IMMUTEP LIMITED

Biotechnology

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goetzpartners SECURITIES

# COMPANY NOTE

## Immutep Limited (IMM-AU)

### Targeting the LAG-3 immune checkpoint

**OUTPERFORM**

Price target AUD0.078
Price AUD0.036

### KEY TAKEAWAY

**We initiate coverage on Immutep with an OUTPERFORM recommendation and a target price ("TP") of A$0.078 per share. Immutep develops therapeutics targeting the Lymphocyte Activation Gene-3 ("LAG-3") immune checkpoint ("IC") involved in T cell regulation. IC inhibitors ("ICIs") targeting CTLA-4 and PD-1 / L1 have revolutionised cancer care owing to their ability to elicit durable responses in advanced cancers. The current focus is on combination therapy to increase response rates. Immutep's lead asset eftilagimod alpha (IMP321, "efti") has shown encouraging efficacy in metastatic melanoma and metastatic breast cancer ("mBC"). We forecast launch in 2020E for mBC based on an ongoing Phase IIb trial expected to read out in 2019E and estimate $2.4bn in peak sales across indications, with Immutep expected to sign a licensing deal.**

**I-O has revolutionised cancer care, but most patients do not benefit**

Immuno-oncology focuses on activating the immune system to fight cancer. ICIs have shown the greatest clinical results, as reflected in responses of up to 10 years in 20% - 50% of patients across advanced tumours. This has led to their rapid adoption since the launch of Yervoy (ipilimumab) in 2011, with total ICI sales reaching $10.5bn in 2017. The race is on to find novel mechanisms of action for combination therapy to augment response rates without increasing toxicity.

**Leader in LAG-3, potentially the third pillar in checkpoint immunotherapy**

LAG-3 is an IC that has been shown to have both stimulatory and inhibitory roles, making it suitable for therapeutic applications in cancer and autoimmune diseases. The search for the third pillar in the ICI toolbox has led to increased activity in the LAG-3 space. Immutep has the broadest LAG-3 targeted pipeline across the biopharma industry and is the only company exploring the stimulatory activity of this checkpoint pathway (most companies focus on inhibitory mAbs).

**Eftilagimod alpha activates antigen-presenting cells to fight cancer**

Efti is a LAG-3Ig fusion protein that drives dendritic cell maturation and activation by binding to MHC class II. It is being developed for combination therapy with chemotherapy or Keytruda (pembrolizumab) in solid tumours. The Phase IIb AIPAC trial in mBC of efti + paclitaxel is expected to read out in 2019E, and a Phase II basket trial in metastatic lung and head & neck cancers exploring efti + pembro starts in Q4/2019E. The latter is based on encouraging proof-of-concept data from a Phase I trial in advanced melanoma (TACTI-mel).

**SoTP valuation suggests share price largely justified by efti in mBC alone**

Our TP for Immutep is based on a sum-of-the-parts valuation that includes NPVs for efti in metastatic breast, lung and head & neck cancer - together accounting for >90% of our fair value, net cash at YE/2018E, and research deals with Novartis and GSK for earlier-stage assets.

| AUD | 2017E | 2018E | 2019E |
|---|---|---|---|
| Sales | 4 | 7 | 7 |
| EBIT | (10) | (9) | (9) |
| Net Cash/Debt ($M) | | | |
| FY Dec | 6.5 | 16.2 | 71.2 |

Source: Immutep, goetzpartners Research estimates. Warning Note: Forecasts are not a reliable indicator of future results or performance. The return may increase or decrease as a result of currency fluctuations.

### FINANCIAL SUMMARY

| | |
|---|---|
| Net Cash/Debt (M): | 16.16 |

### MARKET DATA

| | |
|---|---|
| Price: | AUD0.036 |
| Target Price: | AUD0.078 |
| 52 Week Range: | AUD0.040 - AUD0.020 |
| Total Enterprise Value: | 87 |
| Market Cap (M): | 103 |
| Shares Out (M): | 3,026.1 |
| Float (M): | 2,894.0 |
| Average Daily Volume: | 6,475,085 |

**Target Price: AUD 0.078 / USD 5.8 (ADR)*

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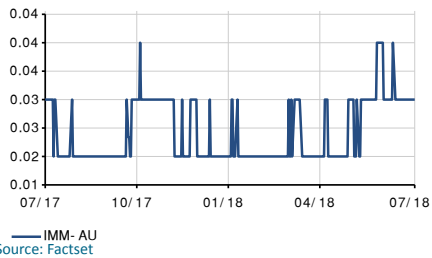
### PRICE PERFORMANCE



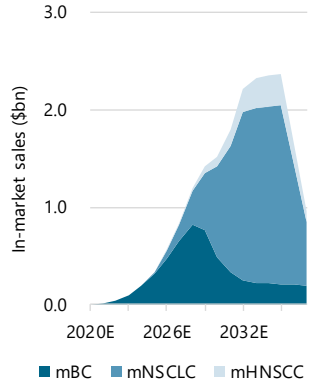

Source: Factset

# Contents

# Launching with OUTPERFORM and TP of A$0.078

We initiate coverage on Immutep, an Australian biotech company focused on immunotherapy for cancer and autoimmune diseases, with an OUTPERFORM recommendation and a target price ("TP") of A$0.078 / share. Immutep is the global leader in the development of therapeutics targeting Lymphocyte Activation Gene-3 ("LAG-3"), an immune checkpoint ("IC") involved in T cell regulation. IC inhibitors ("ICIs") targeting CTLA-4 and PD-1 / L1 have revolutionised cancer care owing to their ability to elicit durable responses in multiple advanced cancers, albeit in less than half of all patients. Hence, the focus is on combination therapy with these agents to increase response rates. Immutep's most advanced asset, immunomodulator eftilagimod alpha (IMP321, "efti"), has shown encouraging efficacy in metastatic melanoma and metastatic breast cancer ("mBC"). We forecast launch in 2020E for mBC based on an ongoing Phase IIb trial and estimate peak sales of c.US$2.4bn across indications (Chart 1), with Immutep expected to realise value through a US$1bn licensing deal likely to be signed in H2/2019E. As the shares only appear to price in sales for efti in mBC, we see room for upside in the next 18 months.

**CHART 1: Eftilagimod alpha in-market sales, 2020E-2037E**

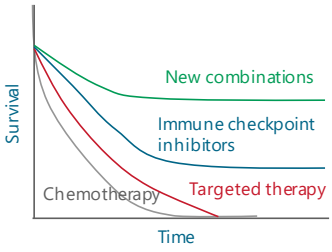



Abbreviations: mBC, metastatic breast cancer; mHNSCC, metastatic head and neck squamous cell carcinoma; mNSCLC, metastatic non-small cell lung cancer
Source: goetzpartners Research estimates

## Immuno-oncology has revolutionised cancer care…

Immunotherapy is an approach that focuses on activating the immune system to fight cancer. Of the strategies that have been tested, immune checkpoint blockade has shown the greatest clinical results, as reflected in durable responses of up to 10 years in 20% - 50% of patients across advanced tumour types. This led to the rapid adoption of ICIs since the launch of BMS's anti-CTLA-4 mAb Yervoy (ipilimumab) in 2011. ICI sales reached US$10.5bn in 2017 and are expected to nearly triple by 2022E.

**CHART 2: The focus in immuno-oncology is on "lifting the tail" of the survival curve**




Source: goetzpartners Research

### …but more than half of patients fail to benefit

The key drawback of the approved ICIs is that more than half of patients fail to respond. Hence, the race is on to develop compounds with complementary mechanisms of action in combination with ICIs to augment response rates without increasing toxicity (Chart 2).

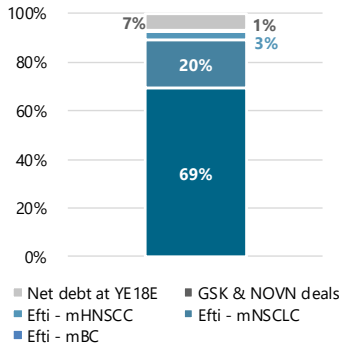
## Immutep is the leader in LAG-3 modulation

Immutep's entire R&D portfolio focuses on modulating LAG-3 for immunotherapy applications. LAG-3 is an immune checkpoint that was first discovered by Immutep's current CSO / CMO Frédéric Triebel in 1990. Extensive experimental work has shown that LAG-3 has both stimulatory and inhibitory roles in a normally functioning immune system, making it suitable for therapeutic applications in both cancer and autoimmune diseases. The search for the third pillar in the ICI toolbox has led to increased activity in the LAG-3 space, with most companies focusing on mAbs that block LAG-3, thus mirroring the mechanism of action of the approved ICIs. In addition to having the broadest LAG-3 targeted pipeline across the biopharma industry, to our knowledge Immutep is also the only company with a LAG-3 approach exploring the stimulatory activity of this checkpoint pathway.

## Eftilagimod: immunomodulator with >US$2bn sales potential

Eftilagimod is a LAG-3Ig fusion protein that has been demonstrated to drive dendritic cell maturation and antigen presenting cell ("APC") activation by binding to MHC class II with high affinity. The current development programme focuses on combination therapy with either chemotherapy or the PD-1 inhibitor pembrolizumab across solid tumours. A Phase IIb trial (AIPAC) in mBC in combination with paclitaxel is expected to read out in 2019E, and a Phase II basket trial in metastatic lung ("NSCLC") and head and neck ("HNSCC") cancers exploring combination therapy with Keytruda (pembrolizumab) is due to start in Q4/2019E. The latter is based on proof-of-concept of the combination from a Phase I trial in metastatic / unresectable melanoma (TACTI-mel), for which encouraging interim efficacy data was presented in May 2018.

**CHART 3: Eftilagimod alpha accounts for >90% of our fair value for Immutep**




Source: goetzpartners Research estimates

## SOTP valuation largely based on eftilagimod alpha

Since Immutep is a clinical-stage, loss-making growth company that is expected to realise much of its value in future years, we value the company using a sum-of-the-parts valuation ("SOTP") based on net present values ("NPVs") for its most advanced assets plus net cash at YE2018E (Chart 4). The NPV for each product is derived from free cash flow ("FCF") forecasts until 2036E, which are discounted using our estimated weighted average cost of capital ("WACC") of 12.7%. We set a terminal value of zero for all products, as we assume that sales will succumb to biosimilar competition following the loss of exclusivity. The FCF forecasts for eftilagimod are based on detailed sales models and further take into account R&D costs for ongoing trials, but not beyond, as we assume that Immutep will sign a global licensing deal prior to commencing late-stage clinical trials.

Lead asset eftilagimod accounts for over 90% of our valuation (Chart 3), mainly because it is the most advanced asset with the largest body of data and fully owned by Immutep (excl. Chinese rights). Net cash and revenue from the company's assets partnered with Novartis (IMP701) and GSK (IMP731) account for the remaining value. We do not currently include a value for IMP761 due to its early stage of development (preclinical); hence, there is future upside potential as and when Immutep discloses more information and progresses this asset into clinical development.

**CHART 4: Immutep SOTP valuation**

| Product | Indications | Stage | Peak sales ($m) | Year | NPV (A$m) | Prob. | Adj. NPV (A$m) | NPV/sh (A$) |
|---|---|---|---|---|---|---|---|---|
| Eftilagimod alpha | HR +ve, HER -ve mBC | Phase IIb | 820 | 2028E | 405 | 40% | 162 | 0.054 |
| Eftilagimod alpha | mNSCLC | Phase II-ready | 1,826 | 2035E | 469 | 10% | 47 | 0.016 |
| Eftilagimod alpha | mHNSCC | Phase II-ready | 326 | 2035E | 73 | 10% | 7 | 0.002 |
| Novartis & GSK deals | Multiple | Phase I/II | n.a. | n.a. | 8 | 25% | 2 | 0.001 |
| Net cash at YE18E | | | | | 16 | 100% | 16 | 0.005 |
| **Fair value (PO)** | | | | | **972** | | **235** | **0.078** |
| Current Share Price (A$) | | | | | | | | 0.034 |
| Upside | | | | | | | | 128% |

Source: goetzpartners Research estimates

### Shares appear to be pricing in only eftilagimod in mBC

Our analysis suggests that eftilagimod sales in mBC alone support the current share price, likely because it is the only indication currently in clinical development where Immutep has generated robust proof-of-concept data. Hence, we see upside potential both for positive Phase IIb data in June 2019, as well as favourable developments for the other indications being addressed, specifically, metastatic lung cancer and metastatic head and neck cancer. We note that we do not include any sales for melanoma in our model and valuation despite the encouraging efficacy seen in the Phase I TACTI-mel trial, as Immutep currently has no plans to develop this indication further. In addition, our valuation reflects limited value for the partnered product candidates, as they are still relatively early stage, clinical data is scarce, and Immutep is entitled to a relatively modest share of value.

## Efti Phase IIb data in mBC in 2019E the key catalyst

The key catalyst for Immutep shares is Phase IIb data for eftilagimod in mBC (AIPAC trial) in 2019E, which would pave the way for a conditional marketing approval in Europe in 2020E (we forecast US launch one year later) and, in our view, trigger a partnering deal for the compound in H2/2019E. Other news flow in the next 12 months includes final Phase I data for eftilagimod in metastatic melanoma, further underpinning the drug's activity in advanced tumours, and single cases from the investigator-led Phase I INSIGHT trial testing different routes of administration in solid tumours (Chart 5).

**CHART 5: Immutep news flow in 2018-2019**

| Event | Timing* |
|---|---|
| Financial results for the year ended June 2018 | Aug-2018 |
| GSK2831781 (IMP731) Phase I data / start of Phase II trial | H2/2018E |
| Efti Phase IIb AIPAC trial in HR-positive mBC fully recruited | Q4/2018 |
| **Efti Phase I data from TACTI-mel trial in metastatic melanoma** | **Nov-2018 (SITC meeting)** |
| Single cases from investigator-led Phase I INSIGHT trial of efti IT and IP | Throughout 2018 |
| LAG525 Phase I data (partnered with Novartis) | Aug-2019 |
| **First PFS data from efti Phase IIb AIPAC trial in HR-positive mBC** | **2019E** |
| **Global efti licensing deal (excl. China) following Phase IIb data in mBC** | **H2/2019E** |

*Dates are as of 9th July 2018.
Abbreviations: HR, hormone-receptor; IP, intra-peritoneal; IT, intra-tumoural; mBC, metastatic breast cancer; PFS, progression-free survival; SITC, Society for Immunotherapy of Cancer. Key events are shown in bold.
Source: Company data, goetzpartners Research estimates

## The key risk is eftilagimod failing in mBC

Based on our valuation analysis and hence interpretation of what is priced in, the key risk to the shares is a negative outcome for the Phase IIb AIPAC trial in mBC. Since the trial has already successfully completed the safety run-in and early efficacy signals as measured by tumour response rates are encouraging, we do not anticipate any unexpected safety issues and therefore expect the trial to continue as planned until final data analysis in 2019E. Other risks to the shares include the following: Immutep is unable to sign a licensing deal for efti in H2/2019 and / or raise funds before the company exhausts its cash reserves in Q4/2019; major delays to the efti trials due to slow recruitment caused by competing immunotherapy trials; lower-than-expected sales in highly competitive markets; and earlier-than-expected generic competition due to efti's use patents not being robust enough (the composition of matter patent has already expired as it was filed in the late 1990's).

# Leader in LAG-3 immunotherapy

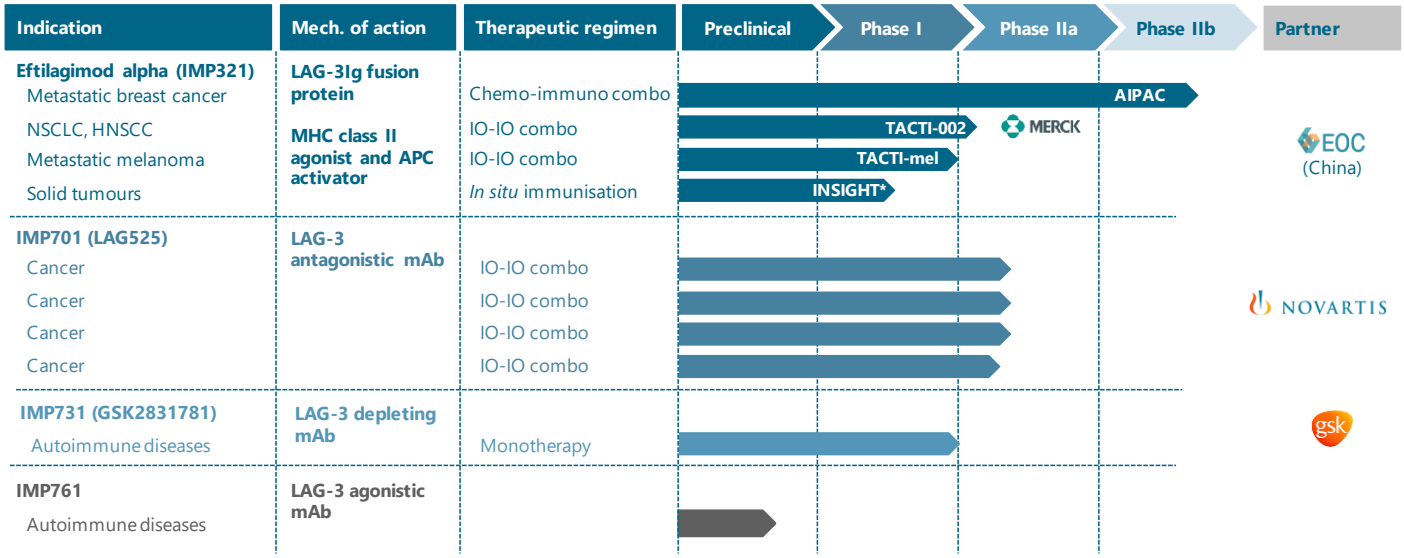
*LAG-3 was discovered in 1990 at the Institut Gustave Roussy by Frédéric Triebel, Immutep's Chief Medical Officer and Chief Scientific Officer*

Immutep (previously known as Prima BioMed until November 2017), an Australian clinical-stage biotech company that develops immunotherapies primarily for cancer, but also autoimmune disease, is the global leader in developing therapeutics that modulate Lymphocyte Activation Gene-3 ("LAG-3"), both alone and together with its large pharma partners. LAG-3 was discovered in 1990 at the Institut Gustave Roussy by Frédéric Triebel, who founded private French biotechnology firm Immutep, later acquired by Prima BioMed in October 2014. Immutep is dual-listed on the Australian Stock Exchange ("IMM") and on the NASDAQ Global Market ("IMMP") in the US (American Depository Receipts), with operations in Europe, Australia, and the US.

## Four approaches targeting the LAG-3 checkpoint pathway

Immutep has four LAG-3 targeted product candidates in development, each with a unique mechanism of action and area of focus. Three are in the clinic and one is preclinical (Chart 6). Lead asset eftilagimod alpha (IMP321) and IMP701 are in development as add-on treatments to chemotherapy and / or anti-PD-1 therapy for advanced solid tumours. IMP731 and IMP761 are being developed for autoimmune diseases, initially as monotherapies. Immutep owns global efti rights except in China, while IMP701 and IMP731 were out-licensed to Novartis and GSK, respectively, in early development.

**CHART 6: Immutep's therapeutic pipeline targets the LAG-3 checkpoint pathway**




*Investigator-led trial
Abbreviations: APC, antigen-presenting cell; HNSCC, head and neck squamous cell carcinoma; IO, immuno-oncology; LAG, lymphocyte activation gene; NSCLC, non-small cell lung carcinoma.
Source: Company data

### Broadest LAG-3 pipeline includes both immune activators and blockers

An analysis of the LAG-3-targeted pipeline across the industry reveals that Immutep has the broadest and diverse pipeline. Notably, most approaches focus on inhibitory mAbs that bind to LAG-3 on T cells to block negative signalling into these cells, thus releasing the breaks on the immune system – similar to how the approved anti-CTLA-4 and anti-PD-1 / L1 mAbs work. In contrast, eftilagimod binds to the physiological LAG-3 ligand MHC class II on antigen-presenting cells ("APCs"), causing their maturation and activation, so that they then activate cytotoxic T cells able to eliminate malignant cells.

## Multiple collaborations with large pharma companies

Immutep currently has collaborations with Merck & Co., Novartis, GSK and China's EOC (Chart 7). The agreement with Merck & Co. is a clinical trial collaboration and supply agreement focused on testing eftilagimod in combination with Keytruda (pembrolizumab) in solid tumours, with Merck providing pembrolizumab for the study. The deals with GSK and Novartis are early-stage licensing deals, with Immutep entitled to milestones and royalties. The partnership with Eddingpharm spin-off EOC is focused on developing eftilagimod for the Chinese market.

**CHART 7: Validation of pipeline assets through collaborations with large pharma partners**

| Company | Date | Asset | Type of agreement | Description |
|---|---|---|---|---|
| **Merck & Co** | Mar-2018 | eftilagimod alpha (IMP321) | Clinical trial collaboration and supply agreement | To evaluate the combination of efti and Merck & Co.'s anti-PD-1 Keytruda (pembrolizumab). Merck supplies Keytruda, but Immutep incurs all other clinical trial costs. |
| **EOC (Eddingpharm[1])** | Oct-2013 | eftilagimod alpha (IMP321) | Licensing deal | Eddingpharm acquired exclusive rights in China, Hong Kong, Macau and Taiwan. Immutep is entitled to milestones and royalties on sales. |
| **Novartis (CoStim Pharma[2])** | Sep-2012 | LAG525 (IMP701) | Licensing deal | Novartis is responsible for all development activities. Immutep is eligible for development-based milestone payments and royalties on sales. |
| **GSK** | 2010 | GSK2831781 (IMP731) | Licensing deal | GSK is responsible for all development incl. costs. Immutep is entitled to upfront and potential milestones of up to £64m (c.A$118m) plus single-digit, tiered royalties on sales. |

1. EOC is a spin-off from Eddingpharm. 2. CoStim signed the original licensing deal with Immutep and was subsequently acquired by Novartis in February 2014.
Source: Company data

## Cash runway to Q4/2019 following three recent fundraises

*The equity capital raise completed in July 2017 was the first using Immutep's American Depository Shares ("ADS") since listing on Nasdaq in 2012*

In the last 12 months, Immutep completed three equity financings that together raised A$19.8m (approx. US$15m) and extended the company's cash runway to Q4/2019 (Chart 8). By this time, Immutep should have progression-free survival ("PFS") data for the Phase IIb AIPAC trial in mBC, data from all four cohorts of the Phase I TACTI-mel trial in metastatic melanoma, and potentially first data from the TACTI-002 trial in metastatic lung and head & neck cancer.

