic enters the market, the average price declines by 48% and steadily drops by about 5%

Figure 3. The Effect of Generic Competition on the Price of Medicines Base on a Particular Compound.



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective (TM), 1999-2004, extracted February 2005

for each of the next four generics on the market thereafter, as figure 3 illustrates. Obviously, generic competition can cause the size of a market to contract quickly.

The fall in price when a generic biologic enters the market is likely not as severe, although there is not a lot of data on it. At least one of reasons generic biologics seem to hold their price longer is the extended period of protection given to the first generic biologic to enter the market.

The nature of the therapeutics market is reflected by the low betas of companies (often in the range of 0.4 to 0.7) that operate in those markets. That is, the market size is not overly influenced by the state of the global economy. Patients still need their medicines when the economic outlook is poor. Increases in market size are simply absorbed, while decreases are hurried along.

Another interesting aspect of the protected medicine markets is the way in which therapeutics are developed and marketing approvals granted, combined with the medical community's requirement for evidence that a therapeutic works. **The biology of many diseases, especially cancer, tend to promote product differentiation, not competition.**

Therapeutics take, on average, 12 years to reach the market. It is commonly accepted that only 5% to 10% that start clinical trials will make it there. Moreover, therapeutics are costly to develop. While the cost does depend on many different factors, numbers like over USD1 billion each are commonly thrown around and supported in literature. Overall, the therapeutic development process is long and risky, no matter how it is measured. Additionally, regulators, specifically the FDA, require that a therapeutic be shown to be safe and efficacious for a highly-defined patient population (i.e., an indication). Even without these requirements, many doctors would not prescribe a therapeutic that has not been shown to be safe and efficacious based on the doctrine of science-based medicine. **This high risk/return environment leaves therapeutic companies looking for ways to manage risk**.

Even a seemingly identical disease between two unrelated patients will almost always differ in their biology at some point, even if that difference comes down to just one base-pair in a patient's, or an infectious agent's, DNA/RNA. The way marketing approvals are granted by regulators means that just about any difference, even the one just described, can be used by a therapeutics company to develop an indication for its medicine. This is especially so for cancer, where the disease changes as it progresses. Oncology medicines also, as a general rule, only work for a period of time for a patient, if they work at all, before a patient stops responding to them. **For every medication, a cancer patient fails, the potential for a new indication is created**. To look at it another way, an anticancer therapeutic may fill a need in the market, but, at the same time, creates a need in patients who have taken the medication and failed it.

A therapeutic will, invariably, work better in some indications than others. Which indications those are is can be predictable. **Thus, choice of indication gives the developer a way to manage risk, from a likelihood of success, and from a competitive, point of view**.

Since there is no need for two companies to compete unless it is profitable for them to do so on a risk-adjusted basis and that therapeutic companies operate in such a risky area, it makes sense for companies to diversify away from direct competition, where possible. Since the available indications in oncology are so numerous, there are more opportunities to manage risk and, of course, companies take advantage of this. The net result is that, while one drug may be able to capture a large share of the market, even the largest companies do not have the resources to take advantage of every opportunity presented, nor is it likely their therapeutic will be the best alternative for every indication.

The message is no matter how dominant one therapeutic may look in an area, there is almost always room for another medicine that will generate solid revenues.

The final point about the oncology therapeutics market is **many of the indications within it sit at the sweet spot on the scale of the number of patients afflicted by a disease and what can be charged for a drug**.

Of course, there is one reason dominant reason that protected cancer therapeutics can sustain such high prices. Without them the patient will die.

At one spectrum of therapeutic indications, you have your orphan and ultra-orphan diseases, like spinal muscular atrophy (SMA). SMA is a rare neuromuscular disorder that results in the loss of motor neurons and progressive muscle wasting. Patients who are born with the most severe form of the disease do have significantly shortened lives, with only a small number (10%) surviving into adulthood. For the three less severe forms, lives well into adulthood are expected. There are three therapeutics approved for SMA, with list prices per year of USD340,000, USD375,000 and USD2.1 million. Zolgensma is the most expensive one and commands such a high price because it is a one-off gene therapy treatment. SMA therapeutics are, in general, much pricier than cancer medicines. However, the prevalence of SMA is only 8,526, 9,429, and 10,333 for types I, II, III respectively (Ref), for a total market of ~25,000 patients. **Despite these prices and the seriousness of SMA, none of the SMA medications are anywhere near the top selling therapeutics based on revenue.** There are not enough patients to get them there.

Type-2 diabetes is huge in terms of the number of patients it afflicts; 34 million Americans have the disease according to the US Center for Disease Control. That is a little more than one in every ten Americans. Trulicity® (dulaglutide, Eli Lilly & Co.) a glucagon-like peptide-1 receptor agonist (GLP-1), is indicated for use, in combination with diet and exercise, by patients with type-2 diabetes. Although Trulicity® is not indicated for every type 2 diabetic, the number of patients it is indicated for dwarfs any single cancer indication by many times. Yet, Trulicity®, as the number one ranked diabetes medicine in terms of revenue in 2019, only came in at number 19 with USD4.3 billion in sales relative to all drugs. **Eleven cancer drugs were above it on the top 20 list**. One of the reasons is that the list price of Trulicity® is only USD844 per month or ~USD10,000. Protected cancer drugs routinely have list prices of more than 10 times that much. Sticking close to home, Merck has a list price of USD170,000 for Keytruda® and GSK's Imfinzi® has a list price of USD180,000.

The number of Americans alive who have or had a cancer diagnosis was estimated at 15.5 million in 2016 (Ref) or roughly half of those with diabetes. That does not mean that 15.5 million currently have cancer or are receiving a cancer therapeutic. Moreover, of the ones taking a therapeutic, the actual therapeutic they are taking will be dependent on cancer type, subtype, stage, line of therapy, etc. **Cancer drug spending is spread across a whole range of sub-markets and therapeutics, with many cancer markets in the range of USD25k patients to 100k.** With diabetes, there are only four market segments, insulin, GLP-1 agonists, DPP-4 inhibitors and SGLT-2 inhibitors. Each one of these has several million people in it and taking a medication.

The unique characteristics of the therapeutics market and, in particular, the oncology sub-markets, has meant that oncology is an extremely attractive market for new product development. More importantly, the structure of these markets is largely artificial and is designed to achieve things society deems as important, such as support for ongoing innovation and the development of new therapeutics that improve the human condition. Overhauling the system so that it still did what it was designed to do, but at a significantly reduced cost, would be a massive and highly disruptive undertaking and one for which a positive outcome is not assured. **For these reasons, the market for therapeutics and, particularly, oncology therapeutics, is likely to remain largely as it is for a long time**.