**CHART 8: Recent financings extended the cash runway to Q4/2019E**

| Date | Event | Security | Proceeds (A$m) | Price | No. securities issued |
|---|---|---|---|---|---|
| **13-Apr-18** | Share purchase plan | Equity | 6.31 | 0.021 A$ | 300,561,089 |
| **12-Mar-18** | Private placement | Equity | 6.85 | 0.021 A$ | 326,192,381 |
| **06-Jul-17** | Registered Direct Offering | Equity | 6.50 (US$5.0m) | 1.90 US$ | 2,631,268 |

Source: Company data, FactSet

# Immunotherapy has revolutionised cancer care

Cancer is the result of mutated cells winning out over the immune system. Immunotherapy is an approach to cancer treatment that focuses on activating the immune system to eliminate cancer. Of the different strategies that have been tested, the inhibition of immune checkpoints has shown the greatest clinical results, as reflected in durables responses of up to 10 years in 20% - 50% of patients across advanced tumour types. This led to the rapid adoption of the ICI class since the launch of BMS's anti-CTLA-4 mAb Yervoy (ipilimumab) in 2011, as reflected in total ICI sales of US$10.5bn in 2017. The key shortcoming of the approved ICIs is that more than half of patients fail to respond. Hence, the race is on to develop compounds with complementary mechanisms of action in combination with ICIs to further augment response rates without increasing toxicity.

## Cancer occurs when a tumour outsmarts the immune system

**CHART 9: The eight hallmarks of cancer**

1. Proliferative signalling
2. Evading growth suppressors
3. Resisting cell death
4. Enabling replicative immortality
5. Inducing angiogenesis
6. Activating invasion and metastasis
7. Reprogramming of energy metabolism
8. Evading immune destruction

Source: Hanahan & Weinberg (2011) *Cell*

In a healthy human being with a functional immune system, the interplay between the innate and the adaptive immune system (Chart 10) combined with a sophisticated system of checks and balances ensures adequate protection against both pathogens and early malignant cells, but also resolution of inflammation, maintenance of tolerance and homeostasis to limit immune-mediated tissue damage and avoid autoimmune reactions. Each cell experiences thousands of mutations each day, which are normally repaired by specific DNA repair pathways with no consequences. Cells where the DNA is not repaired and which subsequently acquire (potentially) malignant changes are usually recognised and eliminated by the tumour immunosurveillance system, predominantly through cell-mediated mechanisms that can differentiate between "self" and "non-self" antigens and recognise tumour-associated-antigens ("TAA") on the cell surface. Some malignant cells can evade the tumour immunosurveillance system using immune evasion strategies, which consist in altering their own characteristics and those of the cells in their close proximity, thus becoming successful tumours.

**CHART 10: Innate vs. adaptive immune system**

| | Innate defense | Adaptive immunity |
|---|---|---|
| **Onset** | Immediate (minutes), first line of defense | Slow (days to weeks) |
| **Specificity** | None, same response to variety of agents | High, directed against specific pathogen and antigen |
| **Diversity** | Limited | Extensive |
| **Potency** | Low | High |
| **Immunological memory** | Absent. Subsequent response to same agent generates same response | Present. Subsequent response to same agent generates a stronger response |
| **Duration** | Short (days) | Long (months to years) |
| **Effector cells** | ▪ Mast cells<br>▪ Dendritic cells ("DCs")<br>▪ Macrophages<br>▪ Natural killer cells ("NK")<br>▪ Granulocytes (i.e. neutrophils, basophils, eosinophils) | ▪ Humoral immunity: B cells, mature into Ab-producing plasma cells<br>▪ Cell-mediated immunity: (1) CD4+ helper T cells; (2) CD8+ cytotoxic T lymphocytes ("CTL") |
| **Activation** | Directly by pathogen | Requires formal presentation by antigen-presenting cells ("APCs") |
| **Regulation** | Limited | High, mediated by regulatory T cells |

Source: goetzpartners Research

### The three phases of immunoediting: elimination, equilibrium and progression

After a long-standing debate in the scientific community concerning the role of the immune system in tumour development, a large body of evidence has led to the acceptance of "cancer immunoediting". This relatively new theory seeks to describe the complex interactions between the immune system and tumours, and forms the basis for novel cancer immunotherapies (Mittal *et al.*, 2014). Cancer immunoediting is a dynamic process classified into three distinct phases during which the host immune system not only protects against cancer development, but also shapes the character of emerging tumours through the activation of both innate and adaptive immune mechanisms (Chart 11). Cancer occurs when the immune system loses the battle, leading to growth of the tumour and its spread to other parts of the body through metastases. Escape from immune control is now recognized to be one of the hallmarks of cancer (Hanahan & Weinberg, 2011; Chart 9).

**CHART 11: Immunoediting consists of three phases**

| Stage | Description |
|---|---|
| Elimination | ▪ Transformed cells are destroyed by a competent immune system |
| Equilibrium | ▪ Sporadic tumour cells manage to survive immune destruction and editing occurs |
| Escape | ▪ Immunologically sculpted tumours begin to grow progressively, become clinically apparent, establish an immunosuppressive tumour microenvironment and metastasise due to loss of control by the immune system<br>▪ Strategies cancer cells employ to escape:<br>o Expression of fewer antigens on the cell surface<br>o Complete loss of MHC class I expression<br>o Ability to protect themselves from T cell attack by expressing immune checkpoint molecules on their surface |

Source: Mittal *et al.* (2014) *Curr Opin Immunol.*; Oiseth *at al.* (2017) *J Cancer Metastasis Treat*

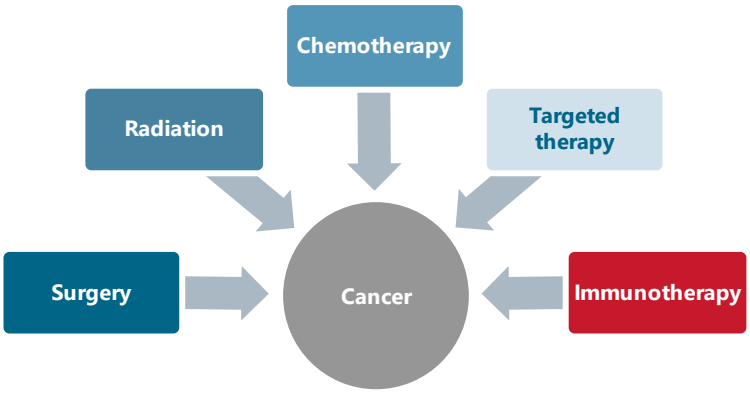
### The tumour microenvironment shields the cancer from the immune system

An additional layer of complexity is that tumours create their own tumour microenvironment by recruiting apparently "normal" immune cells to help shield them from attack by the immune system and create some of the hallmarks described above. Successful tumours produce multiple cytokines and chemokines to generate an immunosuppressive, pro-tumourogenic and prometastatic environment by recruiting and training immune cells such as myeloid-derived suppressor cells ("MDSCs"), tumour-associated macrophages, helper and effector cytotoxic T cells, regulatory T cells ("Tregs"), dendritic cells, as well as pro- and anti-inflammatory cytokines secreted by both cancer and immune cells (Bilusic and Gulley, 2017).

## Harnessing the immune system to fight cancer

It has long been known that the human body possesses natural defences to combat cancer, chiefly through the interplay of CD8+ T cells, NK cells and monocytes / macrophages. Effective immunity against cancer involves complex interactions between the tumour and the host. Cancer immunotherapy uses various strategies to augment tumour immunity and represents a paradigm shift in treating cancer, having become the fifth pillar of cancer therapy joining surgery, radiotherapy, chemotherapy and targeted therapy (Chart 12).

**CHART 12: Immunotherapy is the fifth pillar in the arsenal of cancer treatments**




Source: goetzpartners Research

### Immunotherapy encompasses multiple different strategies

Immunotherapy encompasses multiple concepts and has been a term used for some time (Chart 13). Some of the older types of immunotherapy include the immunostimulatory cytokines interleukin-2 ("IL-2") and interferon ("IFN"), while the first and only (dendritic) cancer vaccine to be approved (in April 2010) was Dendreon's Provenge (sipuleucel-T) for metastatic castrate-resistant prostate cancer. The class that has received the most attention in the last decade owing to its unprecedented clinical success is that of the ICIs, reviewed in more detail in the next section.

**CHART 13: Types of immunotherapies**

| Type | Description | Examples |
|---|---|---|
| Cytokines | ▪ Non-specific biologic modifiers | ▪ IL-2, IFN |
| Vaccines | ▪ Goal is to expose patients to tumour antigens that can elicit an anti-tumour immune response | ▪ Provenge (sipuleucel-T, dendritic cell vaccine) for metastatic prostate cancer (Dendreon / Sanpower) |
| Oncolytic viruses | ▪ Viruses that have been genetically modified to lack virulence against normal cells but are able to infect and lyse (destroy) cancer cells | ▪ Imlygic (talimogene laherparepvec [T-VEC], modified herpes simplex-1 virus ["HSV-1"]) for advanced melanoma (Amgen) |
| Chimeric antigen receptor T cells ("CAR-T") | ▪ Isolation and expansion of tumour-specific T cells, which are then infused back into the patient | ▪ Kymriah (CTL019), first CAR-T therapy to be approved, for ALL and large B cell lymphoma (Novartis) |
| Immune checkpoint modulators / inhibitors | ▪ Antibodies that block checkpoints on T cells or their ligands, thus "releasing the breaks". Includes both mono-specific and bispecific mAbs | ▪ Yervoy (anti-CTLA-4, BMS)<br>▪ Keytruda (anti-PD-1, Merck & Co.)<br>▪ Tecentriq (anti-PD-L1, Roche) |

Abbreviations: ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T cell
Source: goetzpartners Research

## Immune checkpoints play a central role in cancer

*The two checkpoints that have received the most attention are:*
- ***CTLA-4:** cytotoxic T lymphocyte-associated antigen-4*
- ***PD-1:** programmed cell death protein 1*

Checkpoints are a core element of the normal immune system. Their *raison d'être* is to ensure that an immune inflammatory response is not constantly activated, as this could lead to chronic inflammation and immune-mediated tissue damage. Tumour cells hijack checkpoint pathways to "hide" from the immune system and prevent their own destruction. The two checkpoint pairs that have received the most attention are CTLA-4 / B7 (1/2) and PD-1 / PD-L1, as blockade of these checkpoints with monoclonal antibodies has proved to be an effective and durable cancer immunotherapy in 20% - 50% of patients with a variety of tumour types, including advanced disease, with recent long-term follow up analyses demonstrating a dramatic improvement in long-term survival.

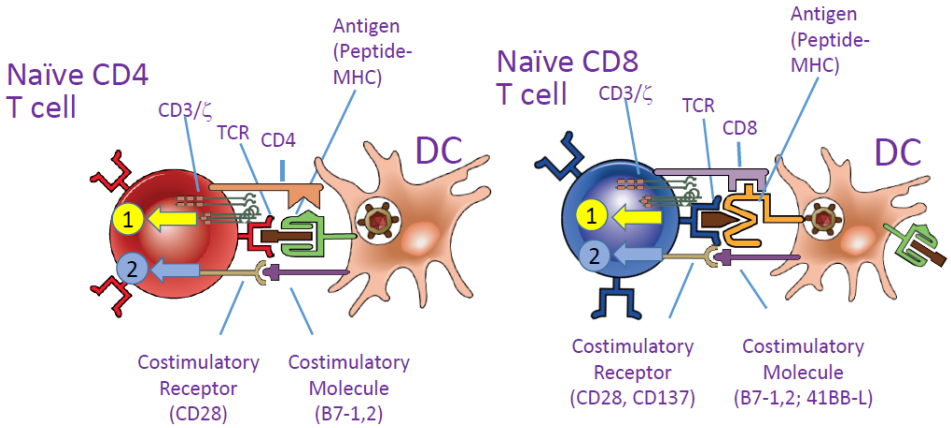
### The anti-tumour T cell response requires two signals: TCR binding to MHC / antigen

*There are 3 types of professional **antigen-presenting cells ("APCs")**:*
- *Dendritic cells ("DCs")*
- *Macrophages*
- *B cells*

***DCs are considered the most effective APCs:***
- *Present in tissues, where they encounter antigens*
- *Highly efficient at ingesting antigens in tissues*
- *Migrate to the lymph nodes, where they encounter T cells*
- *Express both MHC class I and II molecules*
- *Present antigens to T cells*
- *Express co-stimulatory molecules*
- *Critical for cross-talk between innate and adaptive immunity*

T cells are the main mediators of the cell-mediated immunity needed to destroy tumours. To become fully activated, they need to interact with antigen-presenting cells ("APCs"). Specifically, the T cell receptor ("TCR") on the T cell needs to bind to a molecular complex on the APC consisting of tumour-derived antigens (short, linear peptides) bound to major histocompatibility ("MHC") molecules. CD4+ T cells are restricted to MHC class II molecules, while CD8+ T cells are restricted to MCH class I molecules (Chart 14). The two classes of MHC display peptides processed through different molecular pathways and this is important for the type of immune response required.

**CHART 14: T cells require two signals to become activated by APCs**




Source: Lichtman, Harvard Medical School, Lecture

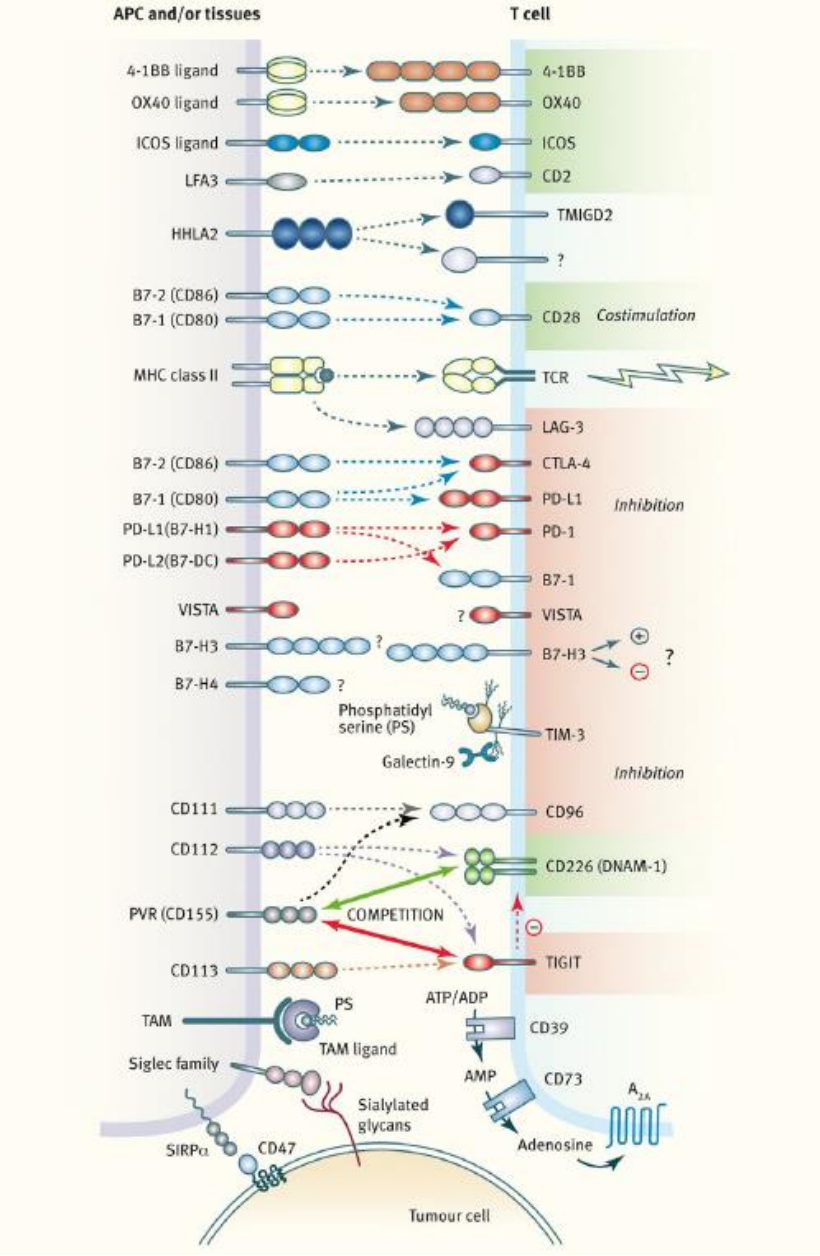
### … and costimulation

While TCR binding to MHC / antigen is *necessary* to trigger the intracellular signals that activate a naïve T cell, it is *not sufficient*. The second signal *required* for full activation results from the binding of co-stimulators on the APC (B7-1 [CD80], B7-2 [CD86]) to costimulatory receptors on the T cell (CD28). Of the three professional APCs, DCs are considered the most effective APCs because they constitutively (i.e. constantly) express high levels of both MHC molecules and have costimulatory activity, while both macrophages and B cells must be activated to express both.

## Inhibitory checkpoints modulate TCR-mediated T cell signals

Immune responses are regulated by a sophisticated system of checks and balances that enable both protective immunity against pathogens and malignant cells, as well as tolerance (Sharpe 2017). This is achieved through the careful regulation of *stimulatory* pathways promoting the activation of naïve T cells as well as effector, memory and regulatory T cell responses, but also *inhibitory* checkpoints that limit the threshold for T cell activation and duration of the immune response. The latter have important effects in regulating the resolution of inflammation, tolerance and homeostasis, and hence protect against immune-mediated tissue damage. Checkpoints are mostly represented by T cell receptor binding to corresponding ligands on cells in their surrounding microenvironment, which leads to T cell downregulation and / or inhibition. They are usually upregulated in suppressed T cells and can be used as markers of T cell exhaustion / dysfunction. Over 20 checkpoint pairs have been identified (Chart 15).

**CHART 15: Overview of innate and adaptive checkpoint pathways**




Source: Sharpe (2017) *Immunological reviews*

## CTLA-4 and PD-1 have taken centre stage. LAG-3 emerging as a relevant checkpoint

CTLA-4 / B7 and PD-1 / PD-L1 have emerged as the two most clinically relevant pathways, leading to the approval of multiple therapies for advanced cancers. Their mechanisms of action are not identical: while CTLA-4 competes with CD28, thus blocking CD28 / B7 costimulation, PD-1 interferes with T cell signalling directly (Chart 16). LAG-3, Immutep's area of focus, is increasingly being recognised as an attractive target and may become the 3rd pillar in immune checkpoint therapy.

**CHART 16: Overview of the immune checkpoints CTLA-4, PD-1 and LAG-3**

| Receptor | Expressing cells | Ligand | Expressing cells | Description |
|---|---|---|---|---|
| **CTLA-4** | ▪ Activated effector T cells and Tregs | ▪ B7-1 (CD80)<br>▪ B7-2 (CD86) | ▪ Professional APCs | ▪ High homology to CD28<br>▪ Higher competitive binding affinity to B7: competitive blockade of CD28 / B7 costimulation<br>▪ CTLA-4 is most effective when B7 expression is low |
| **PD-1** | ▪ Effector T cells and Tregs<br>▪ NK cells and B cells<br>▪ Macrophages | ▪ PD-L1 (B7-H1)<br>▪ PD-L2 (B7-DC) | ▪ PD-L1: APCs, T cells, epithelial, endothelial and tumour cells<br>▪ PD-L2: APCs, DCs, monocytes, other (non)-immune cells | ▪ Does not interfere with costimulation<br>▪ Generates signals that prevent phosphorylation of key signalling molecules, reducing T cell activation |
| **LAG-3** | ▪ Activated T cells, e.g. CD4+, CD8+, Tregs<br>▪ NK cells | MHC class II | ▪ Professional APCs | ▪ Structurally homologous to CD4<br>▪ Higher affinity to MHC class II antigens than CD4 |

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen-4; LAG-3, lymphocyte-activated gene-3; PD-1, programmed cell death protein 1
Source: Oiseth *et al.* (2017) *J Cancer Metastasis Treat*

*Exhausted T cells are dysfunctional T cells unable to kill tumour cells*

### Tumours hijack checkpoints to hide from the immune system

One of the eight hallmarks of cancer is the ability to evade (escape from) the immune system. Checkpoints are key targets, with tumours having found ways to hijack both the CTLA-4 and PD-1 pathways to protect themselves. For example, tumours have been found to increase the production of PD-L1, allowing them to downmodulate and hence inactivate invading T cells. In fact, inhibitory checkpoints are key mediators of T cell exhaustion that develops during cancer. Exhausted T cells are characterised by reduced activation, proliferation and migration; decreased cytokine production; and impaired tumour-killing ability.

## Checkpoint inhibitors "release breaks" on immune system

The critical role inhibitory checkpoints play in cancer is reflected by the dramatic effects of blocking the CLTA-4 and PD-1 checkpoints in cancer with ICIs. The first piece of evidence came in 1996, when Leach, Krummel and Allison reported in *Science* that monoclonal antibodies mAbs against CTLA-4 resulted in the rejection of tumours – including pre-established tumours – in preclinical models. From a mechanistic point of view, ICIs block the negative blockade of T cells, which leads to a strong boost of the immune response against cancer. In other words, they release the breaks on the immune system. The progress made in the field over the last 20 years has been remarkable, with six ICIs now approved for clinical use across many different cancer indications, and thousands of clinical trials ongoing. Approvals of new agents, line extensions for existing agents, the increasing use of combination therapy and potential price increases are expected to expand the ICI market from US$10.5bn in 2017 to over US$28bn in 2022E.

*Immune-related side effects have been a key drawback for the CTLA-4 inhibitor class and led to the focus shifting to the better tolerated and safer PD-1 / PD-L1 pathway*

### Six checkpoint inhibitors currently on the market since approval of Yervoy in 2011

The first ICI and only CTLA-4 inhibitor so far to enter the market was BMS's Yervoy (ipilimumab), based on FDA approval for advanced melanoma in March 2011 (Chart 17, Chart 18). Sales expanded from US$360m in 2011 to US$1.3bn in 2014, but growth has stalled since 2015 following the regulatory approval of Merck & Co's Keytruda (pembrolizumab) and BMS's Opdivo (nivolumab), both PD-1 inhibitors, in September and December 2014, respectively. This is due to their superior efficacy, as well as their less severe immune-related adverse effects of 5% - 20% compared to 10% - 40% (Oiseth *et al.* 2017, Baumeister *et al.* 2016) for Yervoy.

**CHART 17: Of the six approved checkpoint inhibitors, five target the PD-1 / L1 checkpoint**

| Company | Product | mAb | Target | '17 sales (US$m) | Approval | Approved indications | Dosing & administration (adults) |
|---|---|---|---|---|---|---|---|
| **BMS** | Yervoy | ipilimumab | CTLA-4 | 1,244 | Mar-11 | Melanoma, RCC | 3-10mg/kg IV every 3 weeks (195-650mg for 65kg avg. weight) |
| **Merck & Co** | Keytruda | pembrolizumab | PD-1 | 3,809 | Sep-14 | Melanoma, NSCLC, HNSCC, cHL, UC, MSI-H, gastric, cervical, PMBCL | 200mg IV every 3 weeks |
| **BMS** | Opdivo | nivolumab | PD-1 | 4,948 | Dec-14 | Melanoma, NSCLC, RCC, cHL, HNSCC, UC, CRC, HCC | 240 mg IV every 2 weeks or 480 mg every 4 weeks |
| **Roche** | Tecentriq | atezolizumab | PD-L1 | 495 | May-16 | NSCLC, UC | 1,200 mg IV every 3 weeks |
| **Pfizer / Merck KGaA** | Bavencio | avelumab | PD-L1 | 24 | Mar-17 | MCC, UC | 10mg/kg every 2 weeks (650mg for 65kg avg. weight) |
| **AstraZeneca** | Imfinzi | durvalumab | PD-L1 | 19 | May-17 | UC, NSCLC | 10mg/kg every 2 weeks (650mg for 65kg avg. weight) |

Abbreviations: AR, adverse reactions; cHL, classical Hodgkin lymphoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell cancer; MCC, Merkel cell carcinoma; MSI-H, microsatellite instability-high cancer; NSCLC, non-small cell lung cancer; PMBCL, primary mediastinal large B-cell lymphoma; RCC, renal cell carcinoma; UC, urothelial carcinoma
Source: Company data, FDA, prescribing information

**CHART 18: Opdivo and Keytruda's success is due in part to their broad labels**

| Product | FDA-approved indications (first approval in each type of cancer shown in brackets) |
|---|---|
| **Yervoy** (ipilimumab) | **Melanoma (Mar-2011)**<br>▪ Unresectable or metastatic melanoma (label extended to paediatric patients in Jul-2017)<br>▪ Adjuvant treatment in cutaneous melanoma (Oct-2015)<br>**Renal cell carcinoma**<br>▪ Intermediate or poor risk, previously untreated advanced RCC (combination with nivolumab) |
| **Keytruda** (pembrolizumab) | **Melanoma (Sep-2014)**<br>▪ Unresectable or metastatic melanoma<br>**Non-small cell lung cancer (Oct-2015)**<br>▪ 1L treatment of metastatic NSCLC in tumours with high PD-L1 expression (single agent)<br>▪ Metastatic NSCLC in tumours that express PD-L1 (single agent)<br>▪ 1L treatment of metastatic non-squamous NSCLC (combination with pemetrexed and carboplatin) (May-2017)<br>**Head and neck squamous cell cancer (Aug-2016)**<br>▪ Recurrent / metastatic HNSCC after platinum-containing chemoTx<br>**Classical Hodgkin lymphoma (Mar-2017)**<br>▪ Refractory / relapsed after ≥3 prior lines of therapy<br>**Urothelial carcinoma (May-2017)**<br>▪ Locally advanced or metastatic urothelial carcinoma in patients ineligible for cisplatin-containing chemoTx<br>▪ Locally advanced or metastatic urothelial carcinoma following platinum-containing chemoTx / within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemoTx<br>**Microsatellite instability-high cancer (May-2017)**<br>▪ Unresectable or metastatic, microsatellite instability-high ("MSI-H") or mismatch repair deficient (1) solid tumours following progression and w/o alternative treatment options, or (2) colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan<br>**Gastric cancer (Sep-2017)**<br>▪ Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma where tumours express PD-L1<br>**Cervical cancer (Jun-2018)**<br>▪ Recurrent or metastatic cervical cancer with disease progression on or after chemoTx whose tumours express PD-L1 (CPS≥1)<br>**Primary mediastinal large B-cell lymphoma (Jun-2018)**<br>▪ Adult and paediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy |
| **Opdivo** (nivolumab) | **Melanoma (Dec-2014)**<br>▪ BRAF V600 wild-type and mutation-positive unresectable or metastatic melanoma (single agent)<br>▪ Unresectable or metastatic melanoma (combination with ipilimumab) (Oct-2015)<br>▪ Melanoma with lymph node involvement or metastatic disease who have undergone complete resection (adjuvant)<br>**Non-small cell lung cancer (Mar-2015)**<br>▪ Metastatic NSCLC and progression on or after platinum-based chemoTx<br>**Renal cell carcinoma (Nov-2015)**<br>▪ Advanced RCC following prior antiangiogenic therapy (Nov-15)<br>▪ Intermediate or poor risk, previously untreated advanced RCC (combination with ipilimumab)<br>**Classical Hodgkin lymphoma (May-2016)**<br>▪ Classical Hodgkin lymphoma that has relapsed or progressed after (1) autologous hematopoietic stem cell transplantation ("HSCT") and brentuximab vedotin, or (2) ≥3 lines of systemic therapy that includes autologous HSCT<br>**Head and neck squamous cell cancer (Nov-2016)**<br>▪ Recurrent or metastatic HNSCC with disease progression on or after a platinum-based therapy<br>**Urothelial carcinoma (Feb-2017)**<br>▪ Locally advanced or metastatic urothelial carcinoma in patients who have disease progression (1) during or following platinum-containing chemoTx, or (1) within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemoTx<br>**Colorectal cancer (Aug-2017)**<br>▪ Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan<br>**Hepatocellular carcinoma (Sep-2017)**<br>▪ HCC following prior treatment with sorafenib |
| **Tecentriq** (atezolizumab) | **Non-small cell lung cancer (Oct-2016)**<br>▪ Metastatic NSCLC following disease progression during or following platinum-containing chemoTx<br>**Urothelial carcinoma (Apr-2017)**<br>▪ Locally advanced or metastatic urothelial carcinoma in patients (1) ineligible for cisplatin-containing chemoTx, or (2) following any platinum-containing chemoTx, or within 12 months of neoadjuvant or adjuvant chemoTx |
| **Bavencio** (avelumab) | **Merkel cell carcinoma (Mar-2017)**<br>▪ Metastatic MCC<br>**Urothelial carcinoma (May-2017)**<br>▪ Locally advanced or metastatic urothelial carcinoma in patients (1) who have disease progression (1) during or following platinum-containing chemoTx, or (2) within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemoTx |
| **Imfinzi** (durzalumab) | **Urothelial carcinoma (May-2017)**<br>▪ Locally advanced or metastatic urothelial carcinoma following (1) disease progression during or following platinum-containing chemoTx, (2) disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemoTx<br>**Non-small cell lung cancer (Feb-2018)**<br>▪ Unresectable, Stage III NSCLC if (1) disease has not progressed following concurrent platinum-based chemoTx & radiation therapy |

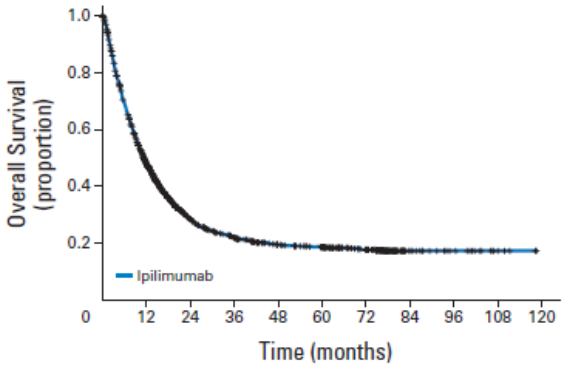
Source: Company data, FDA, prescribing information

*An analysis of pooled trials of ipilimumab in metastatic melanoma showed that >20% of patients were still alive after 10 years. 3-year survival rates were 22% for all patients, 26% for treatment-naïve patients and 20% for previously treated patients*

## Remarkable effect on long-term survival in >20% of patients

The exponential growth of the ICI market particularly since the launch of the PD-1 inhibitors is due primarily to their dramatic effect on long-term overall survival in responsive patients. Results from multiple late-stage clinical trials have shown survival rates of 20% - 30% after 3 years of treatment, together with a plateauing of the survival curves around this time, meaning that these patients experience durable responses where the cancer does not return. This has been further corroborated by 10-year follow-up of patients treated with ipilimumab, with an analysis of pooled Phase II and Phase III trials of ipilimumab in metastatic melanoma demonstrating that >20% of patients were still alive after 10 years of treatment compared to a historical survival rate of <10% (Chart 19).

**CHART 19: Pooled survival data from Phase II and Phase III trials of ipilimumab in unresectable metastatic melanoma**




Source: Schadendorf *et al.* (2015) *J CLin Oncol*

*Some tumours types are mostly inflamed and respond well to checkpoint inhibitors, including melanoma, non-small cell lung and renal cancer. Others are not inflamed and therefore show poor responses to CIs, such as prostate and pancreatic cancer*

## "Hot" tumours such as melanoma more responsive to CI therapy than "cold" tumours

As described earlier, cancers build an immunosuppressive environment around them – the tumour microenvironment – that allows them to survive. A key element is the ability to suppress tumour-fighting CD8+ cytotoxic T cells and prevent them from infiltrating the tumour. Checkpoint inhibitors have been found to be more effective against "hot" tumours with a highly inflammatory microenvironment containing many tumour-infiltrating lymphocytes ("TILs"). In contrast, "cold" tumours with few TILs ("immune deserts" in extreme cases) respond poorly. Melanoma are particularly hot tumours and have therefore been the indication of choice for the leading CI companies. Lung cancers, especially those occurring in smokers due to their higher mutational burden, also respond well to CI therapy.

**CHART 20: Best tumour response rates achieved in the KEYNOTE-006 trial**

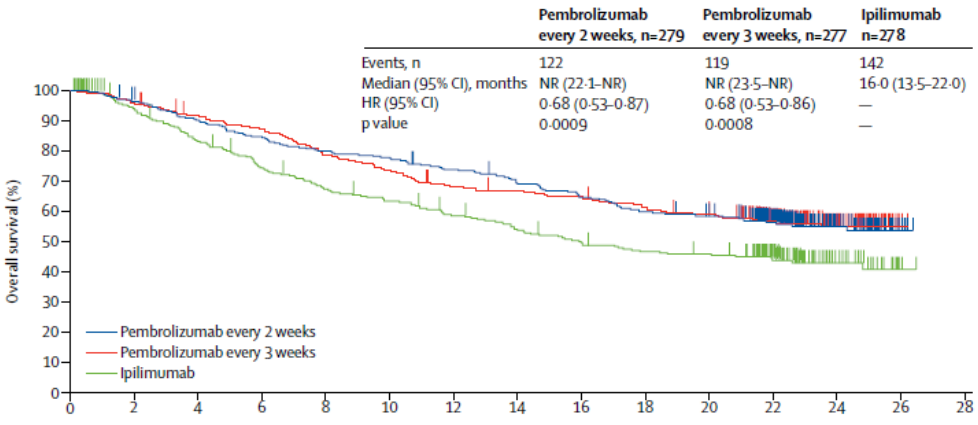
| | pembro 2 wks | pembro 3 wks | ipi |
|---|---|---|---|
| ORR | **37%** | **35%** | **13%** |
| **CR** | 12% | 13% | 5% |
| **PR** | 25% | 23% | 8% |
| SD | **11%** | **11%** | **16%** |

Source: Schachter *et al.* (2017) *The Lancet*

## PD-1 inhibitor Keytruda has demonstrated superior efficacy to CTLA-4 blocker Yervoy

The superior efficacy of Keytruda vs. Yervoy was shown in the 834-patient open-label, randomised Phase III KEYNOTE-006 trial in advanced melanoma. Both Keytruda dosing regimens tested (every 2 weeks and every 3 weeks) showed a significant improvement in both response rates (Chart 20) and overall survival (Chart 21), with all three treatment arms showing remarkable duration of response: after a median follow-up of 22.9 months, median OS was not reached in either pembrolizumab group and was 16.0 months with Yervoy. 24-month OS was 55% in the 2-week group, 55% in the 3-week group and 43% for Yervoy.

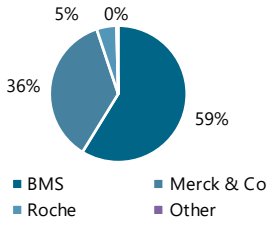
**CHART 21: Pembrolizumab demonstrated superior overall survival compared to ipilimumab in the Phase III KEYNOTE-006 trial in advanced melanoma**




Source: Schachter *et al.* (2017) *The Lancet*

## c.US$10.5bn market to exceed US$28bn in 2022E

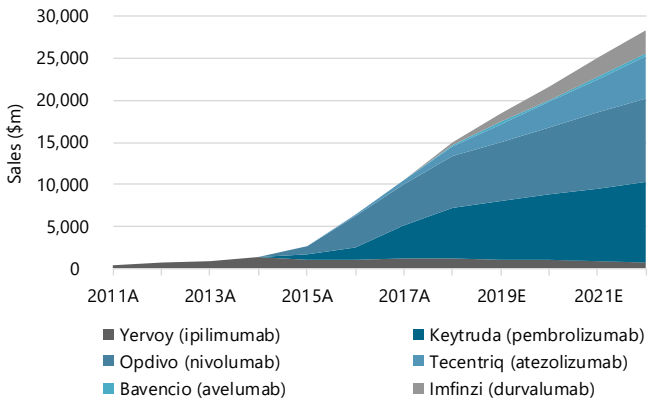
**CHART 22: The ICI market is dominated by 3 companies**




Source: BMS, Merck & Co, Merck KGaA, Pfizer, Roche, AstraZeneca

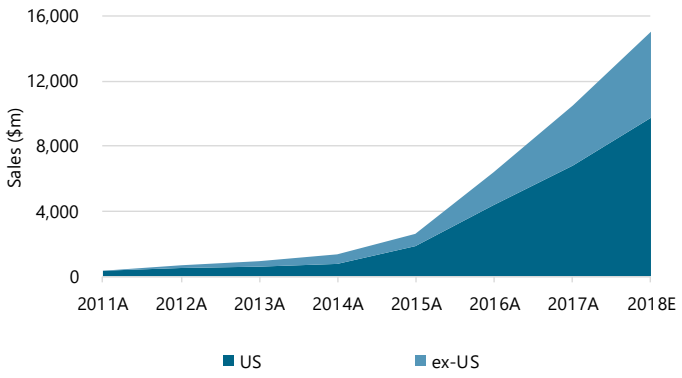
The ICI market reached US$10.5bn in 2017 (Chart 23), posting a 76% CAGR since 2011, led by Opdivo and Keytruda, which together accounted for 83% of global sales. Opdivo established its lead over Keytruda in 2015, based on label expansions into other cancer indications and broader addressable markets, particularly in lung cancer (Chart 18), where use of Keytruda has been restricted to patients whose tumours express (high levels of) PD-1. Sales reached US$4.9bn in 2017, up 31% from US$3.7bn in 2016. That said, Keytruda experienced higher growth of 172% in 2017, with sales up to US$3.8bn from US$1.4bn in 2016, and – according to consensus estimates from EvaluatePharma – will overtake Opdivo in 2018, with sales expected to reach US$6.1bn vs. US$6.0bn. Consensus further sees the ICI market growing to over US$28bn in 2022E based on the marketed products alone, suggesting that the actual figure may be higher. As is common in oncology, the US is the single largest market, commanding a 65% share in 2017 (Chart 24).

**CHART 23: The ICI market grew from US$360m in 2011 to US$10.5bn in 2017**




Source: BMS, Merck & Co, Merck KGaA, Pfizer, Roche, AstraZeneca

**CHART 24: US sales accounted for 56% to 65% of sales in each given year**



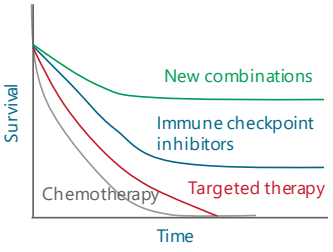

Source: BMS, Merck & Co, Merck KGaA, Pfizer, Roche, AstraZeneca

### BMS leads the pack, followed by Merck & Co

Since inaugurating the ICI market in 2011, BMS has established itself as the clear market leader with a market share of 59% in 2017 (Chart 22), owing largely to Opdivo and aided by US$1.2bn in sales from Yervoy, which posted its first year of growth (+18% YoY) following declines in both 2015 (-14%) and 2016 (-7%). Roche is an ambitious challenger, with its anti-PD-L1 Tecentriq (atezolizumab) currently in third place, and is expected to remain in this position in 2022 with sales of US$4.9bn. Pfizer / Merck KGaA's and AstraZeneca are relatively new contenders in the market and may struggle to establish meaningful sales given the limited differentiation between PD-1 / PD-L1 inhibitors.

## I-O combinations: lifting the tail of the survival curve

**CHART 25: The focus in immune-oncology is on "lifting the tail" of the survival curve**




Source: goetzpartners Research estimates

While checkpoint inhibitors in isolation have shown remarkable, durable effects across tumour types and cancer stages including advanced disease in patients with a poor prognosis, there is still a large proportion of patients who do not respond. Strong preclinical data demonstrated that combining antibodies against PD-1 and CTLA-4 with each other or with other mechanisms of action can increase therapeutic efficacy and the percentage of responders, based on CTLA-4 and PD-1 inhibiting antitumor immunity through complementary, nonredundant mechanisms. Hence, dual blockade synergistically improves anti-tumour responses. This has also been shown in clinical trials in advanced melanoma for both nevolumab / ipilimumab and pembrolizumab / ipilimumab combinations. The goal of combination therapy is to convert cold into hot tumours to increase response rates to CIs and, consequently, continue to "lift the tail" of the survival curve (Chart 25).

**CHART 26: In CheckMate-069, Opdivo plus Yervoy performed significantly better than Yervoy alone**

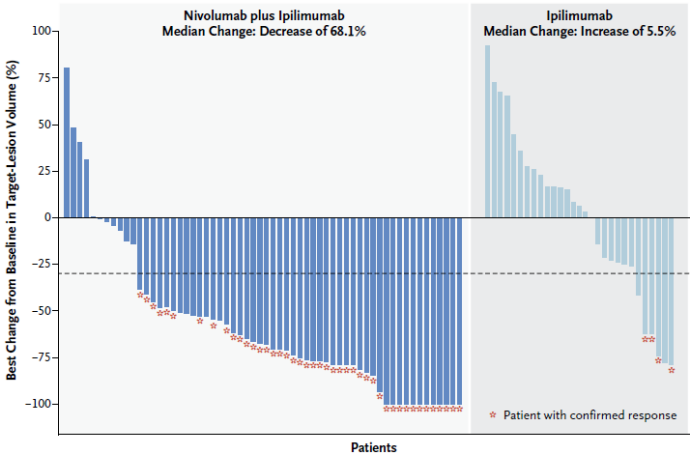
| | nivo / ipi | ipi alone | p-value |
|---|---|---|---|
| **ORR** | **61%** | **11%** | **<0.001** |
| CR | 22% | 0% | |
| PR | 39% | 11% | |
| **PFS*** | **n.a.** | **4.4** | **<0.001** |

*Months
Source: Postow *et al.* (2015) *NEJM*

### Nivolumab / ipilimumab combo more effective than ipilimumab mono, but more toxic

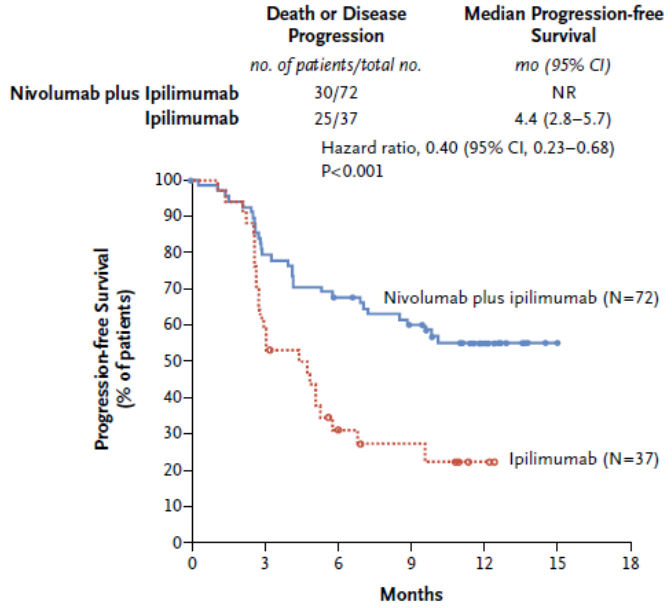
The first ICI combination, Opdivo + Yervoy, for the treatment of BRAF V600 wild-type, unresectable or metastatic melanoma, was approved by the FDA in October 2015. The accelerated approval was granted based on tumour response rates and durability of response from the double-blind, randomised Phase II CheckMate-069 trial in 142 patients with previously untreated unresectable or metastatic melanoma including patients with both BRAF wild-type and BRAF mutation-positive melanoma comparing nivolumab plus ipilimumab to ipilimumab alone (Postow *et al.* 2017). In patients with BRAF wild-type melanoma (n=109, the population on which the primary endpoint was based), combination therapy led to a significantly higher ORR (including some CRs, Chart 26) and median PFS vs. Yervoy alone (Chart 28), and further led to a 60% reduction in the risk of progression (p<0.002).