The PD-1/L1 and CTLA-4 ICI Market

One of the reasons for that last section was to try and help investors understand what is happening in the immuno-oncology market and, in particular, the ICI market. The ICI market is really what has been generating the growth of immuno-oncology and will generate the growth of drugs like efti going forward, which can be paired with ICIs. **It should not, however, be forgotten that efti is likely to have applications outside of being paired with an ICI, as the HER+ mBC trial shows.** The aim of this section is to show the tsunami of licensing and acquisition deals that are likely to be spurred for drugs that can be paired with ICIs simply as a result of the size of the market and the competition that will inevitably be created.

Table 8 details the ICI market's currently approved therapeutics, the indications for which they are approved and their 2020 revenues, among other things. Figure 4 provides a visual view indications for which an approved ICI exists, what those indications are, which ICIs hold particular approvals. The figure is completely up-to-date.

While there is a lot of information in the Table 8, two columns stand out. The first is the one providing the date of the first approval for each ICI and the second is the one outlining the 2020 revenues for each of those ICIs. When ipilimumab was approved by the FDA 10 years ago, very few would have predicted we could assemble this table and that it would look anything like it does.

Adding up all the revenues in Table 8, the market for ICIs has grown from nothing the day ipilimumab was approved, to USD28.5 billion at the end of 2020.

In the near-term and years following, further PD-1/L1 inhibitors are likely to make it to market. Incyte Corporation (NASDAQ: INCY) is awaiting the FDA's decision on retifanlimab for squamous cell carcinoma of the anal canal, while GSK is awaiting a decision on dostarlimab for high and microsatellite stable endometrial cancer.

There are also two other companies expected to enter the ICI market, which are still to get there.

The main company is Novartis. It is the third largest oncology company in the world by revenue and markets the broadest range of anticancer treatments, including targeted therapies, radioligand therapies and, cell and gene therapy products. It must have a PD-1/L1 inhibitor to complete the competitive vision it is hoping to attain in the industry as the pharmaceutical company with the broadest cancer offerings. Novartis has been developing, and continues to develop, spartalizumab, the late-stage compound towards that aim. After spartalizumab failed a trial in melanoma, its entry into the market looked like it might be considerably delayed. To ameliorate that situation, Novartis has just licenced ex-China rights for tislelizumab, the PD-1 inhibitor from BeiGene, as previously mentioned.

Eli Lilly & Co (NYSE: LLY) has a significant oncology franchise and is one to watch. Lilly has teamed up with Innovent, a Chinese company, and is aiming sintilimab at NSCLC, despite the fact that this is an indication that Merck seems to have tied up with Keytruda.

Other companies are looking to develop PD-1/L1's that are easier to give. Pfizer has sasanlimab, given by SC injection, Curis Inc. (NASDAQ: CRIS) and Gilead (NASDAQ: GILD) are developing two oral, small molecule, PD-1/L1 inhibitors, CA-170 and GS4224, respectively.

There are almost certainly others we are missing.

What is attracting them to the market? In some cases, it is a market some companies just need to be in. **Others see ICIs and immuno-oncology therapeutics, in general, eventually becoming mainstays of cancer treatment and are strategically focused on the area for the long haul**.

Evaluate Vantage sees pembrolizumab's sales growing from USD14.4 billion in 2020, to USD16.8 billion in 2021 and to USD26.3 billion in 2026. Bernstein Research has forecast pembrolizumab sales to grow to USD25 billion in 2025, which is a similar figure. Evaluate also sees nivolumab returning to growth strongly, moving from USD7.0 billion in sales in 2020 to USD8.8 billion in 2021. While GlobalData has Nivolumab at USD12.0 billion in 2025. **More broadly, Research and Markets has the overall ICI market at USD40 billion in 2025, almost a third higher than where it is now. Market Data Forecast is more bullish, pegging the overall 2025 ICI market at USD45.4 billion**.

Most investors may look back over the last 10 years' growth and wonder what forecasters think the future holds, asking themselves, "Can the ICI market really grow as forecasters expect and what about beyond 2025?"

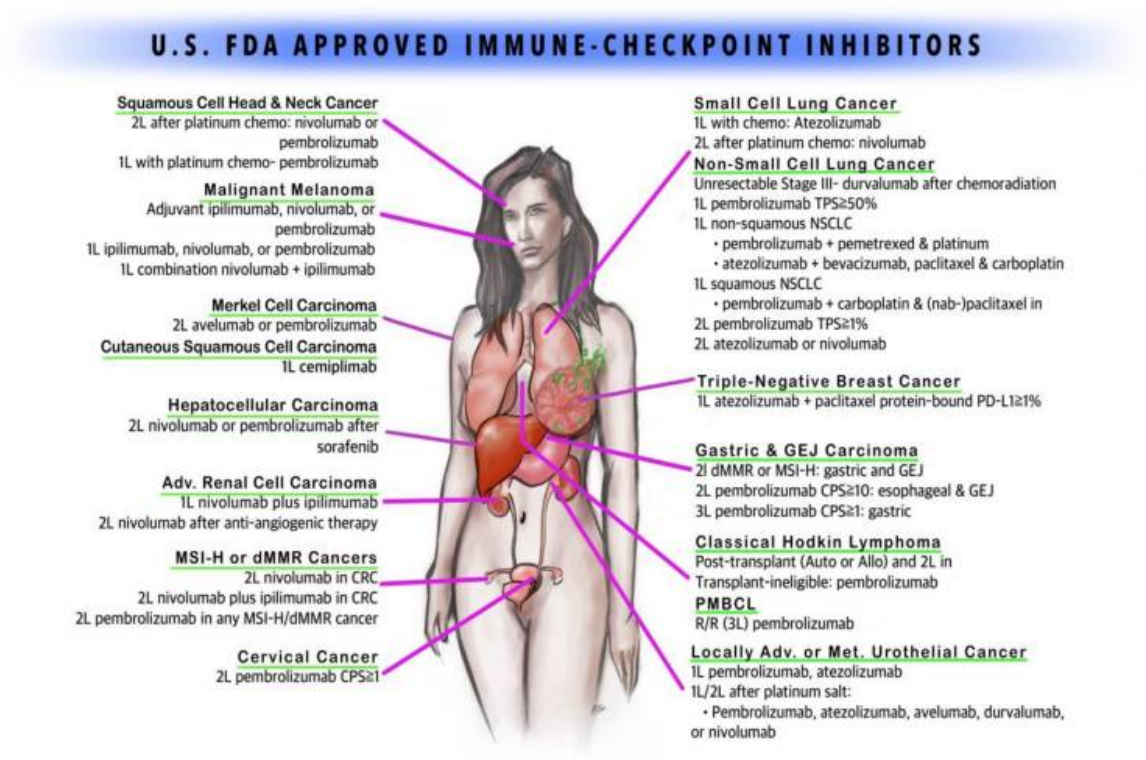
Table 8. The Currently Marketed ICIs, the Number and Nature of Their FDA-Approved Indications and Their Full Year 2020 Revenues.