**CHART 27: Best change in baseline in the target lesions**




Source: Postow *et al.* (2015) *NEJM*

**CHART 28: Progression-free survival**




Source: Postow *et al.* (2015) *NEJM*

The median change in investigator-assessed tumour volume was a 68.1% decrease in the combination group and a 5.5% increase in the ipilimumab monotherapy group (Chart 27). The flipside is that the combination group also experienced more toxicity. This combination has also been shown to provide a survival benefit, with a 2-year follow-up from an 86-patient Phase I dose-escalation trial showing a favourable overall survival rate of 79% at 2 years in addition to high rates of objective response (including CRs) and a prolonged duration of response (Wolchok *et al.* 2013, Sznol *et al.* 2014).

## Big pharma has paid up to acquire promising I-O assets

Large pharma has been paying high prices for oncology companies in general, but particularly I-O companies with promising (usually clinical) assets (Chart 29). By far the largest acquisitions in the last three years were those of the leading pure-play CAR-T companies Juno and Kite, acquired by oncology specialist Celgene for US$9bn and oncology newcomer Gilead for US$11.9bn, respectively.

**CHART 29: Select M&A transactions in the immuno-oncology space**

| Date | Target | Country | Description | Acquirer | EV (US$m) | Rationale |
|---|---|---|---|---|---|---|
| May-18 | **Armo Biosciences** | US | Late-stage IO company with multiple assets in the clinic, incl. lead IO asset pegilodecakin (PEGylated IL-10) | Eli Lilly | 1,600 | Access pegilodecakin, which has shown clinical benefit as single agent and in combination with chemo and CIs across several tumor types |
| May-18 | **BeneVir Biopharm** | US | Specialised in the development of oncolytic viruses for immunotherapy | Janssen (J&J) | 1,040 | Complements own IO research |
| Feb-18 | **Viralytics Limited** | Australia | IO company with oncolytic virus that infects and kills cancer cells | Merck & Co. | 394 | Viralytics's approach of engaging innate immune system complements own IO strategy |
| Jan-18 | **Cascadian Therapeutics** | US | Cancer-focused biotech. Lead asset in clinical development for mBC | Seattle Genetics | 614 | Enhance late-stage pipeline with potentially best-in-class, orally available tyrosine kinase inhibitor ("TKI") that is highly selective for HER2 |
| Jan-18 | **Juno Therapeutics** | US | Pioneer in the development of CAR T and TCR therapies evaluating multiple targets and cancer indications | Celgene | 9,000 | Leverage a novel scientific platform and scalable manufacturing capabilities to complement Celgene's leadership in haematology and oncology |
| Dec-17 | **Ignyta** | US | IO company focused on cancers with specific rare mutations | Roche | 1,700 | Entrectinib gives Roche the opportunity to expand its portfolio of oncology medicines |
| Dec-17 | **Cell Design Labs** | US | Pre-clinical stage company with expertise in custom cell engineering | Gilead | 567 | Addition of synNotch and Throttle technology could lead to the treatment of a broader range of haematological malignancies and solid tumours |
| Aug-17 | **Kite Pharma** | US | Leader in the field of cell therapy | Gilead | 11,900 | Establish Gilead as a leader in cellular therapy |
| Aug-17 | **IFM Therapeutics** | US | Works with innate immunity and its role in regulating the immune system | BMS | 300 | Strengthen oncology pipeline focus on innate immunity by accessing STING and NLRP3 agonists |
| Jun-17 | **Altor BioScience** | US | Focus on immunotherapeutic agents for cancer, viral infections and autoimmune diseases | NantCell | 290 | n.a. |
| Jan-17 | **Dendreon** | US | Develops personalised immune-therapeutics for cancer. First company to launch a cancer vaccine (Provenge) | Sanpower Group | 820 | Promote Provenge outside of the US, starting with China and Southeast Asia |
| Oct-16 | **Ganymed** | Germany | Develops new class of cancer drugs, ideal mAbs, for solid cancers | Astellas | 1,400 | Further expand oncology presence by adding a late-stage mAb with the potential to establish a new pillar following Xtandi (enzalutamide) |
| Jul-16 | **Cormorant** | US | Developer of cancer and rare disease therapies | BMS | 520 | Acquire full rights to HuMax-IL8 (IL-8 mAb). Targeting could complement T-cell-directed antibodies and co-stimulatory molecules |
| Feb-15 | **Flexus Biosciences** | US | Discover agents for the reversal of tumor immunosuppression | BMS | 1,250 | Accelerate ability to explore numerous immunotherapeutic approaches across tumour types through the addition of an IDO inhibitor |

Abbreviations: IL-8, interleukin-8; IO, immune-oncology; mBC, metastatic breast cancer
Source: Mergermarket, Company data

# LAG-3: potential 3rd pillar in immuno-oncology

Immutep's entire R&D portfolio focuses on modulating LAG-3 for immunotherapy applications. LAG-3 is a checkpoint that was first discovered by Immutep's current CSO / CMO Frédéric Triebel in 1990. It has since been shown to be similar to CD4 and be expressed across multiple types of immune cells. Extensive experimental work has shown that LAG-3 has both stimulatory and inhibitory roles in a normally functioning immune system, making it suitable for therapeutic applications in both cancer and autoimmune diseases. The search for the third pillar in the ICI toolbox has led to increased activity in the LAG-3 space, with most companies focusing on mAbs that block LAG-3, thus mirroring the mechanism of action of the approved ICIs. In addition to having the broadest LAG-3 targeted pipeline across the biopharma industry, to our knowledge Immutep is also the only company with a LAG-3 approach exploring the stimulatory activity of this checkpoint pathway.

## MHC class II-ligand expressed on multiple cell types

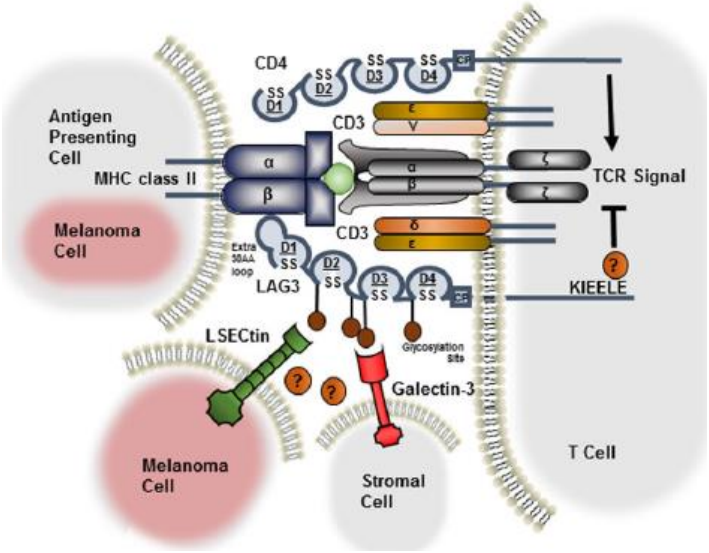
**CHART 30: LAG-3 is expressed on multiple cell types**

| |
|---|
| CD4+ T cells |
| CD8+ T cells |
| Tregs (thymic / peripherally induced) |
| NK cells |
| NKT cells |
| B cells |
| Plasmacytoid dendritic cells |

Source: Baumeister *et al.* (2016) *Annu Rev Immunol*

Lymphocyte activation gene-3 ("LAG3", or CD223), a 498-aminoacid type I transmembrane protein, is a CD4 homolog with four extracellular immunoglobulin superfamily (IgSF)-like domains (D1 – D4). Although the two molecules only share c.20% amino acid homology, the structural motifs are highly conserved, resulting in similar extracellular folding patterns. Hence, LAG-3 binds to MHC class II molecules (Chart 31), albeit at a different site to and with much higher affinity. Other putative ligands include L-SECtin and galectin-3, both expressed in the tumour microenvironment. LAG-3 is expressed on multiple cell types (Chart 30), including cytotoxic and tumour-infiltrating regulatory T cells, as well as immature dendritic cells, and is often co-expressed with PD-1 on dysfunctional or exhausted T cells.

**CHART 31: LAG-3 has a similar structure as CD4, competing for binding to MHC class II on APCs**




Source: Andrews *et al.* (2017) *Immunol Rev*

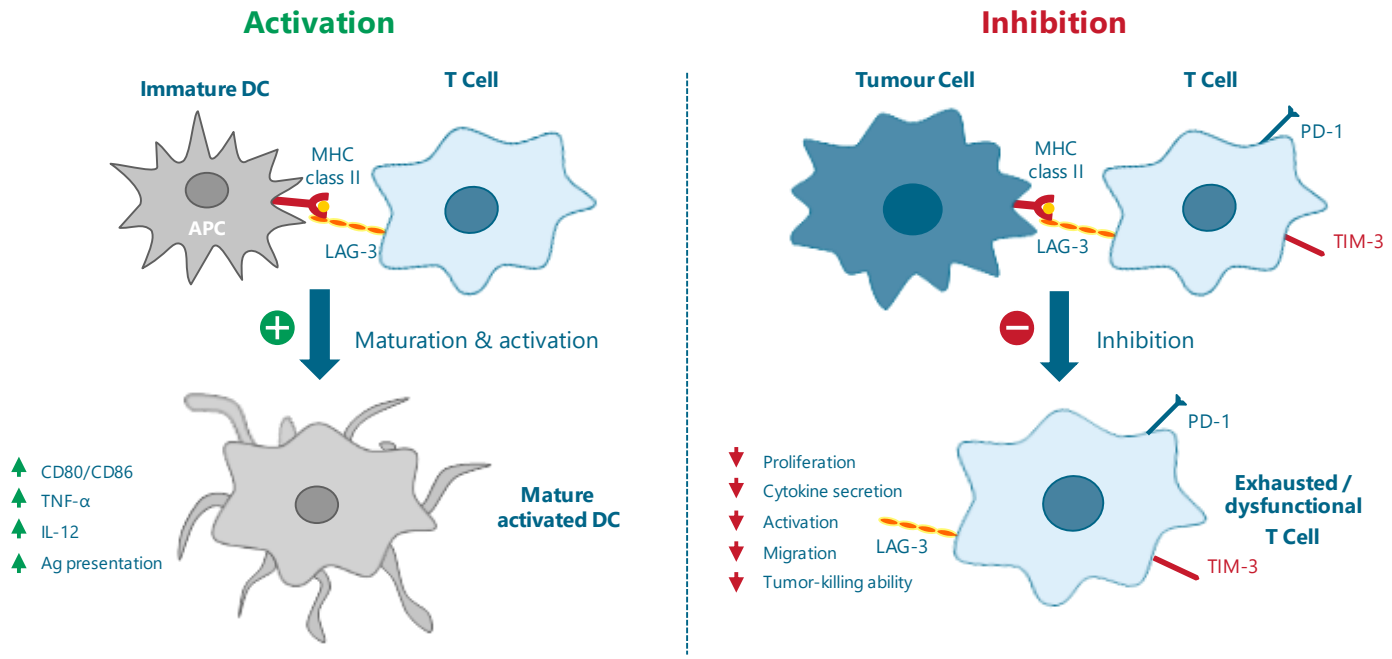
## Dual function: APC activation vs. T cell inhibition

Much experimental work has been carried out over the last two decades to elucidate the role of LAG-3 within the immune system. The evidence suggests that LAG-3 has two different functions: (1) stimulation of APCs expressing MHC class II, and (2) inhibition of T cells expressing LAG-3 (Chart 32).

### 1. APC activation through engagement of MHC class II on immature DCs

DCs are considered the most powerful APCs, as they are the only cell type able to induce primary immune responses (Andreae *et al.* 2003). On encountering a danger signal, DCs undergo a complex maturation process that commences with the uptake of antigen in tissues and is followed by the migration to regional lymph nodes, where they stimulate antigen-specific T cells. Maturation of DCs requires multiple signals. Work completed by Triebel and his lab has shown that engagement of MHC class molecules located on immature DCs leads to their maturation through the up-regulation of CD80/CD86, secretion of the pro-inflammatory cytokines IL-12 and TNF-alpha, morphological changes such as the formation of dendritic projections, and the induction of a specific pattern of chemokines that allows migration of secondary lymphoid organs for priming of naïve CD4+ and CD8+ T cells (reviewed by Andrews *et al.* 2017).

CHART 32: The LAG-3 / MHC class II pathway has two different effects




Source: goetzpartners Research

### 2. Inhibition of T cell function through the transmission of inhibitory signals

LAG-3 expressed on T cells competes directly with CD4 for MHC class II binding on APCs. This triggers an inhibitory signalling cascade through the LAG-3 cytoplasmic domain (the precise signal transduction mechanisms remain unknown) that interferes with T cell activation and negatively regulates CD4+ and CD8+ T cell proliferation, function and homeostasis. Preclinical studies have suggested that LAG-3 functions primarily through this mechanism rather than by disrupting CD4:MHC class II interactions (Workman *et al.* 2002).

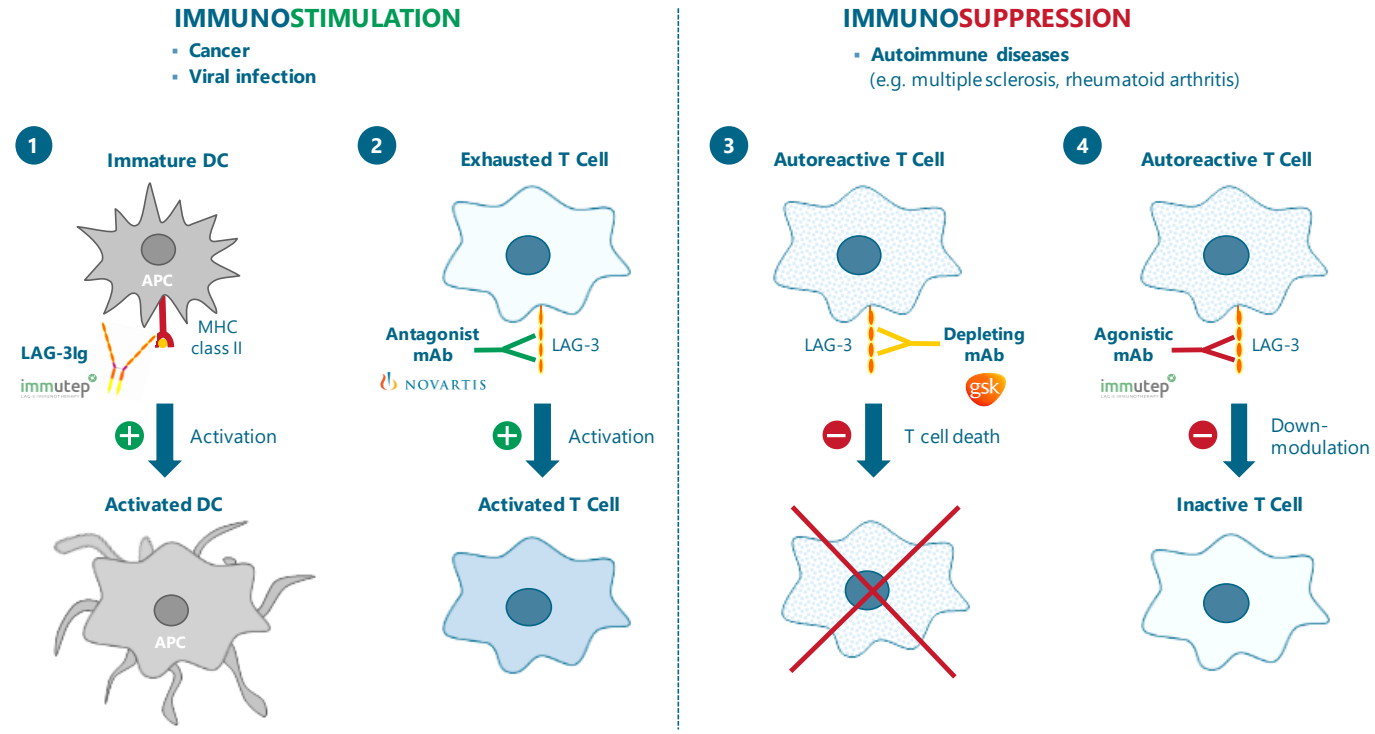
### Sustained LAG-3 expression contributes to exhausted T cell phenotype

Under normal circumstances, LAG-3 upregulation is required to control overt activation and prevent the onset of immunity. However, chronic antigen exposure in the tumour microenvironment and the resulting persistent T cell activation causes sustained co-expression of LAG-3 on T cells that often also express additional inhibitory receptors such as PD-1, CTLA-4, TIGIT, TIM3, CD160 and 2B4 (Zarour, 2016). This in turn leads to what is known as "T cell exhaustion", where T cells display reduced activation, proliferation, migration, cytokine secretion and tumour-killing activity.

## Multiple possible therapeutic strategies focused on LAG-3

The observation that LAG-3 is widely expressed on TILs and cytotoxic T cells makes it a suitable immunotherapy candidate. Based on the current understanding of LAG-3, there are at least four different ways this checkpoint pathway can be tackled for therapeutic purposes both for cancer indications and autoimmune diseases (Chart 33). The two strategies focused on anticancer therapy consist in either (1) stimulating APCs with a soluble version of LAG-3 or (2) blocking LAG-3 on T cells to counter the negative signalling. In the context of autoimmunity, the strategies being employed consist in deploying (3) agonistic LAG-3 mAbs that stimulate LAG-3 signalling in order to down-modulate overactive T cells, and (4) depleting antibodies that remove autoreactive T cells from the circulation. Immutep alone or in collaboration with biopharma partners (Novartis, GSK) has (pre)clinical programmes across all four approaches.

CHART 33: There are multiple therapeutic approaches focused on the LAG3 checkpoint pathway




Source: goetzpartners Research

## Pharma and biotech both driving LAG-3 pipeline expansion

There is increasing interest from large pharma and small biotech alike to develop new therapeutic agents targeting the LAG-3 checkpoint pathway, mainly in combination with PD-1 blockade (Chart 34). The most popular approach by far is the blockade of the LAG-3 surface protein with mAbs to reverse the inhibitory signalling cascade that contributes to the exhausted T cell phenotype. BMS has the largest development programme in this respect focused on relatlimab (BMS-986016), which is being tested in multiple clinical trials across many different solid and haematological tumour types both as monotherapy and in combination with nivolumab (anti-PD-1). Other companies such as F-Star and Macrogenics are working on bispecific approaches focused on dual checkpoint blockade. Immutep is the only company with a soluble LAG-3 molecule that stimulates APCs.

**CHART 34: Immutep has the broadest LAG-3 targeted pipeline**

| Company | Molecule | MoA | Indications (advanced / metastatic) | Therapeutic strategy | Phase* |
|---|---|---|---|---|---|
| Immutep | Eftilagimod alpha (IMP321) | ▪ LAG-3Ig fusion protein<br>▪ APC activator | ▪ Metastatic breast cancer<br>▪ Melanoma<br>▪ Solid tumours (NSCLC, head and neck cancer)** | ▪ Chemo-IO (efti / paclitaxel)<br>▪ IO-IO (efti / pembro)<br>▪ Cancer vaccines<br>▪ Monotherapy | IIb |
| BMS | Relatlimab (BMS-986016) | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | ▪ Melanoma<br>▪ Renal cell carcinoma<br>▪ Gastric cancer<br>▪ Lung cancer (NSCLC)<br>▪ HL, DLBCL<br>▪ Glioblastoma<br>▪ Solid tumours | ▪ IO-IO (relatlimab / nivolumab)<br>▪ Monotherapy | II/III |
| Novartis / Immutep | LAG525 (IMP701) | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | ▪ Solid tumours | ▪ IO-IO (LAG525 / PDR001, an anti-PD-1) | II |
| Merck & Co | MK-4280 | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | ▪ Lung cancer (NSCLC)<br>▪ Solid tumours | ▪ IO-IO (MK4280 / pembrolizumab)<br>▪ Monotherapy | II |
| GSK / Immutep | GSK2831781 (IMP731) | ▪ Anti-LAG-3 mAb<br>▪ Depletes cells expressing LAG-3 | ▪ Plaque psoriasis | ▪ Monotherapy | I |
| BI | BI 754111 | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | ▪ Solid cancers (gastric, esophageal, hepatocellular)<br>▪ Follicular lymphoma<br>▪ Lung cancer (NSCLC) | ▪ IO-IO (BI 754111 / BI 754901, an anti-PD-1)<br>▪ Monotherapy | I |
| Macrogenics | MGD013 | ▪ Bispecific DART protein binding PD-1 & LAG-3<br>▪ Dual checkpoint inhibitor | ▪ Solid tumours<br>▪ Haematologic neoplasms | ▪ IO-IO<br>▪ Monotherapy | I |
| Sanofi / Regeneron | REGN3767 | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | ▪ Advanced malignancies, incl. lymphoma | ▪ IO-IO (REGN3767 / REGN2810, an anti-PD-1)<br>▪ Monotherapy | I |
| Tesaro | TSR-033 | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | ▪ Solid tumours | ▪ IO-IO (TSR-033 / anti-PD-1)<br>▪ Monotherapy | I |
| F-Star / Merck KGaA | FS-118 | ▪ Bispecific antagonist targeting LAG-3 and PD-L1<br>▪ Dual checkpoint blockade | ▪ Malignancies | ▪ Monotherapy | I |
| Symphogen / Shire | SYM022 | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | ▪ Solid tumours | ▪ Monotherapy | I |
| Incyte / Agenus | INCAGN02385 | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | ▪ Malignancies | ▪ Monotherapy | I |
| Eli Lilly / Armo Biosciences | AM0003 | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 inhibitor | n.a. | n.a. | Pre-clinical |
| Immutep | IMP761 | ▪ Anti-LAG-3 mAb<br>▪ LAG-3 stimulation | ▪ Autoimmune diseases | n.a. | Pre-clinical |

Programmes involving Immutep assets are highlighted in blue
*Most advanced phase. **In collaboration with Merck & Co
Abbreviations: APC, antigen-presenting cell; HR, hormone-receptor; IO, immune-oncology; LAG- lymphocyte antigen-3; PD, programmed death
Source: clinicaltrials.gov, Company data

# Efti activates APCs to kick-start immune response

***Eftilagimod alpha (IMP321) profile***

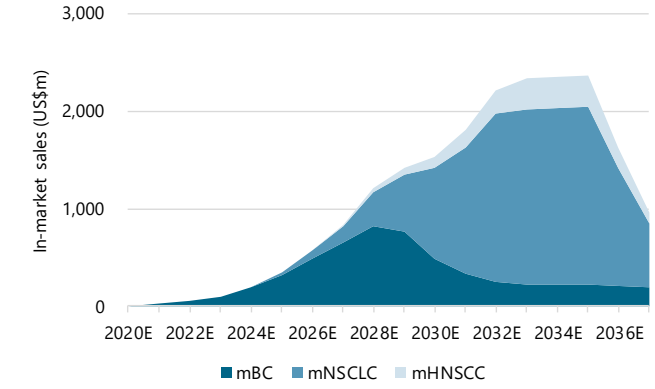
- *Unique, potentially first-in-class LAG-3Ig fusion protein*
- *Binds to MHC class II on APCs*
- *Only LAG-3-targeted molecule that activates APCs*
- *Turns cold tumours hot*
- *Clinical trials in multiple advanced solid tumour types testing chemo-IO or IO-IO combo*
- *Encouraging efficacy shown in Phase I/II metastatic breast cancer trial*
- *Benign safety profile*

Eftilagimod alpha is a LAG-3Ig fusion protein that has been shown to drive dendritic cell maturation and APC activation by binding to MHC class II with high affinity. The current development programme focuses on combination therapy with either chemotherapy or the PD-1 inhibitor pembrolizumab across solid tumours. A Phase IIb trial (AIPAC) in metastatic breast cancer ("mBC") in combination with paclitaxel is expected to read out in 2019E, and a Phase II basket trial in NSCLC and HNSCC cancers exploring combination therapy with pembrolizumab is due to start in Q4/2019E. The latter is based on proof-of-concept of the combination from a Phase I trial in metastatic / unresectable melanoma (TACTI-mel), for which encouraging interim efficacy data was presented in May 2018.

## Peak sales potential of c.US$2.4bn following conditional approval in 2020E

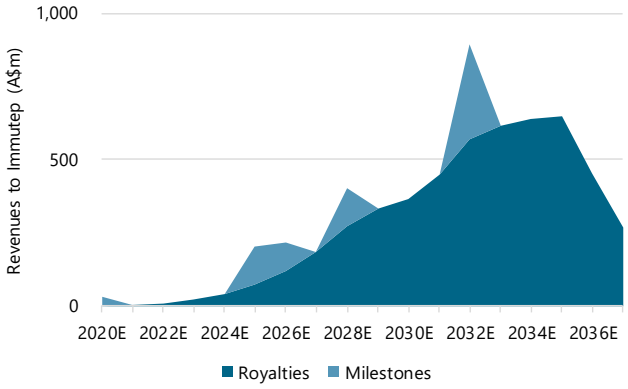
We forecast first launch in 2020 following conditional approval based on Phase IIb data in mBC and peak sales of US$2.4bn in 2034E across all indications, with NSCLC accounting for c.65% of cumulative sales, mBC for 25% and HNSCC for the remainder (Chart 35). We expect Immutep to sign a global licensing deal for eftilagimod in H2/2019 worth US$1bn in upfront and milestone payments plus tiered royalties on sales (Chart 36).

**CHART 35: Eftilagimod alpha in-market sales by indication**




Source: goetzpartners Research estimates

**CHART 36: Eftilagimod revenues to Immutep (milestones and royalties)**



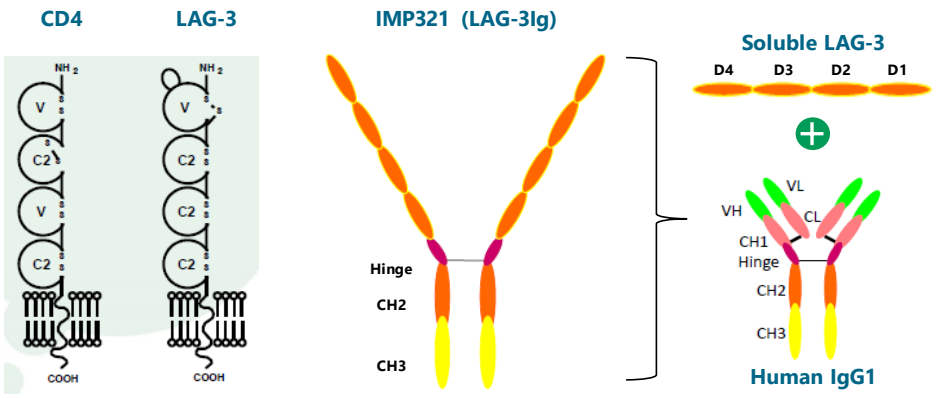

Source: goetzpartners Research estimates

## Potent immune activation to turn cold tumours hot

*Eftilagimod alpha (IMP321) "pushes the accelerator" on the immune response*

Multiple studies both *in vivo* and using human peripheral blood mononuclear cells ("PBMCs") have shown that efti indirectly activates effector CD8+ T cells (incl. long-lived effector memory cells) and NK cells – both heavily involved in the tumour-killing response – through the activation of myeloid DCs. This activation of both arms of the immune system (innate and adaptive) should help turn cold tumours hot.

**CHART 37: Efti is a dimeric LAG-3 fusion protein**




Source: Company data

### Soluble recombinant version of LAG-3 that binds to MHC class II on APCs

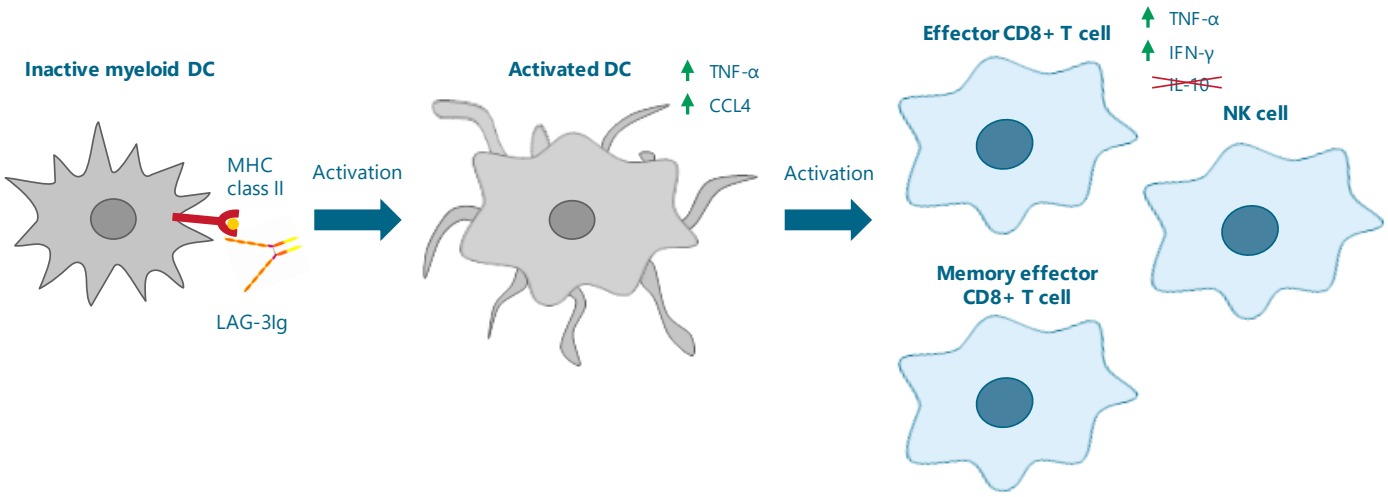
Efti is a soluble recombinant version of the naturally occurring LAG-3 protein. It is a very stable dimeric fusion protein where two copies of the four IgSF domains are fused to the Fc portion plus hinges of human IgG1 (Chart 37).

### Secondary T cell activation via the stimulation of DCs and monocytes

***Cross-presentation of antigens***
*Ability of APCs to ingest, process and present extracellular antigens via MHC class I molecules to CD8+ T cells. Since MHC class I molecules usually only present endogenous antigens from intracellular pathogens, this process is essential for anti-tumour activity*

LAG-3Ig is a high-affinity, high-avidity binder of MHC class II that preferentially binds to myeloid DCs (Brignone *et al.* 2007). LAG-3Ig binds to a restricted subset of MHC class II molecules localised in lipid raft microdomains that account for 15% - 20% of all MHC class molecules on immature DCs. These are required for induction of CD8+ T cell responses to exogenous antigens, i.e. cross-presentation, by inducing DCs to process antigen for MHC class I presentation. Upon MHC class II engagement, DCs become activated and start expressing pro-inflammatory cytokines, particularly tumour necrosis factor alpha ("TNF-α"). This in turn leads to the activation of fully differentiated effector and memory effector CD8+ T cells and also NK cells that express both TNF-α and interferon gamma ("IFN-γ"), but not the anti-inflammatory cytokine interleukin-10 ("IL-10), which suppresses CTL differentiation (Chart 38).

**CHART 38: Efti indirectly leads to the activation of effector T cells by stimulating MHC class II expressing DCs**




Source: Company data, Brignone *et al.* (2007) *J Immunol*

### Stimulation of APCs may be complemented by blocking of LAG-3 on Tregs

It is possible that the effect of LAG-3Ig on recruiting and activating immune effector cells through APC activation as outlined above is reinforced through the blockade of LAG-3 signalling into Tregs, leading to Treg silencing (Brignone *et al.* 2007) in a similar fashion as PD-1 checkpoint blockade. This could be achieved either through (1) direct competition for MHC class II, or (2) the rapid internalisation of MHC class II molecules triggered by LAG-3Ig binding.

## Clinical development: combo Tx for advanced solid tumours

**CHART 39: Possible combination strategies for eftilagimod alpha**

| Combo strategy | Being tested |
|---|---|
| Chemo - IO | ✓ |
| IO - IO | ✓ |
| Cancer vaccine - IO | × |

Abbreviations: IO, immuno-oncology
Source: goetzpartners Research

Eftilagimod alpha is being developed for combination therapy across multiple advanced solid tumours (Chart 39, Chart 40). The choice of these indications is based on earlier Phase I trials and, market size, and further takes into account successful clinical work completed with marketed checkpoint inhibitors. Immutep is currently sponsoring two clinical trials: a Phase IIb study (AIPAC) in hormone receptor-positive mBC, and a Phase I trial (TACTI-mel) in metastatic melanoma. A third trial in metastatic lung and head & neck cancer (TACTI-002) is being planned with partner Merck & Co and scheduled to start in Q4/2019E. There is also an investigator-led trial ongoing (INSIGHT) in advanced solid tumours exploring alternative routes of administration for efti monotherapy, intra-tumoral and intra-peritoneal. Apart from the latter, all clinical trials are exploring efti in combination with either chemotherapy or the PD-1 inhibitor pembrolizumab.

### Preferred dose of 30mg below that of other immunotherapies

The dose that has been emerging as the preferred dose for efti is 30mg every 2 weeks, which is low when compared to that of the checkpoint inhibitors. This is due to IMP321 acting as an APC agonist, which only requires 2-3% target binding, while the ICIs need to achieve relatively high target occupancy to be effective, as they are designed to block a signalling cascade. This has translated to a very benign safety profile, with side effects limited mainly to infusion side reactions.

**CHART 40: Eftilagimod alpha is being tested in four clinical trials**

| Indication | Phase | N | Therapy | Dosing | Design | Objectives | NCT / Data |
|---|---|---|---|---|---|---|---|
| **mBC (stage IV, HR-positive, HER2-negative)** | Phase IIb (AIPAC) started Dec-2015 | 241 | chemo-IO (efti / paclitaxel) | RPTD (30mg SC) | Multicentre (Europe), pcb-controlled, double-blind, 1:1 randomised | ▪ 1ary: RPTD, PFS<br>▪ 2ary: safety & tolerability, OS, PK, QOL, ORR, SD | NCT02614833 Jun-2019 |
| **NSCLC, HNSCC *(partnered with Merck & Co.)*** | Phase II (TACTI-002) starts Q4 / 2018 | Up to 120 | IO-IO (efti / pembrolizumab) | 30mg SC | 12-15 sites in Europe / US / Australia, open label | ▪ ORR, PFS, OS, PK, biomarkers<br>▪ Safety & tolerability | n.a. |
| **Metastatic / unresectable melanoma (stage III, IV)** | Phase I (TACTI-mel) started Feb-2016 | 24 | IO-IO (efti / pembrolizumab) | Single SC injections of 1, 6 and 30 mg every 2 wks | Multicentre in Australia, open-label, dose-escalation | ▪ 1ary: safety & tolerability<br>▪ 2ary: AEs, ORR (RECIST & irRC), PFS | NCT02676869 Jun-2018 |
| **Advanced solid tumours *(investigator-led)*** | Phase I (INSIGHT) started Aug-2017 | 38 | IO (efti monoTx) | IT (6, 12, 24 & 30 mg), IP (1, 3, 6, 12 and 30mg) & SC (as per AIPAC) injections | Explorative, single centre in Frankfurt, Germany, open-label | ▪ 1ary: feasibility<br>▪ 2ary: AEs, PFS, OS, immune response | NCT03252938 Feb-2019 |

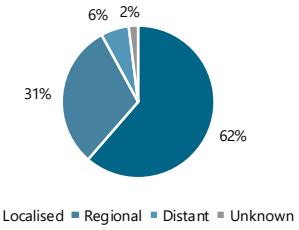
Abbreviations: chemo, chemotherapy; HR, hormone receptor; I-O, immuno-oncology; irRC, immune-related response criteria; IP, intra-peritoneal; IT, intra-tumoural; ORR, overall response rate; OS, overall survival; pcb, placebo; PFS, progression-free survival; QOL, quality of life; RPTD, recommended Phase II dose; SC, subcutaneous; SD, stable disease
Source: Company data, clinicaltrials.gov

## Advanced mBC Phase IIb data possible in 2019

*The regulatory strategy is to apply for conditional approval in Europe based on PFS data from the Phase IIb AIPAC trial. This would require a PFS of at least 3-4 months, in our view*

Efti is being tested in combination with paclitaxel chemotherapy in the Phase IIb AIPAC (Active Immunotherapy PAClitaxel) clinical trial as first-line agent for hormone receptor ("HR")-positive, human epidermal growth factor receptor 2 ("HER2")-negative metastatic breast cancer ("mBC", adenocarcinoma stage IV). The choice is based on this being a readily identifiable patient population accounting for 60% - 65% of all mBC patients, the lack of approved immunotherapy, and scientific advice from the EMA. The 2-stage trial design includes a safety-run in that was successfully completed and presented at the ASCO 2017 meeting. The data confirmed efti's benign safety profile, efficacy signals as seen in the 30-patient Phase I/II trial in a similar population (ORR of 47% vs. 50%, disease control rate of 87% vs. 90%, respectively), and the recommended dose for the randomised portion of the trial. Recruitment is expected to be completed in Q4 and PFS data should become available in 2019, which – if positive – is expected to pave the way for a conditional approval in Europe.

**CHART 41: Percentage of breast cancer patients by stage**




Source: SEER database

### Breast cancer is the most common cancer diagnosed in women

Breast cancer is the most commonly diagnosed cancer worldwide, with the incidence highest among white women over 40 years of age, and the leading cause of cancer-related death in women. Although breast cancer mortality has been declining for nearly three decades, the unmet need remains high, particularly for metastatic disease, which is treatable, but not curable. The National Cancer Institute estimates that 266,120 cases of invasive breast cancer will be diagnosed in 2018 and 40,920 will die of the disease in the same year. In Europe, the age-adjusted incidence was estimated at 94.2 per 100,000 in 2012 (Senkus *et al.* 2015). Survival in breast cancer correlates with the original size of the tumour, the extent of regional spread and the histological features of malignancy (Triebel *et al.* 2006). Although only a minority of women are diagnosed with metastatic disease (Chart 41), in many others the disease progresses to this stage over time.

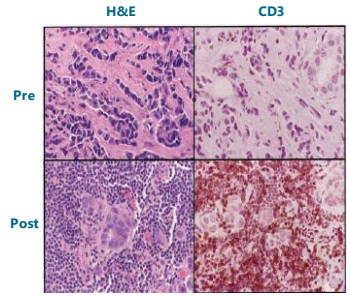
### Hormone receptors and HER2 status determine treatment approach

A central component of the treatment of breast cancer is an understanding of the extent of disease and biologic features, which are key in predicting response to therapy. The three most important markers used to guide treatment relate to the presence of estrogen ("ER") and progesterone ("PR") receptors, collectively referred to as HR status, and HER2 status. The treatment approach depends on which of these markers are present on the tumour cells of each patient.

### Treatment for metastatic disease prolongs survival, but is not curative

The treatment algorithm for breast cancer includes surgery and or radiotherapy for local disease, and chemotherapy, endocrine therapy, biologic therapy or combination of these for systemic treatment (NCCN Guidelines Version 1.2018, Breast Cancer). Efti is being developed for stage IV (metastatic), HR-positive, HER2-negative disease, where the treatment goal is to extend life and enhance quality of life. Women whose tumours are HR-positive are candidates for initial endocrine therapy. Once they become refractory, they become eligible for chemotherapy. A variety of chemotherapy agents – including the taxane paclitaxel, which is used in the AIPAC trial – are currently recommended, and single agent is preferred over combination chemotherapy due to the lower toxicity and risk of dose reduction.

**CHART 42: Large tumour infiltration by T cells following neoadjuvant paclitaxel therapy in breast cancer**




Note: The images are from a patient who achieved a complete clinical response. The lower images show substantial post-treatment lymphocytic infiltrate. T cells are seen infiltrating and disrupting residual tumour cell nests.
Source: Demaria *et al.* (2001) *Clin Cancer Res*

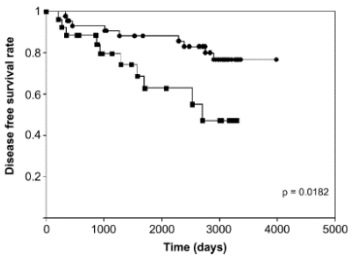
## Breast cancer tumours may be more immunogenic than previously thought

Until recently, it was thought that breast cancer was a weekly immunogenic tumour, due to the limited number of TILs present within the tumour microenvironment and the observation that checkpoint blockade led to response rates of approx. 10% across trials (Mittendorf, interview at Miami Breast Cancer Conference 2018). However, breast tumour-associated antigens have now been identified, and immunocytochemistry on a large number of tumours has shown the presence of immune infiltrates. Hence, the current strategy in breast cancer is to augment the number of T cells. One such approach is to combine ICIs with chemotherapy.

## Combo with chemo leverages activation of immune system that follows cytotoxicity

The effect of chemotherapy – still the standard of care for the treatment of advanced cancer due to its rapid and dramatic effect (in less than 3 months) – was traditionally believed to be due to the direct cytotoxicity and induction of tumour cell death. However, increasing evidence suggests that chemotherapy also leads to activation of the immune system (see Chart 42 for an example), in part triggered by the release of tumour antigen from dying tumour cells. This has led to the development of combinations with immunotherapy. Many of these combinations have been successful (Zitvogel *et al.* 2011), for example leading to the regulatory approval of Keytruda plus pemetrexed and carboplatin for first-line treatment of metastatic non-squamous NSCLC in May 2017. The goal of adding a non-specific immunopotentiator such as efti to paclitaxel in the treatment of metastatic breast cancer is to enhance chemotherapy-induced T cell responses through the induction of APCs, which is expected to turn the (often) short-lived responses from chemotherapy alone into durable tumour remission.

**CHART 43: sLAG-3 levels at time of first diagnosis predict survival in breast cancer patients***




*Data shows results for sub-group of patients with progesterone-positive tumours. The outcome for estrogen-positive tumours was similar.
Source: Triebel *et al.* (2006) *Cancer Letters*

## Pre-treatment serum levels of soluble LAG-3 predict survival in breast cancer

In addition, Triebel *et al.* (2006) discovered that patients with HR-positive (estrogen or progesterone) breast cancer with detectable levels of soluble LAG-3 ("sLAG-3") at the time of first diagnosis benefited from higher disease-free and overall survival than those with undetectable levels of sLAG-3 (Chart 43). This paved the way for the study of LAG-3Ig in metastatic breast cancer.

## AIPAC trial design in HR-positive patients in line with previous Phase I/II

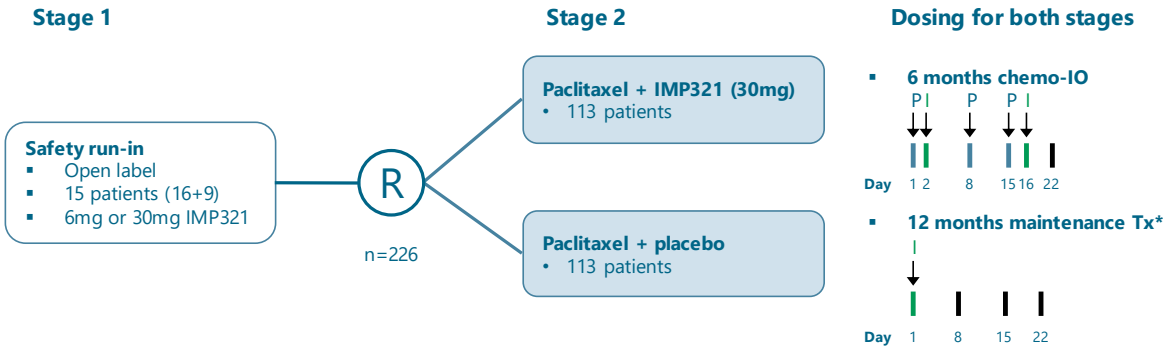
Chart 44 below shows the design of the ongoing Phase IIb AIPAC trial in mBC. The trial includes a total of 241 patients and is split into two stages. The first stage is an open-label run-in in 15 patients designed to determine the recommended Phase II dose, while the second stage randomises 226 patients to assess safety and efficacy of the higher 30mg dose. Both stages include both a chemo-IO phase during which efti is administered in combination with paclitaxel, and a maintenance phase during which responders continue to receive efti. The primary endpoint is PFS. Other assessments include ORR and OS. As of April 2018, 33 out of the planned 34 clinical trial sites were active, with full recruitment anticipated in Q3/2018E. The administration schedule is such that efti is administered every 2 weeks and always the day after the paclitaxel infusion (Chart 45).