ICI	Brand Name	Target	First Date of Approval	Company	No. of Indications	General Indications	2020 Revenues Million USD
ipilimumab	Yervoy®	CTLA4	March 2011	BMS	11	Melanoma, Metastatic, Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Malignant Pleural Mesothelioma	$765
pembrolizumab	Keytruda®	PD-1	Sept 2014	Merck	23	Melanoma, Metastatic, Non-Small Cell Lung Cancer, Head and Neck Cancer, Hodgkin's Lymphoma, Urothelial Carcinoma, Gastric Cancer, Cervical Cancer, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Renal Cell Carcinoma, Small Cell Lung Cancer, Oesophageal Carcinoma, Endometrial Cancer, Squamous Cell Carcinoma	$14,380
nivolumab	Opdivo®	PD-1	Dec 2014	BMS	21	Melanoma, Metastatic, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, Hodgkin's Lymphoma, Head and Neck Cancer, Urothelial Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma, Small Cell Lung Cancer, Oesophageal Carcinoma, Malignant Pleural Mesothelioma	$6,992
atezolizumab	Tecentriq®	PD-L1	May 2016	Roche	10	Bladder Cancer, Non-Small Cell Lung Cancer, Breast Cancer, Small Cell Lung Cancer, Hepatocellular Carcinoma, Melanoma, Metastatic	$3,821
avelumab	Bavencio®	PD-L1	March 2017	A) Pfizer B) Merck KGaA	4	Merkel Cell Carcinoma, Urothelial Carcinoma, Renal Cell Carcinoma	A) $178 B) $156 $334[1]
durvalumab	Imfinzi®	PD-L1	May 2017	AstraZeneca	4	Non-Small Cell Lung Cancer, Small Cell Lung Cancer	$2,042
cemiplimab-rwlc	Libtayo®	PD-1	Sept 2018	A) Regeneron B) Sanofi	3	Squamous Cell Carcinoma, Basal Cell Carcinoma, Non-Small Cell Lung Cancer	A) $97 B) $67 $164
dostarlimab	Jemperli®	PD-1	April 2021	GSK	1	Recurrent or Advanced Endometrial Cancer	N/A N/A

Source: Drugs.com, company filings and M. Sinatra research; 1 Pfizer did not breakout its revenues from Bavencio in the FY20 report. We have estimated Pfizer's revenue for Bavencio® based on a reported, but unconfirmed, profit-share agreement between the two companies of 53.3% to Pfizer.

That question is one of the reasons we examined the key attributes of the oncology therapeutics market in this report. Investors need to keep in mind that this is an unusual market. It is one driven by factors insensitive to cost and evolved to be able to support rapid growth. A large part of the question hinges on how many cancers and indications not only PD-1/L1 therapeutics will be able to treat, but how many new cancers and indications these drugs will treat when they are combined with additional therapeutics like efti and LAG-3 inhibitors.

Figure 4. FDA Approved ICIs.by Anatomical Site.



Source: Raju Vaddepally, et al.

Haslam & Prasad estimated the market size in terms of the number of patients that ICIs could eventually address and how much of the market they were addressing at the time of the research. They looked at the period from March 2011, when ipilimumab was first approved, to August 2018, just before cemiplimab-rwlc was approved. During that period six ICIs gained approval for 14 indications (full or conditional). To estimate the total number of cancer patients in the market, they used the number of patients who died in a given year from any cancer as a proxy for the available ICI market. This assumes a number of things:

- ICIs would only be used in later lines of cancer therapy when a patient had an average of one year of life left.
- There would eventually be one ICI for every for every cancer indication.
- Patients would only be treated with one ICI over the remainder of their life.

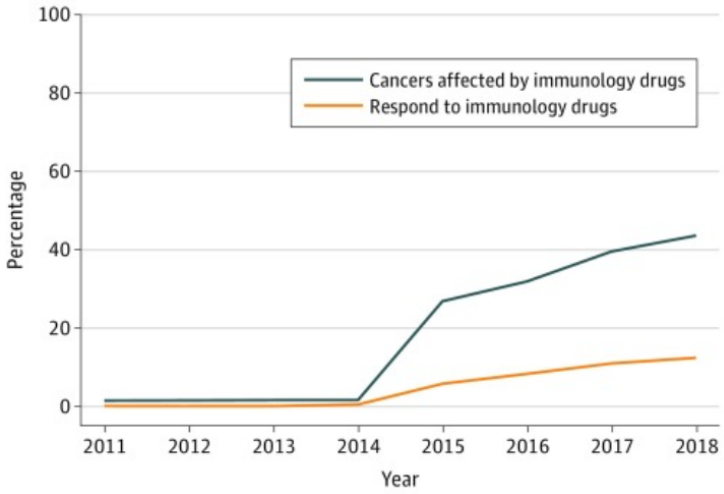
Using this assumption, the overall market size for ICIs in the US would have been:

- 572,000 patients in 2011.
- 589,000 in 2015.
- 610,000 in 2018.

The authors calculated the number of patients who would have received an ICI each, by adding up the number of patients who died of a particular cancer type for which there was a currently available ICI. Additionally, the authors used the response rates from the pivotal trial(s) which led to the ICIs approval for that particular cancer indication (or the trial which led to the conditional approval for that cancer) to determine the percentage of overall patients who would have benefited from the availability of ICIs. That data was then used to compile figure 5.

The lines of the graph are largely flat between 2011 and 2014 because ipilimumab was the only ICI available over that period of

Figure 5. The Estimated Percentage of Cancer Patients in the United States Eligible for an Immunotherapy Drug and the Percentage Who Respond.



Source: Haslam & Prasad

time and it was only approved for the small number of patients who develop late-stage melanoma. The steep rise in the graph corresponds to the approval of ICIs for lung cancer. Lung cancer may seem over-represented; however, we are looking at cancer deaths and the ratio of incident lung cancers to deaths per year is 59.3%. For colorectal cancer, the ratio is 36.0% and breast cancer it is 15.3% (M. Sinatra Research).

By 2018, 43.6% of cancer deaths each year occurred for an indication covered by ICI. The percentage of patients responding to the ICIs was 13% by 2018. We would expect the percentage of cancers covered by an ICI to have moved up significantly since this study was undertaken, although it is likely the patients responding to the therapies has remained the same or declined a bit as ICIs are approved for indications where they do not work as well as they did in those initially targeted indications.