**CHART 44: Phase IIb (AIPAC) trial testing IMP321 alpha plus paclitaxel in stage IV (metastatic) breast adenocarcinoma**

| Parameter | Description (NCT02614833) |
|---|---|
| No. of participants | 241 (15 in stage 1, 226 in stage 2. Full recruitment expected in Q3/2018E) |
| Target population | Hormone receptor-positive adenocarcinoma of the breast stage IV |
| Comparator | Placebo |
| Randomisation | 1:1 eftilagimod alpha / paclitaxel combo vs. placebo / paclitaxel (double-blind) |
| Design | 2-stage design starting with a safety run-in in 15 patients<br>▪ **Stage 1:** open-label, safety run-in consisting of cohort 1 and 2 to confirm the recommended Phase II dose ("RPTD") of IMP321 in combination with paclitaxel<br>▪ **Stage 2:** placebo-controlled, double-blind randomisation stage, paclitaxel + IMP321 at the RPTD vs. paclitaxel + placebo<br>In both stages, Tx consists of a chemo-IO phase followed by a maintenance phase<br>▪ **Chemo-IO phase (6 months):** 6 cycles with weekly paclitaxel at Days 1, 8 and 15, and either IMP321 or placebo on Days 2 and 16 of each 4-week cycle<br>▪ **Maintenance phase (12 months):** responding or stable patients will receive study agent (IMP321 or placebo) every 4 weeks for an additional 12 injections |
| Dosing | ▪ IMP321<br>o Stage 1: 6mg or 30mg SC<br>o Stage 2: 30mg IMP321 SC<br>▪ Paclitaxel: 80mg/m$^2$ IV |
| Locations | >30 sites in Europe (BE, FR, GER, HU, NL, PL, UK) |
| Primary endpoint | ▪ Stage 1: RPTD<br>Stage 2: Progression-free survival ("PFS") up to 37 months |
| Secondary endpoints | ▪ Safety and tolerability (up to 19 months)<br>OS (up to 48 months) and PK, QOL, ORR, SD (up to 37 months) |
| Timing | Started December 2015, primary completion date 2019 |

Abbreviations: IV, intravenous; ORR, overall response rate; OS, overall survival; PK, pharmacokinetics; QOL, quality of life; SC, subcutaneous; SD, stable disease
Source: clinicaltrials.gov, Company data

**CHART 45: Design of AIPAC trial includes a safety run-in**

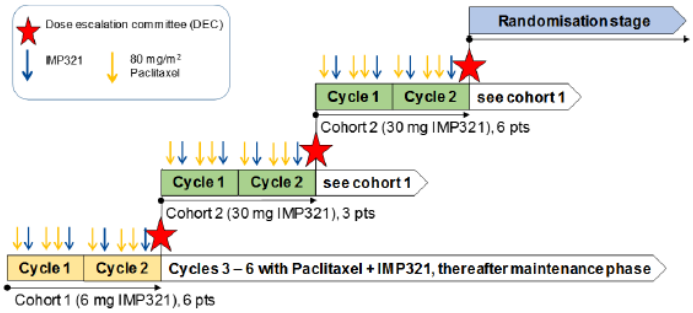



Source: Company data

## Safety run-in successfully completed and presented at ASCO 2017

The safety run-in stage of the trial (Chart 46) was completed and the data presented at ASCO 2017, showing the following: (1) Efficacy signals consistent with those observed in the previous Phase I/II trial (Chart 47); (2) a clean safety profile, with the only notable adverse event injection site reactions grade 1 and 2 occurring in almost all patients; and (3) selection of the 30mg dose for Stage 2 of the trial.

**CHART 46: Design of safety run-in**




Source: Duhoux *et al.* (2017) ASCO annual meeting

**CHART 47: Encouraging response rates observed in safety run-in**

| Response parameter | Paclitaxel / IMP321 (n = 15) |
|---|---|
| Complete response ("CR") | 0% |
| Partial response ("PR") | 47% |
| **Overall response rate ("ORR")** | **47%** |
| Stable disease ("SD") | 40% |
| **Disease control rate ("DCR")** | **87%** |
| Progressive disease ("SD") | 13% |

*Note: two of the responses occurred after six months and six patients are still receiving treatment*

Source: Duhoux *et al.* (2017) ASCO annual meeting

**CHART 48: Phase I/II trial design**

| Parameter | Description |
|---|---|
| N | 30 |
| Indication | HER2-negative mBC |
| Therapy | IMP321 / paclitaxel |
| IMP321 doses | 0.25mg, 1.25mg and 6.25mg |
| Design | Open label |
| Duration | 6 months |
| Assessment | RECIST1.1 |

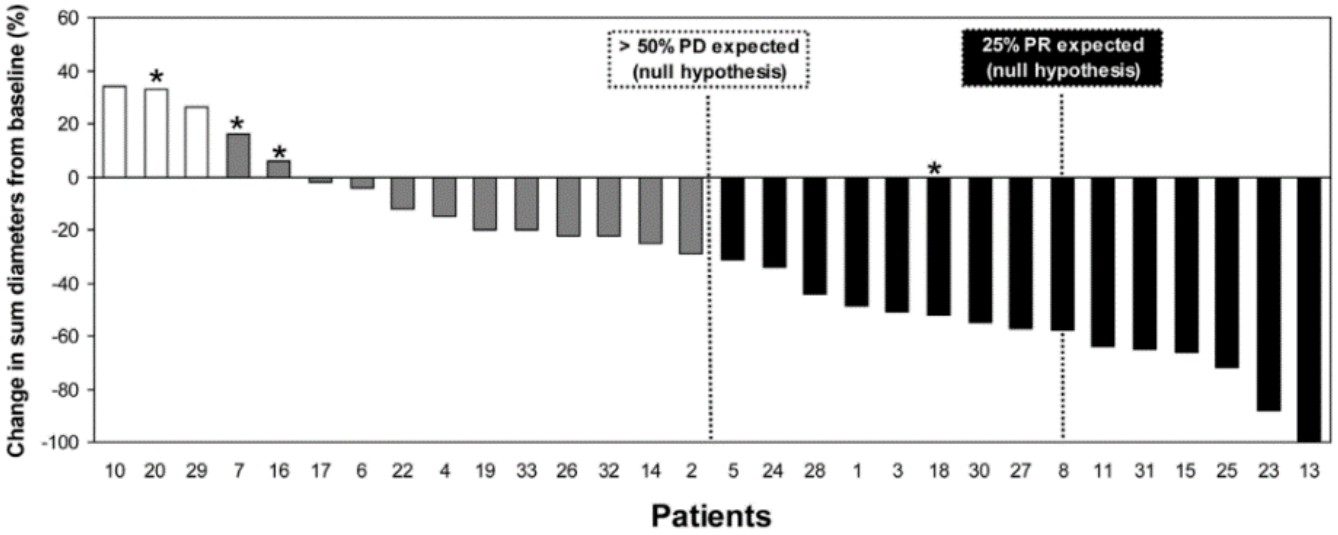
Source: Brignone *et al.* (2010) *J Transl Med*

## Phase I/II trial reveals encouraging efficacy signals and clean safety profile

IMP321 was previously tested in a multi-centre, open-label, non-randomised, 30-patient Phase I/II trial (Brignone *et al.* 2010, Chart 48). The dosing schedule was similar to the ongoing AIPAC trial, with IMP321 administered SC every 2 weeks and always the day after the paclitaxel dose, for a total of 6 months. The trial excluded human epidermal growth factor receptor 2 ("HER2")-positive patients (who are eligible for treatment with Herceptin [trastuzumab]) and those who had received prior chemotherapy for metastatic disease. Key findings include the following:

- **Encouraging efficacy signals:** ORR of 50%, which compares favourably to the ORR of 25% in the control group of the ECOG2100 study (Miller *et al.* 2007), 90% benefited from treatment (i.e. only 10% of patients had progressive disease, Chart 49);
- **Further significant tumour regression was observed for IMP321 during the maintenance phase**, i.e. after the first 3 months of treatment, especially at the 6.25mg dose, whereas with paclitaxel alone, most of the tumour responses normally occur during the first 3 months. This supports earlier findings that it takes time for active immunotherapy to reinforce the immune system;
- **The chance in tumour size correlated with the absolute number of monocytes** per µl of blood at D1, which is in line with monocytes being the primary MHC class II target cells for IMP321;
- **Significant increases in IMP321 target cells**, including monocytes, NK cells and activated CD8+ T cells, as well as a increase in the proportion of the effector memory T cell subset. The latter are long-lived, terminally differentiated CD8 T cells able to home into inflamed tissue such as the TME that may play a crucial role in the long-term effect of active immunotherapies;
- **No significant local or systemic IMP321-related adverse events.**

**CHART 49: Waterfall plot showing the percentage change in the sum of tumour diameters after 6 months of treatment**




Notes: White: progressive disease ("PD"); grey: stable disease ("SD"); black: partial response ("PR"). *These four patients received 3 months instead of 6 months of treatment. Dotted lines shows data from the paclitaxel / placebo group of the ECOG2100 study comparing paclitaxel / bevacizumab to paclitaxel / placebo (Miller *et al.* [2007] *N Eng J Med*
Source: Brignone *et al.* (2007) *J Transl Med*

## Melanoma trial provides proof-of-concept for pembro combo

*The rationale underlying the decision to carry out the TACTI-mel trial for proof-of-concept of the eftilagimod / pembrolizumab combination is as follows:*

- *Melanoma has been shown to be a highly immunogenic tumour, and both Keytruda and Yervoy were initially developed for this indication;*
- *Large melanoma patient population in Australia;*
- *Keytruda is publicly reimbursed in Australia.*

In melanoma, efti is being tested in combination with pembrolizumab in a 24-patient Phase I trial in Australia, TACTI-mel. Part A of the study (18 patients) is fully recruited and interim results presented in late May 2018 showed encouraging efficacy signals. Additional trial data may be available in time for the Society for Immunotherapy of Cancer ("SITC") meeting from 7-11 November 2018. The importance of this trial is that it is the first one to provide proof-of-concept for eftilagimod + pembrolizumab, with melanoma chosen as first indication due to the positive results seen with the first wave of ICIs. We note, however, that Immutep currently has no plans to continue development in melanoma.

### A recent wave of (immuno-)therapies have more than doubled the 5-year survival rate

Until recently, the average survival time for metastatic melanoma was 6-12 months and the 5-year survival rate <10% when treated with traditional therapies, such as dacarbazine and high-dose IL-2 (Zhu *et al.* 2016). This changed with the approval of the first immunotherapies, the checkpoint inhibitors Yervoy (in 2011), Opdivo (2014) and Keytruda (2014), as well as multiple targeted therapies (e.g. selective BRAF inhibitors vemurafenib (2011) and dabrafenib (2013), as well as MEK inhibitor trametinib (2013), more than doubling 5-year survival.

### Melanoma has been the "poster child" of immunotherapy, particularly ICIs

The first cancer indication for both the CTLA-4 inhibitor ipilimumab and the two PD-1 inhibitors nivolumab and pembrolizumab was metastatic melanoma. The reason is that melanoma has been known for a long time to be particularly susceptible to immunotherapy, particularly ICIs, due to the presence of large numbers of TILs in these tumours. This is thought to be the result of mutations caused by ultraviolet light, which give rise to neoantigens recognised by the immune system as foreign.

### Combination with PD-1 blocker: releasing the brakes and pushing the accelerator

Below we briefly summarise the rationale underlying the combination of eftilagimod with an anti-PD1.

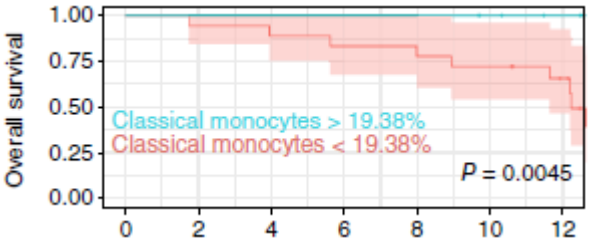
- **Many coinhibitory receptors are co-expressed with PD-1 on dysfunctional / exhausted T cells** in tumours, and TILs expressing multiple coinhibitory receptors are more dysfunctional than TILs expressing only PD-1. Hence, attacking more than one inhibitory pathway is expected to increase the chance of an anti-tumour response;

- **In preclinical models, LAG-3 / PD-1 co-blockade synergise to enhance an antitumor response** (Woo *et al.* 2012). In a different type of experiment, mice lacking both LAG-3 and PD-1 developed lethal, systemic autoimmunity (Okazaki *et al.* 2011), highlighting the synergy between these two pathways in controlling T cell tolerance;

- **PD-1 blockade relieves suppression in the tumour microenvironment.** Adding an agent that increases tumour antigen presentation by APCs to re-energised T cells is expected to help direct these cells to attack the tumour;

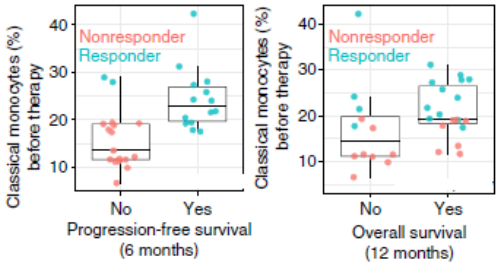
- **The frequency of (CD14+CD16–HLA-DR$^{hi}$) monocytes prior to the initiation of anti-PD-1 therapy is a strong predictor for PFS and OS**, as shown by a recent study looking for predictive biomarkers for anti-PD-1 therapy published recently in *Nature Medicine* (Krieg *et al.* 2018, Chart 50 and Chart 51). Efti works by activating and expanding monocytes and has been shown to push this population above the 19% threshold identified in the work carried out by Krieg and colleagues, which should therefore increase responses to anti-PD-1 therapy.

**CHART 50: The level of monocytes at baseline predicts response to anti-PD-1 therapy**




Source: Krieg *et al.* (2018) *Nat Med*

**CHART 51: Patients with high levels of monocytes at baseline are more likely to respond to anti-PD-1 therapy**




Source: Krieg *et al.* (2018) *Nat Med*

## TACTI-mel in advanced melanoma patients with sub-optimal response to pembro

Chart 52 shows the design of the ongoing Phase I TACTI-mel trial in metastatic melanoma taking place in Australia. The trial includes 24 patients and is split into two parts. Part A consist of a dose-escalation (IMP321 1mg to 30mg) over 9 cycles of pembrolizumab (24 weeks), while in Part B, patients are treated with the 30mg dose over 19 cycles (54 weeks).

**CHART 52: Phase I (TACTI-mel) trial testing IMP321 plus pembrolizumab in stage III / IV (metastatic) melanoma**

| Parameter | Description (NCT02676869) |
|---|---|
| No. of participants | 24 (4 cohorts of 6 patients. The trial was expanded in Feb-2018 to include the 4$^{th}$ cohort) |
| Target population | Patients with locally advanced (unresectable stage III) or metastatic (stage IV) melanoma who are currently receiving pembrolizumab and after 3 cycles achieved either:<br>▪ Asymptomatic irPD: slowly progressive disease, not requiring any intervention, with stable performance status;<br>▪ Sub-optimal response, irSD or irPD, as demonstrated in imaging assessments within 6 weeks prior to study start |
| Design | Open label, dose-finding study consisting of 2 parts:<br>▪ **Part A:** the dose is escalated following a safety observation period of the previous cohort. Patients receive 9 cycles pembrolizumab plus IMP321 (18 patients)<br>▪ **Part B:** dose defined based on the dose escalation. Total Tx duration of 19 cycles in the combined Tx (6 patients) |
| IMP321 dosing | SC every 2 weeks in combination with pembrolizumab (2mg/kg IV every 3 weeks)<br>▪ **Part A:** 1mg (cohort 1), 6mg (cohort 2), 30mg (cohort 3), starting with cycle 5 of pembrolizumab*<br>▪ **Part B:** 30mg, starting with cycle 1 of pembrolizumab |
| Locations | 7 sites in Australia |
| Primary endpoint | Recommended Phase II dose ("RPTD") |
| Secondary endpoints | ▪ Best ORR according to irRC and RECIST1.1 (until 30 days after end of treatment), time to next treatment, PFS, and OS (Part B only) up to 12 months |
| Timing | Started Feb-2016, primary completion date Jul-2018 (data possible at SITC meeting in November), study completion Aug-2019 |

*Patients are treated with pembrolizumab monoTx for 3 cycles, the screening is carried out during the 4$^{th}$ cycle, and IMP321 is added on in cycle 5
Abbreviations: ORR, overall response rate; OS, overall survival; SC, subcutaneous; SITC, Society for Immunotherapy of Cancer
Source: clinicaltrials.gov, Company data

The primary endpoint is the RPD2, and the company will further assess ORR, PFS and OS. The trial focuses on patients receiving pembrolizumab with a sub-optimal response, and excludes those who have had >4 lines of prior lines of therapies for advanced / metastatic disease, and currently cancer therapies other than pembrolizumab.

## Early data presented in May 2018 shows encouraging efficacy signals

On 19$^{th}$ May 2018, Immutep presented interim data for the 18 patients who completed Part A of the trial. The response rates are very encouraging and compare favourably to results reported for similar patient groups in prior pembrolizumab trials (Chart 53). That said, there are a number of caveats that need to be taken into account: (1) the number of patients treated is very small and a larger trial would be required to perform a reliable statistical analysis; (2) the patients in the Keynote trials appear to have poorer health, based on more being classified as ECOG 1 vs. ECOG 0; and (3) the analysis of the responses was carried out using irRC in TACTI-mel vs. RECIST in the Keynote trials. Based on RECIST, the number of CRs in TACTI-mel would be two instead of one, making the result more compelling vs. the Keynote trials. Importantly, the safety profile was benign thus confirming that IMP321 can be combined with pembrolizumab without significantly increasing the toxicity.

**CHART 53: Interim analysis of Phase I TACTI-mel trial shows promising response rates**

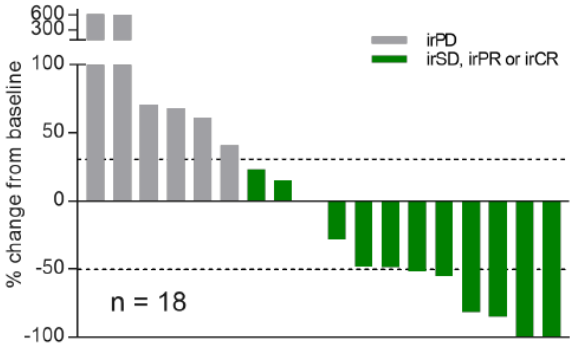
| Parameter | Tacti-mel (C5/D1)[1, A] | Tacti-mel (C1/D1)[1, B] | Keynote-006[2, C] | Keynote-002[2, D] |
|---|---|---|---|---|
| Metastasis stage M1c[3] | 83% | 83% | 68% | 82% |
| ECOG 0 / 1 | 22% / 78% | 22% / 78% | 32% / 68% | 45% / 55% |
| CR | 6% | 6% | 6% | 2% |
| PR | 28% | 56% | | |
| SD | 33% | 28% | | |
| PD | 33% | 11% | | |
| ORR (CR + PR) | 33% | 61% | 33% | 21% |
| Progression-free at 6 mos | n.a. | 66% | 46% | 34% |

(1) Responses were analysed according to irRC; (2) Responses were analysed according to RECIST; (3) Metastatic disease is classified into 3 categories, M1a, M1b and M1c. Patients with M1c have extra-pulmonary visceral metastases and hence the worst prognosis.
(A) Responses measured starting on Day 1 of the first cycle of pembrolizumab; (B) Responses measured starting on Day 1 of the fifth cycle of pembrolizumab, corresponding to the first day of the first cycle of pembrolizumab during the combination therapy part of the trial; (C) ipilimumab-naïve patients; (D) ipilimumab pre-treated patients.
Abbreviations: CR, complete response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Source: Company data, goetzpartners Research

Two key findings include the following:

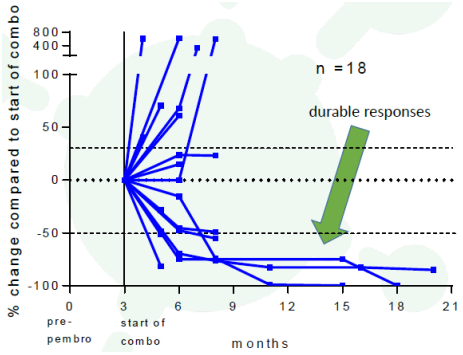
- 2 patients experienced a complete disappearance of all target lesions (Chart 54), including one patient in the PR group, which occurred after 11 and 18 months, respectively (Chart 55), again highlighting that immunotherapy including combination therapy takes time to show an effect. These responses occurred at the lower dose levels of 1mg and 6mf of IMP321;
- Treatment and follow-up of three patients in the third cohort (30mg) are still ongoing.

**CHART 54: Waterfall plot starting at Cycle 5 of pembrolizumab (Cycle 1 of Tacti-mel combination therapy portion)**




Source: Company data

**CHART 55: Spide plot shows that 2 patients achieved complete disappearance of all target leasions after a relatively long period of time of 11 and 18 months**




Source: Company data

## Phase II trial with pembro in solid tumours starts Q4/2018

*In a basket trial, patients are not grouped by tumour site as has historically been the case, but by genetic signature*

In March 2018, Immutep entered into a clinical trial collaboration and supply agreement with Merck & Co. to evaluate combination therapy consisting of pembrolizumab and IMP321 in solid tumours. Specifically, the two partners are planning a basket Phase II trial, TACTI-002 (Two ACTive Immunotherapies) that includes three different indications in lung (first and second line) and head and neck (second line) cancer. The trial, which will enrol up to 120 patients, including in the US (the first time US patients will receive eftilagimod), is expected to start in Q4/2018E and report first data in mid-2019E (Chart 56). Lung cancer represents an important commercial opportunity for Immutep, as (1) it is one of the three most common cancers and the one that causes the highest numbers of deaths worldwide, and (2) Keytruda has firmly established itself as the dominant ICI in advanced lung cancer having completed five randomised, controlled trials that all showed an overall survival benefit.

**CHART 56: Preliminary design of Phase II (TACTI-002) basket trial in solid tumours**

| Parameter | Description |
|---|---|
| No. of patients and locations | 120 patients in the US, Europe and Australia (12-15 sites) |
| Patient populations | 1. 1L NSCLC, PD-1 / PD-L1 naïve<br>2. 2L NSCLC, PD-1 / PD-L1 refractory<br>3. 2L HNSCC, PD-1 / PD-L1 naïve |
| Design | Simon two-stage, non-comparative, open-label, single-arm, multicentre |
| Treatment | IMP321 (30mg SC) + pembrolizumab (200mg IV) for 12 months, followed by up to 12 months pembrolizumab monotherapy |
| Primary endpoint | Overall response rate ("ORR") according to irRECIST |
| Other endpoints | Safety & tolerability, PFS, OS, PK, exploratory biomarker analysis |
| Expected timing | Starts in Q4/2018E, data in mid-2019E |

Abbreviations: 1L, first line; 2L, second line; HNSCC, head and neck squamous cell carcinoma; irRECIST, immune-related Response Evaluation Criteria in Solid Tumours; NSCLC, non-small cell lung cancer
Source: Company data

# Multi-billion US$ sales potential across tumour types

**CHART 57: Indications currently included in our eftilagimod forecasts**

| Indication | First launch | Peak sales (US$m) |
|---|---|---|
| mBC | 2020E | 820 |
| mNSCLC | 2025E | 1,800 |
| mHNSCC | 2025E | 326 |

Abbreviations: mHNSCC, metastatic head and neck squamous cell carcinoma; mBC, metastatic breast cancer; mNSCLC, metastatic non-small cell lung cancer
Source: goetzpartners Research estimates

Immunotherapy is a relatively new, but high-growth and rapidly changing market. The sheer number of new agents in clinical development coupled with the large number of ongoing trials – which has ballooned from a handful in 2010 to around 1,000 in 2018 – means that it is hard to predict how the market will evolve both in the near and long term. As the only LAG-3 approach focused on APC activation, eftilagimod therefore addresses a multi-billion-dollar market. We have focused our forecasts and valuation on the three tumour types that are currently being pursued and / or where clinical data is available (Chart 57). We assume that efti is first approved for the treatment of mBC in 2020 based on data from the ongoing Phase IIb (AIPAC) trial, followed by launches in mNSCLC and mHNSCC in 2025. We do not include melanoma as Immutep does not currently plan to continue development in this tumour. Immutep intends to partner eftilagimod in the coming 12-18 months and we therefore assume that the company enters a back-end loaded US$1bn global licensing deal with a large pharma partner in H2/2019E consisting of a US$50m upfront payment, milestones, plus tiered double-digit royalties on sales.

## Current forecasts are based on sales in mBC, mNSCLC and mHNSCC

Our key assumptions are outlined below. The bottom-up sales model for eftilagimod including a potential global partnering deal with a large pharma partner in H2/2019E is shown in Chart 58.

- **Sales are based on three indications:** mBC, NSCLC and HNSCC. The target patient pools include patients with metastatic disease only, both individuals first diagnosed at the metastatic stage, plus those who progressed to metastatic disease following previous rounds of therapy;

- **First launch in late 2020E following conditional regulatory for mBC based on Phase IIb AIPAC trial:** Immutep's strategy is to submit eftilagimod for conditional regulatory approval based on tumour response rates and PFS data from the ongoing Phase IIb AIPAC trial in mBC. A confirmatory Phase III trial would then be conducted post-marketing by Immutep's potential partner to convert the conditional to a standard approval. We see this as a plausible approach, since many other drugs have received conditional approval for advanced cancers with high unmet need, and there is currently no immunotherapy approved for mBC;

- **Approval in mNSCLC and mHNSCC requires a Phase III trial:** the TACTI-002 Phase II trial testing eftilagimod in up to 120 patients is due to start enrolling patients before YE/2018. We assume data in Q4/2020E or Q1/2021E, start of Phase III in mid-2021E and data in H2/2024E, followed by filing in early 2025E and approval before the end of 2025E;

- **Peak penetration of 10% - 15% within each defined patient sub-group:** we conservatively assume that eftilagimod will be used in a minority of patients and believe that uptake will ultimately be driven by the strength of the data. A strong improvement in overall survival in the potential confirmatory trial in mBC could drive significantly higher uptake;

- **Pricing at a c.50% discount to Keytruda:** a course of therapy with Keytruda costs around US$150,000 per patient. To encourage uptake and make combination therapy affordable to patients and payors, we assume that eftilagimod is priced at a c.50% discount to Keytruda in the US, equating to US$75,000 per patient per year, and set the ex-US price at approx. 60% (US$45,000) of the US price;

- **Market exclusivity until 2028E (chemo combo) and 2036E (pembrolizumab combo):** eftilagimod was first patented by Frédéric Triebel in the late 1990's and the composition of matter patent has

therefore already expired. The compound is currently protected mainly by use patents for combination regimens. Excluding any patent term extensions, we understand that efti is protected until at least October 2028 for combination with chemotherapy and until at least January 2036 for combination with PD-1 / PD-L1 inhibitors (any, not just pembrolizumab);

- **Future supply secured through agreement with leading CDMO:** Immutep has partnered with China's WuXi Biologics as the exclusive global manufacturer for eftilagimod and retains the option to extend the agreement to other developmental products in its pipeline.

### Global partnering deal expected in H2/2019E

The process of finding a licensing partner for eftilagimod (excluding China, which has already been partnered with EOC as outlined below) is already underway and we believe that the window of opportunity has opened following the encouraging data for metastatic melanoma presented in May. Additional data from the TACTI-mel trial expected in Q4/2018E should further increase the chance of a deal, as would positive Phase IIb data in mBC in 2019E. Ultimately, the timing and size of a transaction will depend on the number of interested parties and the resulting competitive tension. We conservatively assume that a deal is signed in H2/2019E following the release of the mBC Phase IIb data, as we think that this is the key data point any potential partner will focus on given the potential of filing based on this data set.

### Our forecasts reflect a US$1bn back-end loaded global licensing deal

We assume a back-end loaded licensing deal worth US$1bn in total upfront (US$50m) and milestone payments plus tiered double-digit royalties on sales in the range 15% - 25%, leading to a blended rate of 15% - 21% (see Chart 58 for details). Our model currently includes only US$600m in regulatory and sales-based milestones related to mBC, mNSCLC and mHNSCC, as we assume that US$400m is related to other indications yet to be identified / announced.

### Chinese rights licensed to Eddingpharm spin-off EOC in 2013. Trial starts in 2018E

The Chinese rights of eftilagimod were licensed to Chinese pharma company Eddingpharm (which also has licensing deals with e.g. Eli Lilly, Cardiome and Amarin) in May 2013 and transferred to spin-out company EOC in January 2015. Under the terms of the deal, EOC will pay for the manufacturing of drug supply, with Immutep additionally entitled to milestone payments and royalties on sales in China. The deal has already yielded a US$1m milestone payment to Immutep following the granting of the IND application in China in February. EOC plans to start a clinical trial this year. We do not explicitly forecast Chinese sales; rather, they are included in our RoW forecasts.

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**CHART 58: Eftilagimod alpha (IMP321, LAG3-Ig) global sales model**

| Dec YE | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E | 2027E | 2028E | 2029E | 2030E | 2031E | 2032E |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **eftilagimod alpha (IMP321, LAG-3Ig)** | | | | | | | | | | | | | | | |
| **Metastatic breast cancer (mBC) \| Combo with paclitaxel** | | | | | | | | | | | | | | | |
| US breast cancer incidence | 266,120 | 268,012 | 269,918 | 271,838 | 273,771 | 275,718 | 277,678 | 279,653 | 281,642 | 283,644 | 285,661 | 287,693 | 289,739 | 291,799 | 293,874 |
| **Distant (metastatic)** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** | **6%** |
| De novo incidence of mBC | 15,967 | 16,081 | 16,195 | 16,310 | 16,426 | 16,543 | 16,661 | 16,779 | 16,898 | 17,019 | 17,140 | 17,262 | 17,384 | 17,508 | 17,632 |
| Recurrent disease | 39,459 | 40,396 | 41,353 | 42,329 | 43,326 | 44,342 | 45,379 | 46,438 | 47,517 | 48,619 | 49,743 | 50,890 | 52,060 | 53,253 | 54,471 |
| **Total incidence of mBC in the US** | **55,426** | **56,477** | **57,548** | **58,640** | **59,752** | **60,885** | **62,040** | **63,217** | **64,416** | **65,638** | **66,883** | **68,151** | **69,444** | **70,761** | **72,103** |
| % Hormone-receptor positive mBC | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% |
| **Patients with HR-positive mBC** | **44,341** | **45,182** | **46,039** | **46,912** | **47,802** | **48,708** | **49,632** | **50,573** | **51,533** | **52,510** | **53,506** | **54,521** | **55,555** | **56,609** | **57,683** |
| HER2-negative mBC | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% | 80% |
| **Patients with HR +ve / HER-2 -ve mBC** | **35,472** | **36,145** | **36,831** | **37,529** | **38,241** | **38,967** | **39,706** | **40,459** | **41,226** | **42,008** | **42,805** | **43,617** | **44,444** | **45,287** | **46,146** |
| eftilagimod penetration | | | | 0.3% | 0.9% | 1.8% | 3.4% | 5.3% | 8.3% | 11.3% | 15.0% | 13.8% | 6.0% | 3.0% | 2.0% |
| eftilagimod price per Tx course | | | | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** |
| **eftilagimod US sales in mBC** | | | | **8** | **26** | **53** | **101** | **159** | **255** | **354** | **482** | **450** | **200** | **102** | **69** |
| growth | | | | | 205.7% | 103.8% | 91.1% | 58.5% | 60.1% | 39.0% | 35.9% | (6.6%) | (55.5%) | (49.1%) | (32.1%) |
| **Total incidence of mBC in Europe** | **87,066** | **88,350** | **89,653** | **90,975** | **92,316** | **93,678** | **95,059** | **96,461** | **97,883** | **99,327** | **100,791** | **102,278** | **103,786** | **105,316** | **106,869** |
| **Patients with HR +ve / HER-2 -ve mBC** | **55,722** | **56,544** | **57,378** | **58,224** | **59,082** | **59,954** | **60,838** | **61,735** | **62,645** | **63,569** | **64,507** | **65,458** | **66,423** | **67,403** | **68,396** |
| eftilagimod penetration | | | 0.1% | 0.4% | 0.8% | 1.7% | 3.0% | 5.0% | 7.0% | 9.0% | 10.0% | 8.8% | 7.0% | 5.0% | 3.0% |
| eftilagimod price per Tx course | | | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** |
| **eftilagimod EU sales in mBC** | | | **3** | **10** | **21** | **46** | **82** | **139** | **197** | **257** | **290** | **260** | **209** | **152** | **92** |
| growth | | | | 305.9% | 102.9% | 115.6% | 79.1% | 69.1% | 42.1% | 30.5% | 12.7% | (10.4%) | (19.6%) | (27.5%) | (39.1%) |
| RoW sales as % of US sales | | | 0.0% | 0.0% | 0.0% | 5.0% | 7.5% | 10.0% | 10.0% | 10.0% | 10.0% | | | | |
| **eftilagimod RoW sales in mBC** | | | **-** | **-** | **-** | **3** | **8** | **16** | **26** | **35** | **48** | **60** | **71** | **80** | **88** |
| growth | | | | | | | 186.6% | 111.3% | 60.1% | 39.0% | 35.9% | 25.0% | 18.0% | 12.0% | 10.0% |
| **eftilagimod global sales in mBC** | | | **3** | **19** | **47** | **101** | **190** | **314** | **478** | **647** | **820** | **770** | **480** | **333** | **249** |
| **Metastatic non-small cell lung cancer (NSCLC) \| Combo with Keytruda (pembrolizumab)** | | | | | | | | | | | | | | | |
| US lung cancer incidence | 234,030 | 235,694 | 237,370 | 239,058 | 240,758 | 242,470 | 244,195 | 245,931 | 247,680 | 249,441 | 251,215 | 253,001 | 254,801 | 256,613 | 258,437 |
| **Distant (metastatic)** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** | **57%** |
| De novo incidence of metastatic NSCLC | 133,397 | 134,346 | 135,301 | 136,263 | 137,232 | 138,208 | 139,191 | 140,181 | 141,178 | 142,181 | 143,193 | 144,211 | 145,236 | 146,269 | 147,309 |
| Recurrent disease | 14,179 | 14,516 | 14,859 | 15,210 | 15,568 | 15,934 | 16,306 | 16,686 | 17,074 | 17,470 | 17,874 | 18,286 | 18,707 | 19,135 | 19,573 |
| % progressing to metastatic | 16% | 16% | 16% | 17% | 17% | 17% | 18% | 18% | 18% | 18% | 19% | 19% | 19% | 20% | 20% |
| **Total incidence met. lung cancer in the US** | **147,576** | **148,861** | **150,161** | **151,473** | **152,800** | **154,142** | **155,497** | **156,867** | **158,252** | **159,652** | **161,067** | **162,497** | **163,943** | **165,405** | **166,882** |
| % non-small cell lung cancer (NSCLC) | 85% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% |
| **Patients with mNSCLC in the US** | **125,439** | **126,532** | **127,636** | **128,752** | **129,880** | **131,020** | **132,173** | **133,337** | **134,514** | **135,704** | **136,907** | **138,123** | **139,352** | **140,594** | **141,850** |
| eftilagimod penetration | | | | | | | | 0.2% | 0.6% | 1.2% | 2.3% | 3.5% | 5.5% | 7.5% | 10.0% |
| eftilagimod price per Tx course | | | | | | | | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** |
| **eftilagimod US sales in mNSCLC** | | | | | | | | **20** | **61** | **122** | **231** | **363** | **575** | **791** | **1,064** |
| growth | | | | | | | | | 202.6% | 101.8% | 89.2% | 56.9% | 58.5% | 37.6% | 34.5% |
| **Patients with mNSCLC in Europe** | **197,048** | **197,941** | **198,841** | **199,749** | **200,664** | **201,587** | **202,517** | **203,455** | **204,401** | **205,355** | **206,317** | **207,287** | **208,265** | **209,252** | **210,246** |
| eftilagimod penetration | | | | | | | | 0.1% | 0.3% | 0.5% | 1.1% | 2.0% | 3.3% | 4.6% | 5.9% |
| eftilagimod price per Tx course | | | | | | | | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** |
| **eftilagimod EU sales in mNSCLC** | | | | | | | | **6** | **24** | **48** | **103** | **182** | **305** | **428** | **553** |
| growth | | | | | | | | | 301.9% | 100.9% | 113.5% | 77.3% | 67.5% | 40.7% | 29.2% |
| RoW sales as % of US sales | | | | | | | | 0.0% | 0.0% | 5.0% | 7.5% | 10.0% | 10.0% | 10.0% | 10.0% |
| **eftilagimod RoW sales in mNSCLC** | | | | | | | | **-** | **-** | **6** | **17** | **36** | **57** | **79** | **106** |
| growth | | | | | | | | | | | 183.7% | 109.2% | 58.5% | 37.6% | 34.5% |
| **eftilagimod global sales in mNSCLC** | | | | | | | | **26** | **84** | **176** | **351** | **581** | **937** | **1,298** | **1,724** |
| **Metastatic head and neck squamous cell carcinoma (HNSCC) \| Combo with Keytruda (pembrolizumab)** | | | | | | | | | | | | | | | |
| US incidence of laryngeal cancer | 13,150 | | | | | | | | | | | | | | |
| US incidence of oral cavity & pharynx cancer | 51,540 | | | | | | | | | | | | | | |
| US H&N cancer incidence | 64,690 | 65,150 | 65,613 | 66,080 | 66,550 | 67,023 | 67,500 | 67,980 | 68,463 | 68,950 | 69,440 | 69,934 | 70,431 | 70,932 | 71,437 |
| **Distant (metastatic)** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** | **20%** |
| De novo incidence of metastatic H&N | 12,938 | 13,030 | 13,123 | 13,216 | 13,310 | 13,405 | 13,500 | 13,596 | 13,693 | 13,790 | 13,888 | 13,987 | 14,086 | 14,186 | 14,287 |
| Recurrent disease | 8,251 | 8,310 | 8,369 | 8,428 | 8,488 | 8,549 | 8,609 | 8,671 | 8,732 | 8,794 | 8,857 | 8,920 | 8,983 | 9,047 | 9,112 |
| % progressing to metastatic | 16% | 16% | 16% | 16% | 16% | 16% | 16% | 16% | 16% | 16% | 16% | 16% | 16% | 16% | 16% |
| **Total incidence of H&N cancer in the US** | **21,189** | **21,340** | **21,491** | **21,644** | **21,798** | **21,953** | **22,109** | **22,267** | **22,425** | **22,584** | **22,745** | **22,907** | **23,070** | **23,234** | **23,399** |
| % HNSCC | 90% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% |
| **Patients with mHNSCC in the US** | **19,070** | **19,206** | **19,342** | **19,480** | **19,618** | **19,758** | **19,898** | **20,040** | **20,182** | **20,326** | **20,470** | **20,616** | **20,763** | **20,910** | **21,059** |
| eftilagimod penetration | | | | | | | | | 0.2% | 0.7% | 1.4% | 2.7% | 4.2% | 6.6% | 9.0% |
| eftilagimod price per Tx course | | | | | | | | | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** | **75,000** |
| **eftilagimod US sales in mHNSCC** | | | | | | | | | **4** | **11** | **22** | **42** | **65** | **104** | **142** |
| growth | | | | | | | | | | 202.1% | 101.4% | 88.8% | 56.7% | 58.3% | 37.3% |
| **Patients with mHNSCC in Europe** | **29,956** | **30,045** | **30,133** | **30,221** | **30,310** | **30,399** | **30,489** | **30,578** | **30,668** | **30,758** | **30,849** | **30,939** | **31,030** | **31,122** | **31,213** |
| eftilagimod penetration | | | | | | | | | 0.1% | 0.3% | 0.6% | 1.4% | 2.4% | 4.0% | 5.6% |
| eftilagimod price per Tx course | | | | | | | | | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** | **45,000** |
| **eftilagimod EU sales in mHNSCC** | | | | | | | | | **1** | **4** | **9** | **19** | **34** | **56** | **79** |
| growth | | | | | | | | | | 301.2% | 100.6% | 113.1% | 77.0% | 67.2% | 40.4% |
| RoW sales as % of US sales | | | | | | | | | 0.0% | 5.0% | 7.5% | 10.0% | 10.0% | 10.0% | 10.0% |
| **eftilagimod RoW sales in mHNSCC** | | | | | | | | | **-** | **1** | **2** | **4** | **7** | **10** | **14** |
| growth | | | | | | | | | | | 202.1% | 151.8% | 56.7% | 58.3% | 37.3% |
| **eftilagimod global sales in mHNSCC** | | | | | | | | **-** | **5** | **16** | **33** | **65** | **105** | **170** | **235** |
| **Global eftilagimod sales** | | | **3** | **19** | **47** | **101** | **190** | **340** | **567** | **840** | **1,204** | **1,416** | **1,523** | **1,801** | **2,208** |
| **Global licensing deal** | | | | | | | | | | | | | | | |
| Royalty rate | | | 15.0% | 15.2% | 15.4% | 15.6% | 15.8% | 16.0% | 16.2% | 16.7% | 17.3% | 17.9% | 18.5% | 19.1% | 19.7% |
| Royalties to Immutep | | | 0.4 | 3 | 7 | 16 | 30 | 54 | 92 | 140 | 208 | 253 | 282 | 344 | 435 |
| **Royalties to Immutep (into P&L)** | | | **0.5** | **3.8** | **9.5** | **20.6** | **39.2** | **71.0** | **119.9** | **182.9** | **271.7** | **330.7** | **367.5** | **448.9** | **567.5** |
| Upfront payment (amortised over 10 years) | | 50.0 | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Regulatory milestones | | | 25.0 | | | | | 75.0 | 25.0 | | | | | | |
| Sales-based milestones | | | | | | | | 25.0 | 50.0 | | 100.0 | | | | 250.0 |
| **Total milestones (into P&L)** | | **-** | **32.6** | **-** | **-** | **-** | **-** | **130.5** | **97.9** | **-** | **130.5** | **-** | **-** | **-** | **326.2** |

Source: goetzpartners Research estimates, SEER database, NCCN guidelines

# Complementary LAG-3 targeting pipeline assets

In addition to eftilagimod, Immutep has been building a pipeline of products focused on different LAG-3 targeted approaches as outlined in Chart 6. The most advanced of these programmes is IMP701 (partnered with Novartis), a LAG-3 blocking mAb in Phase II development across multiple tumour types, followed by IMP731 (partnered with GSK), a LAG-3 depleting mAb which is being explored in Phase I in autoimmune indications. Both were partnered prior to entry into the clinic and the economics are relatively modest. Immutep further has an early-stage LAG-3 agonist in preclinical development for autoimmune diseases. While promising based on their respective mechanisms of action and preclinical data, we do not currently include any of these assets in our valuation due to the paucity of available clinical data, although we do include small milestone payments in our revenue forecasts.

## IMP701 (LAG525): anti-LAG-3 antibody for cancer (Novartis)

In September 2012, Immutep and CoStim Pharmaceuticals (a privately held immuno-oncology start-up acquired by Novartis in February 2014) entered into a commercial licensing and collaboration agreement under which CoStim obtained a licence to develop and commercialise antagonistic LAG-3 antibodies. Novartis is responsible for all development activities, with Immutep eligible for development-based milestone payments and royalties on potential sales. The first clinical milestone payment (which we estimate at c.A$150k) was received in August 2015 following the start of the first Phase I trial.