While the study is interesting, **its biggest limitation will almost certainly turn out to be the use of cancer deaths as a proxy for the number of patients in the market. Some of those limitations are:**

1) The further up ICIs move in terms of the line of treatment they are used at and, likely, the stage of cancer they are used at, will actually grow the market beyond the numbers of 572K, 589K and 610K patients used by the authors. One of the more interesting things to know, that the paper did not address, was the median OS of the patients covered by ICIs. That provides some idea of how accurate their use of cancer deaths as a proxy for the ICI market size was, at least in the near term, because it tells how long an ICI or ICIs would need to add to the life of your average cancer patient for the market to start pushing up against the arbitrary period of a year that the authors assumed.
2) The high percentage of non-responders is another issue. Based on their numbers, while 43.6% of patients may be eligible for a drug, only 30% are responding. That means 70% of patients are only using enough of the therapeutic to determine whether they are not responding. You also need to know how long your average patient will be on a therapeutic.
3) Combination therapies, such as efti + pembrolizumab, are likely to make ICIs applicable to more patients and increase the durability of their responses, which will mean more patients on drug and for longer. Relatimab, a LAG-3 inhibitor, which BMS has been studying in combination with nivolumab, just returned positive results from a pivotal trial with previously untreated metastatic or unresectable melanoma patients**. It looks likely to be the first ICI beyond the PD-1/L1 inhibitors to be approved and more will come.**

There are issues with this study. But, as the authors point out, assumptions have to be made, and even if they end up being wrong, maintaining methodological consistency across studies can point toward an answer of what is likely to happen in the future through how wrong they turn out to be.

Still the analysis does serve to highlight that the market for ICIs is starting to get crowded in terms of how applicable they are today. That means companies competing in the market will be looking for drugs to pair with their PD-1/L1's to give them an edge over rivals.

Recently there were 1,512 clinical trials of pembrolizumab in the ClincalTrials.gov database. A total of 1,066 trials are listed as active (recruiting or not), with another 139 listed on ClinicalTrials.gov yet to start. One hundred and forty-seven (147) trials involving pembrolizumab are listed as completed, although this number needs to be taken with a grain of salt, as it is thought many investigators do not update trial entries once a trial is complete. Merck's websites suggest the company is involved 176 current studies of pembrolizumab. The ClinicalTrials.gov numbers are similar for BMS's nivolumab. Unfortunately, unlike Merck, BMS does not seem to make it as easy to find out how many clinical trials of nivolumab it is involved in at any one time.

For reference purposes, Avastin® (bevacizumab) is a therapeutic that stops tumours from growing their blood supplies, slowing the growth of tumours. In its day, like the PD-1/L1's, it was considered to be a revolutionary therapeutic. Additionally, and also like the PD-1/L1's, it is a therapeutic that was/is broadly applicable to different cancers. Unlike the PD-1/L1's, bevacizumab faced little competition, presumably due to the nature of Roche's intellectual property around it. Since 2017, bevacizumab has faced competition from generic biologics. It was first approved by the FDA in February 2004 and has since been approved for 12 indications. Its most recent approval was in December 2018, when it was approved for use with Tecentriq and chemotherapy for the initial treatment of metastatic NSCLC. There are 2,758 trials that have been entered in the ClinicalTrials.gov database. There are 550 active trials of bevacizumab, with 115 studies that have been planned, but have not yet started to recruit patients. **A total of 1,475 studies are listed as complete. Pembrolizumab and nivolumab, combined, have already surpassed bevacizumab in the number of trials they are in after just six years on the market.**

Various observations can be made from these numbers:

- There is intense interest from the medical research community to conduct investigator-sponsored studies of PD-1/L1 inhibitors.
- There could be thousands of new trials started in the future, given we have only looked at the two most prominent PD-1/L1 inhibitors.
- There will be a steady stream of journal articles published from these and future studies likely for, at least, two decades.
- In depth knowledge regarding nearly every aspect of PD-1/L1 inhibitors will be uncovered and the performance of the drugs will increase as a result.
- Merck is intensely focused on generating new data with pembrolizumab and it will likely seek many new indications going forward and that is likely to be the case for the other PD-1/L1 inhibitors, as well.

Again, all of that data indicates the PD-1/L1 inhibitor area will be highly competitive and that the larger pharmaceutical companies will be looking for a competitive edge.

Table 9 looks at the largest pharmaceutical companies in the world by revenue and their current interest in PD-1/L1 ICIs. Its contents are amazing. **Twelve of the top 15 companies by revenue have a direct interest in a PD-1/L1 ICI, where an interest is signified by either one in the market, waiting for marketing approval or, at least, in clinical trials**. Of the three that do not, two do not have cancer franchises. The other, Amgen, had its shot with rovalpituzumab, but when that was discontinued in 2019 after several clinical trial failures, the company appears to have decided to sit on the sidelines, at least for now. It, too, may decide to buy its way into the ICI market once some of the risk has been taken out of the available bets. The 12 in the race range from the market leader Merck, with Keytruda®, through to Gilead, which wants to be a player in the oncology arena but appears to have missed the boat. It is hoping that it will have some luck with its oral small molecule PD-1 inhibitor down track in three to five years or so and that the market will break its way.

Yet again, further data that indicates this will be, if it is not already, a highly competitive market.

Table 9. The 15 Largest Pharmaceutical Companies Overall (2020) and Their PD-1/l1 ICI Status.

Ranking	Company	2020 Revenue USD Billion	PD-1/L1	Note
1	J&J	$82.6	cetrelimab	In six current trials, including a phase III for bladder cancer
2	Roche	$64.6	**Tecentriq®**	
3	Novartis	$48.5	spartalizumab, tislelizumab	The latter in partnership with BeiGene.
4	Merck & Co	$48.0	**Keytruda®**	
5	GSK	$46.4	dostarlimab	Awaiting a decision from the FDA on its application for endometrial cancer
6	AbbVie	$45.8	None	Rovalpituzumab tesirine was discontinued after several trial failures
7	Sanofi	$43.15	**Libtayo®**	In partnership with Regneron
8	Pfizer	$41.9	**Bavencio®**	Also developing a PD-1 inhibitor capable of being given by S/C injection
9	BMS	$42.5	**Opdivo®**	
10	Abbott	$34.6	None	**Does not have a cancer franchise**
11	AstraZeneca	$26.6	**Imfinzi®**	
12	Amgen	$25.4	AMG404	Very late comer. Just started a solid tumour trial in 2019
13	Eli Lilly	$24.5	sintilimab	Received Chinese approval for NSCLC in Feb 2021. ROW plans unclear
14	Gilead	$24.4	GS-4224	Oral small molecule PD-1 inhibitor in a phase I/II solid tumour trial started in 2019
15	Novo Nordisk	$20.4	None	**Does not have a cancer franchise**

Sources: Company reports, company websites, ClinicalTrials.gov, M Sinatra Research.

Overall, our interpretation of the information presented is that the PD-1/L1 market has been, and will continue to be, an extremely fast-growing market. More importantly, however, **the big players in oncology therapeutics clearly believe that as well**. There are so many studies being undertaken with PD-1/L1 ICIs that it is also clear that researchers believe there is still a lot to learn and that companies still see a range of indications as possible areas for further regulatory approvals. **Where it seems highly likely demand for compounds is likely to develop are those that can be combined with ICIs.**

Currently, the players in the market all still have room to run relatively freely. A potential exception may soon become the very large market for NSCLC, where Keytruda® and Opdivo® fought and Keytruda® is on top for now. Given its size, though, many will look to carve out a niche there and it could become very crowded very quickly, as others join the three ICIs already approved for its treatment. Strangely enough, urothelial cancer is the most crowded of the indications in which approved ICIs sit (figure 4). **Five of the eight approved ICIs have some sort of an approval for the indication**. Eventually, more and more indications will start to look like that of urothelial cancer **Eyes will continue to turn to what other compounds these companies can bring in that will help them protect and expand the markets/indications they are currently in and open new markets in others. Typically, there is a trickle of activity until some sort of unseen threshold is met and the next thing you know, all of the compounds that can be helpful in this respect will have been brought into the fold.**

The Likely Evolution of the Immuno-oncology Landscape

The future of immuno-oncology is clearly combination treatments. There is very little doubt about that and PD-1/L1 inhibitors are currently the base therapy and are likely to remain so for some time.

There are numerous compounds in development which aim to influence the interaction between the human immune system and tumours. These include immune system activators, compounds targeting additional checkpoints, like LAG-3, compounds which aim to help T-cells penetrate the tumours better and several other lines of development. All have the potential to be combined with PD-1/L1 inhibitors. As these new compounds make it through clinical trials, they will be combined in many different ways and the best combinations will sort themselves out. And it is unlikely to simply be two drug combinations, but, even, three or more.

These combinations will then replace the PD-1/L1 monotherapies and efti is in a very good position to be amongst those being used in combination therapies in the clinic in the future.

Immune System Activators

While there are around 10 programs targeting anti-LAG-3 in development, there do not appear to be too many looking to activate the immune system. Efti is the only immune system activator that we were able to find that targets pMHCII on APCs. Some caution needs to be exercised here, though, because programs can be easily missed since these therapies do not have a formal class if you like. That is, it is difficult to screen for them.

There are two therapeutics that are in the later stages of development which aim to activate the immune system that we could identify. They are N-803 (previously, ALT-803) from ImmunityBio (NASDAQ: IBRX) and bempegaldesleukin (NKTR-14) from Nektar Therapeutics (NASDAQ: NKTR). A review which covers these two and a couple of other immune system activators can be found here: Ref.

N-803 is intended to be an IL-15 (interleukin-15) superagonist. Normal IL-15 serves to support the survival and proliferation of certain immune cells. N-803 is a recombinant protein comprised of IL-15, IL-15Rα and the Fc region of an IgG1 antibody. The protein is structured this way because under normal circumstances in the body IL-15Rα is cell membrane bound. In a simple formulation, N-803 could be looked at as such, IL-15Rα-IL-15. It is this complex which is required for signal transduction to occur and that happens when N-803 binds to the IL-15Rβ receptor on certain immune cells, likely primarily APCs and T_C. This is thought to cause those cells to become more prone to damaging tissues (Ref) and ImmunityBio is hoping these damaging actions will be inflicted on patients tumours. So far, N-803 has been shown to be safe and tolerable, and capable of initiating a tumour-response in the absence of a PD-1 inhibitor in NSCLC (Ref). In combination with nivolumab in immunotherapy-naïve NSCLC patients, N-803 returned an ORR of 29% (6/21), with all responses being partial. Currently, N-803 is in a 1,538 patient, randomised, open label, phase III trial in combination with pembrolizumab in the first-line treatment of NSCLC. This study is expected to read out in July 2023.

Nektar's bempegaldesleukin was granted FDA Breakthrough Therapy Designation after it combined with nivolumab produced a 53% ORR and 34% CR in a phase I/II trial in melanoma (Ref). Interleukin-2 (IL-2) is produced upon antigen stimulation and results in T-cell growth, activation and differentiation. IL-2, alone, was approved by the FDA for the treatment of renal cell cancer and melanoma, after producing complete response rates of 6% to 8% and partial responses in about 10% of patients. Systemic toxicity and a poor blood half-life limited its use. Conjugation of IL-2 with polyethylene glycol addressed these issues and, as a result, bempegaldesleukin was produced. The conjugate is currently in a range of phase III trials in combination with nivolumab where **BMS is either listed as the collaborator or sponsor**. The phase III trials are:

- A 623-patient open label study in advanced metastatic renal cell carcinoma. The estimated primary completion date for this trial is December 2021.
- A 764-patient open label trial in patients with previously untreated unresectable metastatic melanoma. The estimated primary completion date for this trial is April 2022.
- A 540-patient open label study in patients with muscle invasive bladder cancer. The estimated primary completion date for this trial is August 2023.
- A 950-patient open label study in melanoma patients who have had a complete resection but are at a high risk of recurrence. The estimated primary completion date for this trial is July 2027.

It is easier to know what to make of bempegaldesleukin, than N-803. The former clearly has something going for it and it will be interesting to see what the near-term renal cancer results like. Had TACTI-mel been a bit larger, we could have been able to line these results up with those of bempegaldesleukin + nivolumab's phase I/II study mentioned above. Efti + pembrolizumab did produce a 50% ORR in the expansion cohort of TACTI-mel, but that was only in six patients and that is not enough for any comparison. These are substantial studies and BMS is involved with Nektar in all of them. **Bempegaldesleukin could well be a good drug**.

N-803 seems to have jumped straight from a phase I/II trial in NSCLC into a large phase III trial. There have been, and currently are, quite a number of investigator-led studies being undertaken with N-803, so the company would have had more data than we can see when it made its decision to commence the phase III trial. However, **the compound also got stuck in a corporate tussle between shareholders and that could have caused the compound's development to be 'accelerated', possibly faster than is wise**. Time will tell.

Immutep - What More Can Be Done?

In November of 2020, Immutep entered into a license and collaboration agreement with Laboratory Corporation of America Holdings (LabCorp, NYSE: LH) to develop immuno-oncology products or services. The aim here is to exploit Immutep's considerable knowledge in LAG-3 biology in the development of diagnostic tests. A possibility, if Immutep knows of a suitable marker, would be to develop a test that could predict patients response to efti. Under the terms of the agreement, Immutep will receive USD125k upfront, potential commercial milestones and service payments.

There are three potential commercial milestone payments which are based on the commercialisation of new drugs or new indications of existing drugs that require the use of an immuno-oncology diagnostic being developed by LabCorp.

The use of an assay measuring a patient's tumour expression of PDL-1 in Merck's case allowed pembrolizumab to leapfrog BMS and nivolumab to become the leading PD-1/L1 inhibitor on the market, as we previously mentioned. **The point is that not only could the development of these tests be a source of revenue for Immutep, but they could also be commercially important for Immutep's drugs.**

What Is the End Game?

No matter how you look at it, it does seem clear that efti, about to start a randomised, controlled, phase IIb trial (TACTI-003) in the first-line treatment of HNSCC, is at the top echelon of potential therapies ready to be paired with PD-1 inhibitors. It also has shown the potential to be developed as a standalone agent in the first-line treatment of, at least, some subgroups of HER+ mBC patients. However, Immutep almost certainly does not want to be in the sales and marketing game or if it wants to be, it is likely misguided. **At the end of the day, efti will be worth more to one of the large immunotherapy-focused companies, than it will be to Immutep shareholders, because of the larger company's increased sales reach, ability to coformulate with other therapies and ability to compete for new patients and defend areas of the market already won.**

Being a one-of-a-kind immune system activator also means that efti offers something to the larger pharmaceutical companies others do not. That is the ability to compete in markets from a unique angle. **That is the sort of attribute that companies who desperately feel they need to be in the ICI market, but are not quite in the right position to do so, may well pay handsomely for**.

Merck has played in the Australian listed market before with respect to its immuno-oncology franchise centred around pembrolizumab.

A few years ago, Immutep's collaborator in the TACTI-002 trials, Merck, provided pembrolizumab and collaborated with another listed Australian drug development company, called Viralytics Ltd (previously, ASX: VLA). The clinical trials that Viralytics undertook in the Merck collaboration show striking similarities between those and the TACTI-002 trial, although they never progressed into a phase IIb trial. The point of the trials was not only to help advance Viralytics oncolytic virus, termed Cavatak, toward a marketing approval, but to help both Viralytics and Merck understand how Cavatak was working in conjunction with pembrolizumab. This enabled Merck to envision, with a reasonable degree of clarity, how Cavatak could be used to its advantage. Merck bought Viralytics for approximately AUD500m. **A value that many in the Australian biotechnology community felt was half what it should have been, according to discussions we had with funds and sophisticated Viralytics shareholders at the time**. Shareholders who bought in at the right time did do well, though.

Viralytic's Cavatak, which is an oncolytic virus injected directly into tumours, is a niche product. Efti is broadly applicable to a large swathe of cancers. Merck must be interested in efti. It is performing well with pembrolizumab and Merck also has a LAG-3 Inhibitor in development and paring the three of them up would seem to be appealing. It also seems likely that Merck would have negotiated a first right of refusal into its collaboration agreements with Immutep, so if somebody else does make a bid for Immutep, Merck will be involved one way or another. If Merck can keep rolling efti in a direction that is compatible with its plans, it will be happy to wait. Neither should Immutep keep poking Merck to make a bid. That signals a desire to do deal sooner rather than later, and the result will be what happened with Viralytics. It got its bid, but it was a lot less than it should have been. **To get a good price, Immutep needs to wait until Merck must move, not when Immutep wants it to move.**

It is notably difficult to create competitive tension among the larger therapeutics' companies, but it can be done. Certainly, Immutep's collaborators (i.e., Merck, Novartis, GSK, etc.) should allow it to build relationships and trust, and, importantly, interest not only in efti, but in its autoimmune disease program, as well.

In the meantime, Immutep needs to keep doing what it is doing - moving efti towards a marketing application, while generating as much positive data as it can. The activity of efti in breast cancer may well have raised the eyebrows of others in the market and further trials in the breast cancer space will only keep the eyes on it, while, hopefully, attracting new eyes. **Efti stands on its own in breast cancer and there could be substantial value in that, whether it be developing efti for breast cancer indications or bolstering Immutep's negotiating position with those who might want to pair efti with their PD-1/L1 inhibitor**. A further trial with avelumab may also work to Immutep's benefit, by demonstrating to other companies that there is little risk that combining their PD-1/L1 inhibitor with efti will result in a poor outcome.

A large licensing transaction for efti would be the other obvious possibility for moving efti into a company with a suitable sales and marketing force. That sort of deal would also allow Immutep to retain some of the upside of efti's post-licencing future.

A two-to-five-year timeline on some sort of transaction is reasonable in our eyes.

Table 10. Patent within Immutep's Patent Portfolio.

Patent Family	Title	Status	Expiry Date
550 Immutep S.A.S.& INSERM	Cytotoxic anti-LAG-3 monoclonal antibody and its use in the treatment or prevention of organ transplant rejection and autoimmune disease	**Pending in** China, US, Europe; **Granted in** US, Canada, Europe and Japan (x2)	2028
650 - Immutep S.A.S.	Use of recombinant LAG-3 or the derivatives thereof for eliciting monocyte immune response	**Pending in** China, Europe, Hong Kong and US; **Granted** in Australia, Europe (x4), Japan (x2) and US (x2)	2028
660 - Immutep S.A.S.	Combined preparations for the treatment of cancer	**Pending in** China, Europe, Japan, Korea, US and Hong Kong (x2); **Granted** in Australia, US, Europe and Japan	2034
661 - Immutep S.A.S.	Treatment of cancer	**Pending in** UK (priority) application filed	2041
670 - Immutep S.A.S.	Combination of IMP321 and a checkpoint inhibitor	**Pending in** Europe, Russia, US, Canada, Mexico, Australia, New Zealand, China, Korea, Japan, India, Brazil, and Israel; **Granted** in Europe and US (x2)	2036
700 - Immutep S.A.S. & Novartis	Antibody molecules to LAG-3 and uses thereof	**National phase** in 50 territories; **Granted in** US, Europe, Australia, Japan, Iraq, Lebanon, Algeria and Colombia	2035
710 - Immutep S.A.S.& Novartis	Combination therapies comprising antibody molecules to LAG-3	**Pending in** US; **granted** in Europe	2036
761 - Immutep S.A.S.	Anti-LAG-3 antibodies	**Pending in** Europe, Russia, US, Canada, Mexico, Brazil, Australia, New Zealand, China, Hong Kong, Korea, Japan, India, Israel, Indonesia, Malaysia, Philippines and Singapore; **Granted in** Europe, South Africa and Nigeria	2036
762 - Immutep S.A.S.	Anti-LAG-3 binding molecules	PCT application filed	2040
763 - Immutep S.A.S.	Anti-LAG-3 binding molecules	PCT application filed	2040
800 - Immutep S.A.S.	Binding assay	**Pending in** Europe, Russia, US, Canada, Mexico, Australia, New Zealand, China, Korea, Japan, India, Brazil, and Israel	2037
810 - Immutep S.A.S.	Assays	PCT application filed	2040

Source: Immutep's FY20 10-F filing with recent updates from the ASX.

Intellectual Property

In addition to the usual trade secrets, know-how and other confidential information that forms part of a company's intellectual property, Immutep owns 12 patent families covering its product candidates efti (IMP321), IMP761, LAG525 (IMP701) and GSK2831781 (IMP731). These are listed in Table 10.

In particular, these patent families are directed to methods of use of efti alone (or in combination with chemotherapy or PD-1/L1 therapy) in the treatment of cancer and infectious disease. The patent families also provide composition of matter type protection to

IMP761 and the antibodies licensed to Novartis and GSK. Some of these patents may also be eligible for some patent term extensions which can push out a patents expiry date.

While patents are important, there are also various regulatory exclusivities that a smart company can avail itself of to give it added protection above the strength afforded by patents. Under current laws, because efti is a protein and classified as a biologic, it qualifies for eight years of market exclusivity plus four years of data exclusivity in the US (8 + 4), effectively protecting the therapeutic from generic competition for 12 years. In the EU, a new active substance is automatically given eight years of data exclusivity and 2 years of market exclusivity, which can be increased by a further one year, if, in the meantime, the new active substance is approved for a new therapeutic indication that provides a significant clinical benefit (8 + 2 + 1).

Drugs or biologics that are developed for orphan indications are automatically provided with seven years of market exclusivity in the US. In the EU, ten years of market exclusivity is granted to a drug approved for an orphan indication.

A smart company can use these exclusivities to protect itself from generic competition for quite a long time.

Can they do it?

Each year we have watched listed Australian life science companies, dating back to Biota Holdings in the early 1990s. And recognising the importance of good management is increasing every year. Good, and even great, technologies do not develop themselves. Whether the board hopes the company will be bought or built into a powerhouse, so much needs to be right, that average management will not do. They must have talent and be able to identify talented people, including employees and consultants (scientific, regulatory, manufacturing, etc).

With Immutep, two key people stand out:

CEO, Marc Voigt.
Mr Voigt began his career in finance and moved into venture capital, working with a specialist healthcare-focused firm in Berlin. He gained managerial experience in biotechnology working as an investment manager and then in various roles with several biotechnology companies. He joined Immutep in 2011 as its general manager, then its chief business officer, before becoming the coming company's chief financial officer. In July 2014, Mr Voigt was appointed executive director and CEO and has been instrumental in developing Immutep's strategy. His experience has given him a solid understanding of how successful biotechnology companies can be developed, bringing Immutep to where it is today.

Dr Frédéric Triebel
When you examine a biotechnology without a CEO with an education in medicine or science, you must determine whether a suitable alternative exists. With Immutep, it is **Dr Frédéric Triebel** its **co-chief scientific and medical officer.** A trained physician with a PhD who discovered LAG-3 in the 1990s and was instrumental in establishing Immutep, where he has remained focused on LAG-3. There is no better professional to fill those roles, move Immutep's research and development candidates further, or best placed to interact with scientific advisory boards, the investigators of Immutep's clinical trials and other company stakeholders. Dr Triebel is also well placed to answer LAG-3-related questions when Immutep is undergoing due diligence by potential partners and suitors.

The management team surrounding Mr. Voigt is equally capable.

Ms Deanne Miller, general counsel and company secretary. A graduate with a Law Degree and a Bachelor of Commerce with a double major in accounting and finance from the University of Sydney. Ms Miller held legal, investment banking, regulatory compliance and tax advisory positions before joining Immutep in 2012.

Mr. Christian Mueller, director clinical development and regulatory affairs since 2016. Mr Meuller has a Master of Science in Biotechnology from the Technical University, Berlin, and has focused on developing biologics and coordinating oncology clinical trials. He has run many phase I and II trials, as well as the large phase IIb (n=200+) trial of a lead asset that helped seal a UAS1.2 billion trade sale with Astellas (TYO: 4503).

Dr. Claudia Jacoby, director of manufacturing, has more than 20 years' experience in biotechnology. Dr Jacoby joined Immutep in 2015 and has been head biochemist and head of manufacturing at different European biotech companies since gaining her PhD from the Institute for Biotechnology of the Martin-Luther-University of Halle-Wittenberg, Germany.

Dr. James Flinn, intellectual property and innovation director, a qualified patent attorney who joined Immutep in 2017. Dr Flinn has worked in private practice and corporate patent practice. Prior to joining Immutep, he worked for GlaxoSmithKline for seven years as Senior Patent Counsel where he managed the global patent portfolio of GSK's dermatology business unit. Dr Flinn gained his PhD from the University of Melbourne.

Mr. David Fang, finance director and assistant company secretary. Mr Fang has over 12 years' accounting and auditing experience across biotechnology, manufacturing and healthcare. Prior to joining Immutep in 2018, he was group finance manager at ASX-listed Kazia Therapeutics Limited. Mr Fang is a member of CPA Australia, has a Master of Professional Accounting from Western Sydney University and Master of Commerce in Information System and Technology from Macquarie University.

Immutep has exceptionally well experienced and qualified individuals and is clearly capable of moving the company forward and maximising its opportunities for success.

Lastly, while not part of management, small biotechnology companies must rely on others to help them develop their compounds. Having licensed its compounds to GSK and Novartis, Immutep is in good hands. Similarly, EOC and CYTLIMIC have good pedigrees. To make its drug product, Immutep sought out quality by contracting with Wuxi Biologics. Wuxi is one example of a quality company Immutep engages with to achieve its aims, and is involved with many others, always doing its due diligence to bring in the right company, Never the cheapest or the most expensive, the right one.

Corporate Connect Research Pty Ltd Independent Research Report Disclaimer

General disclaimer and copyright

This report ("report" or "Research") has been commissioned by the Company the subject of this report ("Company") and prepared and issued by (Analyst name and AR number) of Corporate Connect Research Pty Ltd ("Corporate Connect Research") (ABN 95640 464 320 – Corporate Authorised Representative (1283214) of Australian Financial Services Licence (AFSL) Number 88045)in consideration of a fee payable by the Company. Corporate Connect Research may be paid additional fees for the provision of additional services to the Company but Corporate Connect Research is not remunerated for any investment banking or similar services. Corporate Connect Research never accepts payment in stock, options or warrants for any of its services.

Where Corporate Connect Research has been commissioned to prepare content and receives fees for its preparation, fees are paid upfront in cash and NO part of the fee, compensation or employee remuneration paid will either directly or indirectly impact the content provided.

Accuracy of content:

All information used in the publication of this report has been compiled from publicly available sources that are believed to b**e** reliable, however Corporate Connect Research does not guarantee the accuracy or completeness of this report and have not sought for this information to be independently verified.

Opinions contained in this report represent those of the Analyst of Corporate Connect Research (Analyst name) at the time of publication**.**

The analyst has received assistance from the Company in preparing this document. The Company has provided the analyst with access to senior management and information on the Company and industry. The Analyst holds/does not hold an economic interest in the securities covered in this report or other securities issued by the subject issuer.

From time to time, Corporate Connect Research's representatives or associates may hold interests, transact or hold directorships in, or perform paid services for, companies mentioned in this report. Corporate Connect Research and its associates, officers, directors and employees, may, from time to time hold securities in the companies referred to in this report and may trade in those securities as principal and in a manner which may be contrary to recommendations mentioned in this report.

As part of due diligence, the analyst has independently and critically reviewed the assistance and information provided by the Company to form the opinions expressed in the report. However, due diligence site visits have not been undertaken at this time. Care has been taken by the analyst to maintain objectivity in preparing this report and making any recommendation. The analyst is responsible for ensuring that this report accurately reflects his or her view of the matters set out in it and that it was prepared in an independent manner**.**

Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results and estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations. This report is prepared as at the date stated in it, and to the maximum extent permitted by law, Corporate Connect Research (on its own behalf and on behalf of the analyst) disclaims any responsibility to inform any recipient of this report of any matter that subsequently comes to its notice which may affect any of the information contained in this report.

Exclusion of liability:

To the fullest extent allowed by law, Corporate Connect Research (on its own behalf and on behalf of the analyst) shall not be liable to any person for any direct, indirect or consequential losses, loss of profits, damages, costs or expenses incurred or suffered by you or any other person arising out or in connection with the access to, use of or reliance on any information contained in this report.

No guarantees or warranties regarding accuracy, completeness or fitness for purpose are provided by Corporate Connect Research (on its own behalf and on behalf of the analyst), and under no circumstances will any of Corporate Connect Research's analysts, representatives, associates or agents be liable for any loss or damage, whether direct, incidental or consequential, caused by reliance on or use of the content.

General Advice Warning

This report and any other Research must not be construed as personal advice or recommendation nor as an inducement to trade the report's named company or any other security. Corporate Connect Research encourages investors to seek independent financial advice regarding the suitability of investments for their individual circumstances and recommends that investments be independently evaluated. Investments involve risks and the value of any investment or income may go down as well as up. Investors may not get back the full amount invested. Past performance is not indicative of future performance. Estimates of future performance are based on assumptions that may not be realised. If provided, and unless otherwise stated, the closing price provided is that of the primary exchange for the issuer's securities or investments. The information contained within the Research is published solely for information purposes and is not a solicitation or offer to buy or sell any financial product or participate in any trading or investment strategy.

Analysis contained within the Research is based upon publicly available information and may include numerous assumptions. Investors should be aware that different assumptions can and do result in materially different results. The Research is distributed only as may be permitted by law. It is not intended for distribution or use by any person or entity located in a jurisdiction where distribution, publication, availability, or use would be prohibited. Corporate Connect Research makes no claim that the Research content may be lawfully viewed or accessed, whether inside or outside of Australia. Access to the Research content may not be legal for certain persons and in certain jurisdictions. If you access this service or content from outside of Australia, you are responsible for compliance with the law**s** of your jurisdiction and/or the jurisdiction of the third party receiving such content. The Research is provided to our clients through its website and our distribution partners (www.sharecafe.com.au and www.informedinvestor.com.au).

Some Research products may also be made available to its clients via third party vendors or distributed through alternative electronic means as a convenience. Such alternative distribution methods are at Corporate Connect Research's discretion.

Access and Use

Any access to or use of the Research is subject to the Terms and Conditions of Corporate Connect Research. By accessing or using the Research you hereby agree to be bound by our Terms and Conditions [https://corporateconnect.com.au/financialservices-guide/] and hereby consent to Corporate Connect Research collecting and using your personal data (including cookies) in accordance with our Privacy Policy (https://corporateconnect.com.au/privacy/), including for the purpose of a) setting your preferences and b) collecting readership data so Corporate Connect Research may deliver an improved and personalised service to you. If you do not agree to our Terms and Conditions and/or if you do not consent to Corporate Connect Research's use of your personal data, please do not access this service.

Copyright of the information contained within the Research (including trademarks and service marks) are the property of the irrespective owners. The Research, or any portion thereof, may not be republished, reprinted, sold, or redistributed without the prior and written consent of Corporate Connect Research.

Australia

Corporate Connect Research Pty Ltd is a Corporate Authorised Representative (1283214) of PacReef Asset Management Pty Ltd who holds an Australian Financial Services Licence (Number: 488045) which allows Corporate Connect Research to offer financial service advice to [retail and]wholesale clients. Any advice given by Corporate Connect Research is general advice only and does not consider your personal circumstances, financial situation, needs or objectives. You should, before acting on this advice or making any investment decision or a decision about whether to acquire or dispose of a financial product mentioned in any Research, consider the appropriateness of the advice, having regard to your objectives, financial situation, and needs. If our advice relates to the acquisition, or possible acquisition, of a particular financial product you should read any relevant Product Disclosure Statement or like instrument, and also seek independent financial, legal and taxation advice.

New Zealand

The research in this document is intended for New Zealand resident professional financial advisers or brokers This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or financial advice, is intended only as a "class service" provided by Corporate Connect Research within the meaning of the FAA (i.e. without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision.

United Kingdom

This document is prepared and provided by Corporate Connect Research for information purposes only and should not be construed as an offer or solicitation for investment in any securities mentioned or in the topic of this document. A marketing communication under FCA Rules, this document has not been prepared in accordance with the legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of investment research.

This Communication is being distributed in the United Kingdom and is directed only at (i) persons having professional experience in matters relating to investments, i.e. investment professionals within the meaning of Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "FPO") (ii) high net-worth companies, unincorporated associations or other bodies within the meaning of Article 49 of the FPO and (iii) persons to whom it is otherwise lawful to distribute it. The investment or investment activity to which this document relates is available only to such persons. It is not intended that this document be distributed or passed on, directly or indirectly, to any other class of persons and in any event and under no circumstances should persons of any other description rely on or act upon the contents of this document.

This Communication is being supplied to you solely for your information and may not be reproduced by, further distributed to or published in whole or in part by, any other person.

United States

Corporate Connect Research relies upon the "publishers' exclusion" from the definition of investment adviser under Section202(a)(11) of the Investment Advisers Act of 1940 and corresponding state securities laws. This report is a bona fide publication of general and regular circulation offering impersonal investment-related advice, not tailored to a specific investment portfolio or the needs of current and/or prospective subscribers. As such, Corporate Connect Research does not offer or provide personal advice and the research provided is for informational purposes only. No mention of a particular security in this report constitutes are commendation to buy, sell or hold that or any security, or that any particular security, portfolio of securities, transaction or investment strategy is suitable for any specific person.

Sydney

79 Kent St
Millers Point
Sydney NSW 2000

Phone: +61 400 897 559
Email: enquiries@corporateconnect.com.au
https://www.corporateconnect.com.au/