### Clinical programme focused on combo with NOVN's developmental PD-1 inhibitor

Novartis is developing IMP701 (LAG525) in combination with its own developmental PD-1 inhibitor spartalizumab (PDR001) (Chart 59), which is currently being tested in an ambitious programme spanning over 30 ongoing clinical studies, including one Phase III trial (advanced melanoma). The rationale for combining a LAG-3 inhibitor with an anti-PD-1 is that many coinhibitory receptors are co-expressed with PD-1 on dysfunctional T cells in tumours, and tumour infiltrating lymphocytes expressing multiple coinhibitory receptors are more dysfunctional than TILs expressing only PD-1. In addition, it has been shown that mice lacking both LAG-3 and PD-1 develop lethal, systemic autoimmunity (Okazaki *et al.* 2011), highlighting the synergy between these two pathways in controlling T cell tolerance.

**CHART 59: IMP701 (LAG525) is currently undergoing four clinical trials in combination with Novartis's experimental anti-PD-1**

| Indication | Phase | N | Therapy[1] | Design | Objectives | NCT / Start date / Primary completion date[2] |
|---|---|---|---|---|---|---|
| Solid & haematologic malignancies[3], relapsed and/or refractory to SoC | II | 160 | spartalizumab (PDR001)[4] + LAG525 | Open-label, parallel-cohort, US only | ▪ 1ary: CBR at 24 weeks, PFS<br>▪ 2ary: ORR, TTR, safety & tolerability, DOR, TTP | NCT03365791<br>Jan-2018<br>Jan-2020 |
| Triple-negative breast cancer ("TNBC"), 1L or 2L | II | 126 | spartalizumab + LAG525 + carboplatin | Open label, randomised, parallel assignment, 3-arm | ▪ 1ary: ORR<br>▪ 2ary: DOR, OS, PK, TTR, CBR, ADAs | NCT03499899<br>Jun-2018<br>Dec-2019 |
| Advanced solid tumours (TNBC, mesothelioma, NSCLC, melanoma, RCC) | I/II | 515 | spartalizumab + LAG525 | Open-label, parallel assignment, dose-escalation followed by dose-expansion | ▪ 1ary: DLTs, ORR<br>▪ 2ary incl. ADAs, IFN-gamma expression, AEs, PFS, DOR, DCR | NCT02460224<br>Jun-2015<br>Aug-2019 |
| Previously treated unresectable or metastatic melanoma | II | 160 | spartalizumab + LAG525 / capmatinib / canakinumab | Randomised, open-label, open platform | ▪ 1ary: ORR<br>▪ 2ary: DOR, OS, PFS, DCR, ADAs, biomarkers | NCT03484923<br>Aug-2018<br>Dec-2020 |

(1) LAG525 is administered as an IV infusion over 30min once every 3 weeks. LAG525 will be given first, followed by PDR-001
(2) Data as of 9th July 2018
(3) Includes small cell lung cancer, gastric adenocarcinoma, esophageal adenocarcinoma, castration-resistant prostate adenocarcinoma, soft tissue sarcoma, ovarian adenocarcinoma, advanced well-differentiated neuroendocrine tumors, diffuse large B cell lymphoma
(4) PDR001 is a high-affinity, ligand-blocking, humanised anti-PD-1 IgG4 mAb
Abbreviations: ADAs, anti-drug antibodies; CBR, clinical benefit rate; DLT, dose-limiting toxicities; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; SoC, standard of care; TTP, time to progression; TTR, time to response
Source: Company data, clinicaltrials.gov

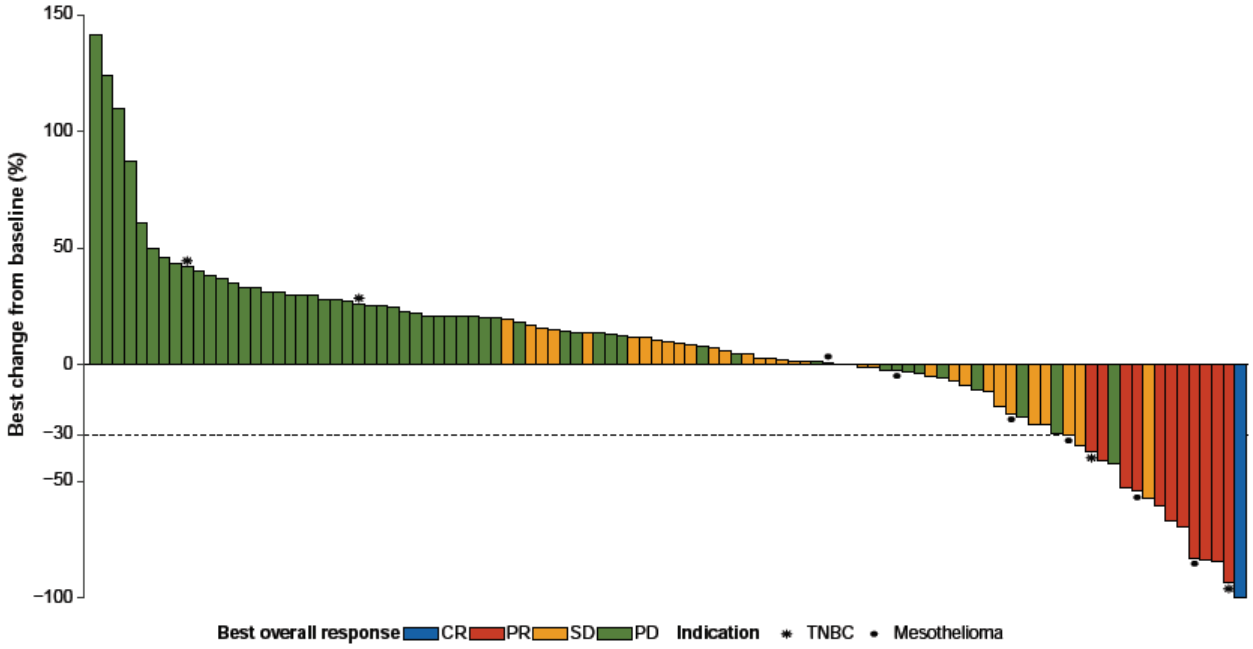
### Preliminary results in solid tumours show first signs of efficacy

Novartis presented first clinical data for LAG525 from the Phase I/II trial in solid tumours at the ASCO 2018 clinical meeting. Patients were divided into a large number of dosing groups that received either LAG525 monotherapy (every 2 or 4 weeks) or combination therapy with spartalizumab. Preliminary results show first signs of efficacy for LAG525 + spartalizumab combination therapy, but not LAG525 monotherapy, with one patient (with thymoma) achieving a complete and 11 patients a partial response (Chart 60). LAG525 was safe and well tolerated both as monotherapy and in combination with spartalizumab, although combination therapy led to a higher incidence of AEs.

Key findings are summarised below:

- **Safe and well tolerated:** dose-limiting toxicity occurred in 4 patients in each study arm without clear dose relationship, and a maximum tolerated dose was not reached for single-agent LAG525 or LAG525 + spartalizumab;
- **Preliminary anti-tumour activity:** as of January 2018, 12/121 (10%) complete (1) or partial (11) responses were observed (based on RECIST v1.1), all of whom received LAG525 + spartalizumab combination therapy across a broad range of dose levels/schedules (Chart 60). No responses were observed in patients treated with LAG525 monotherapy;
- **Durable responses:** most responses are ongoing after one year, including in patients in metastatic TNBC and mesothelioma;
- **Immune activation of cold tumours in breast cancer:** biomarker data from 2/5 responding patients with TNBC showed on-treatment immune activation of baseline immune-cold tumours.

**CHART 60: Best percentage change from baseline in sum of diameters of target lesions for patients treated with LAG525 + spartalizumab**




Source: Hong *et al.*, ASCO 2018 clinical meeting

## IMP731: LAG-3 depleting mAb for autoimmune disease (GSK)

IMP731 (GSK2831781) is a humanised monoclonal afucosylated antibody with enhanced antibody-dependent cell cytotoxicity ("ADCC") that depletes activated T cells by specifically binding to LAG-3 on their cell surface. It was partnered with GSK in January 2011 under a standard licensing deal where GSK assumed all development and commercialisation costs. Immutep received an upfront payment and is eligible for up to £64m in total milestones plus single-digit, tiered royalties on sales. The first-in-human Phase I trial focused on safety and tolerability was launched in Europe (Germany and the UK) in July 2014 (Chart 61). As of July 2018, the trial had been completed (March 2018). GSK might disclose data in the coming months and we would expect a Phase II trial to start in H2/2018.

**CHART 61: IMP731 (GSK2831781) recently completed a Phase I trial**

| Indication | Phase | N | Therapy | Design | Objectives | NCT / Data |
|---|---|---|---|---|---|---|
| **Plaque psoriasis** | I (FIH) | 67 | GSK2831781 (IV) | Randomised, placebo-controlled, double-blind, single-ascending dose in 2 parts:<br>▪ **Part A (n=40, delayed type hypersensitivity [DTH] cohorts):** safety, tolerability, PK, PD and immunogenicity administered to healthy subjects prev. vaccinated w/ BCG<br>▪ **Part B (n=27):** patients with plaque psoriasis | ▪ 1ary: safety & tolerability<br>▪ 2ary: PK, PD, clinical response, biomarkers | NCT02195349<br>Started Jul-2014, primary completion date Mar-2018 |

Abbreviations: BCG, Bacillus Calmette Guérin; FIH, first-in-human; PD, pharmacodynamics; PK, pharmacokinetics
Source: Company data, clinicaltrials.gov

# Board of Directors and Executive Management

Immutep's international management team is led by CEO Marc Voigt, a biotech industry veteran who started his professional career in finance, and includes CSO / CMO Frédéric Triebel, the scientist who discovered LAG-3 in 1990 and then went on to found French biotech company Immutep in 2001.

### Marc Voigt | Executive Director & CEO

Marc Voigt was appointed CEO and Executive Director in July 2014 following his tenure as CFO and CBO since 2012. He has more than 14 years of experience in the corporate and biotechnology sectors. Mr Voigt started his career at Allianz Insurance and subsequently worked for the German investment bank net.IPO.AG in business development and German securities offerings. He then moved into the biotechnology sector where he has held different executive positions in companies including Heidelberger Beteiligungsholding AG, Caprotec Bioanalytics GmbH, Revotar Biopharmaceuticals AG. Mr Voigt holds a Master's in Business Administration from the Freie Universität of Berlin.

### Frédéric Triebel | Chief Medical Officer & Chief Scientific Officer

Prof. Frédéric Triebel founded Immutep in 2001 and served as its Scientific and Medical Director from 2004. He discovered the LAG-3 gene in 1990 while working at the Institut Gustave Roussy, a large cancer centre in Paris. After the acquisition of Immutep by Prima BioMed in December 2014, he was appointed Chief Medical Officer and Chief Scientific Officer. Before starting Immutep, he was Professor in Immunology at Paris University, and from 1991 to 1996 Director of an INSERM Unit. Prof. Triebel holds a PhD in immunology from Paris University. He has authored 144 publications and was the inventor of 16 patents.

### Deanne Miller | Chief Operating Officer, General Counsel & Company Secretary

Deanne Miller joined Immutep as General Counsel and Company Secretary in October 2012 and was promoted to Chief Operating Officer in November 2016. She has broad commercial experience having held legal, investment banking, regulatory compliance and tax advisory roles at RBC Investor Services, Westpac Group, Macquarie, Australian Securities and Investment Commission, and KPMG. Ms Miller has a Combined Bachelor of Laws (Honours) and Bachelor of Commerce, Accounting and Finance (double major) from the University of Sydney. She is admitted as a solicitor in New South Wales ("NSW") and is member of the Law Society of NSW.

### Jay Campbell | Vice President, Business Development and Investor Relations

Jay Campbell joined Immutep in February 2017. He has over 13 years of experience in the financial services industry and as an independent business development consultant, the majority of which focusing on the life sciences industry. Prior to joining Immutep, Mr Campbell was Senior Director of Business Development and Investor Relations at Kolltan Pharmaceuticals and a business development consultant to ISTA Pharmaceuticals. Before that, he worked for the Royal Bank of Scotland, Rothschild and Schroders, among others. Mr. Campbell is currently a member of the board of directors of Update Pharma. He has a BSBA in Management from Bucknell University and minored in Spanish.

### Russell Howard | Non-Executive Chairman

Dr Russell Howard is a scientist, executive manager, and entrepreneur. He recently won the 2014 Advance Global Australian Award for his global impact on the biotechnology field and green chemistry. Dr Howard has held major positions in leading research laboratories around the world, including the Immunoparasitology Laboratory at the Walter & Eliza Hall Institute and the National Institutes of Health. He was the President and Scientific Director of Affymax and the co-founder and CEO of Maxygen. Dr Howard is currently Executive Chairman of NeuClone and was a Director of Circadian Technologies from 2013 to 2015. He is the inventor of five patents and authored over 150 scientific publications. Dr Howard has a PhD in biochemistry from the University of Melbourne.

### Grant Chamberlain | Non-Executive Chairman

Grant Chamberlain is a corporate adviser and entrepreneur with over 20 years of experience in investment banking and has advised on numerous large M&A transactions in Australia. He worked as head of M&A and Financial Sponsors Australia at Bank of America Merrill Lynch, and prior to that held senior positions at Nomura Australia and Deutsche Bank. He is currently a principal of One Ventures, Australia's leading venture capital firms. Mr Chamberlain has a Bachelor of Laws with Honours and a Bachelor of Commerce from the University of Melbourne.

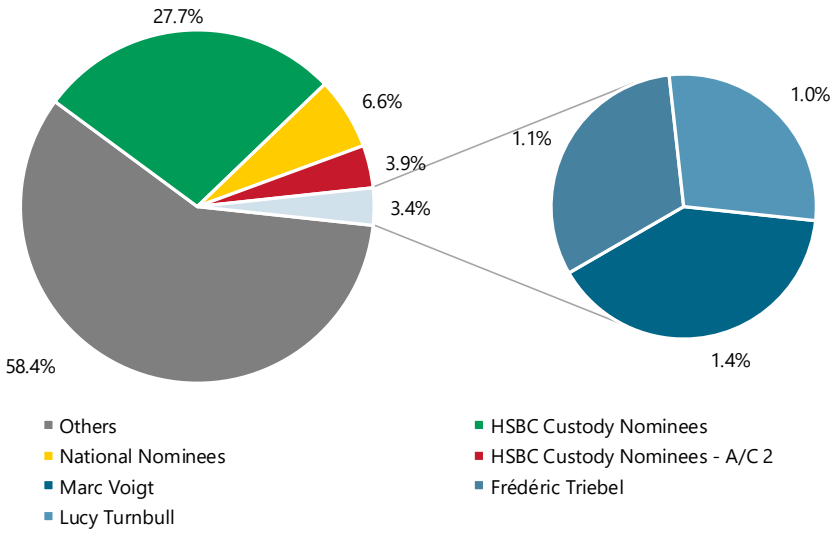
### Pete Meyers | Non-Executive Chairman and Deputy Chairman

Pere Meyers is the Chief Financial Officer of Eagle Pharmaceuticals. Prior to that he served as the Chief Financial Officer of Motif BioSciences. Mr Meyers has over 18 years of experience in healthcare investment banking having worked for institutions including Dillon, Read & Co., Credit Suisse First Boston, and as Co-Head of Global Healthcare Investment Banking at Deutsche Bank. He earned a Bachelor of Science degree in Finance from Boston College and an MBA from Columbia Business School.

# Largest shareholders

Chart 62 shows Immutep's largest shareholders as of 30 June 2018. CEO Marc Voigt and CMO / CSO Frédéric Triebel together own 2.4%. The combined shareholding of members of the executive management team is 3.4%. Lucy Turnbull, Immutep's former Chairman (she stepped down in November 2017) owns 1% of the company. Other substantial shareholders include Australian Ethical (under National Nominees) and Platinum (under HSCB Nominees), who held 7.4% and 3.5%, respectively, as of 31 March 2018, and Ridgeback (under HSCB Nominees A/C 2).

**CHART 62: Immutep shareholder base**




Source: Company data

# Financial assumptions and models

Our financial models for Immutep are shown in Charts 63 – 65. Kay assumptions are summarised below.

## Profit and loss model

- **Revenues mainly related to eftilagimod:** the key driver is revenue related to eftilagimod alpha, based on Immutep signing a licensing deal in H2/2019E and its partner launching the drug for metastatic breast cancer in 2020E, metastatic non-small cell lung cancer in 2025E and metastatic head & neck cancer in 2026E.
  - **License income:** we assume that all revenues from licensing and other partners are booked in license income. The estimated US$50m upfront payment for the eftilagimod licensing deal is amortised over ten years.
  - **Other income:** this line includes grant income. Immutep receives cash rebates from the Australian and other governments for R&D activities. We assume 30% of prior year R&D expenses, booked in grant income.

- **Modest R&D expenses:** we expect R&D expenses to remain roughly stable over the next three years. The remaining spend for the AIPAC trial is approx. €5m, which we split into 2018 and 2019. The remaining spend in 2018 is mainly related to the TACTI-mel trial, which should complete later this year. In 2019, declining costs from TACTI-mel will be offset by rising costs from TACTI-002.

- **Corporate admin expenses:** the >40% estimated increase in 2018 is mainly related to the fundraises completed in H1/2018, and we therefore assume modest increases in the next 2-3 years.

## Balance sheet and cash flow statement

- **Robust cash balance to last until Q4/2019E:** Immutep ended calendar year 2017 with A$13.7m in total cash and, including the two fundraises completed in H1/2018E, the company should have sufficient cash to fund operations until Q4/2019E excluding any new partnering deals. Based on our forecasts, which assume a licensing deal for eftilagimod in H2/2019E including a US$50m upfront payment, Immutep does not require further fundraises until reaching profitability in 2020E.

- **Convertible bond does not pose a liquidity risk:** Immutep issued a convertible bond in May 2015 that included a cash consideration worth A$13.75m. We assume that the bond is repaid in full when it matures in August 2025, by which time we expect Immutep to be profitable with a comfortable cash balance well in excess of the value of the convertible bond.

CHART 63: Immutep P&L model

| Profit & Loss Statement | 2016A | 2017A | H1 2018 | H2 2018 | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jun YE (A$k except EPS) | 30-Jun-16 | 30-Jun-17 | 31-Dec-17 | 30-Jun-18 | 30-Jun-18 | 30-Jun-19 | 30-Jun-20 | 30-Jun-21 | 30-Jun-22 | 30-Jun-23 | 30-Jun-24 | 30-Jun-25 |
| **Revenue** | **2,029** | **4,222** | **5,645** | **1,670** | **7,315** | **6,545** | **45,557** | **17,243** | **24,075** | **35,573** | **54,600** | **217,917** |
| growth | (3%) | 108% | 241% | (35%) | 73% | (11%) | 596% | (62%) | 40% | 48% | 53% | 299% |
| License income | 175 | - | 2,580 | - | 2,580 | 3,631 | 42,649 | 14,277 | 20,985 | 32,353 | 51,242 | 213,792 |
| % sales | 9% | 0% | 46% | 0% | 35% | 55% | 94% | 83% | 87% | 91% | 94% | 98% |
| growth | 4% | (100%) | | | | 2% | 2% | 2% | 2% | 2% | 2% | 2% |
| Other income | 1,854 | 4,222 | 3,065 | 1,670 | 4,735 | 2,914 | 2,907 | 2,965 | 3,090 | 3,221 | 3,357 | 4,125 |
| % sales | 91% | 100% | 54% | 100% | 65% | 45% | 6% | 17% | 13% | 9% | 6% | 2% |
| growth | (4%) | 128% | 85% | (35%) | 12% | (38%) | (0%) | 2% | 4% | 4% | 4% | 23% |
| R&D and intellectual property | (7,060) | (7,526) | (4,648) | (3,102) | (7,750) | (7,689) | (7,843) | (8,218) | (8,611) | (9,024) | (11,539) | (22,423) |
| % sales | 348% | 178% | 82% | 186% | 106% | 117% | 17% | 48% | 36% | 25% | 21% | 10% |
| growth | (21%) | 7% | 72% | (36%) | 3% | (1%) | 2% | 5% | 5% | 5% | 28% | 94% |
| Corporate administrative expenses | (6,983) | (4,347) | (3,996) | (2,254) | (6,250) | (6,375) | (6,503) | (6,633) | (6,765) | (6,965) | (9,017) | (11,183) |
| % sales | 344% | 103% | 71% | 135% | 85% | 97% | 14% | 38% | 28% | 20% | 17% | 5% |
| growth | 22% | (38%) | 89% | 1% | 44% | 2% | 2% | 2% | 2% | 3% | 29% | 24% |
| D&A expenses | (1,993) | (1,702) | (895) | (630) | (1,525) | (1,402) | (1,290) | (1,190) | (1,102) | (1,019) | (945) | (881) |
| % sales | 98% | 40% | 16% | 38% | 21% | 21% | 3% | 7% | 5% | 3% | 2% | 0% |
| growth | 49% | (15%) | 3% | (25%) | (10%) | (8%) | (8%) | (8%) | (7%) | (8%) | (7%) | (7%) |
| Other external expenses | (49,182) | (752) | (432) | - | (432) | - | - | - | - | - | - | - |
| % sales | 2424% | 18% | 8% | 0% | 6% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| growth | 168% | (98%) | (25%) | (100%) | (43%) | (100%) | | | | | | |
| **Total costs & operating expenses** | **(65,217)** | **(14,326)** | **(9,970)** | **(5,987)** | **(15,957)** | **(15,466)** | **(15,635)** | **(16,041)** | **(16,478)** | **(17,008)** | **(21,501)** | **(34,487)** |
| **EBIT** | **(63,188)** | **(10,105)** | **(4,325)** | **(4,317)** | **(8,642)** | **(8,921)** | **29,922** | **1,202** | **7,597** | **18,565** | **33,098** | **183,430** |
| Interest expenses | (8) | - | - | - | - | - | - | - | - | - | - | - |
| **Profit/Loss before tax** | **(63,196)** | **(10,105)** | **(4,325)** | **(4,317)** | **(8,642)** | **(8,921)** | **29,922** | **1,202** | **7,597** | **18,565** | **33,098** | **183,430** |
| growth | 96% | (84%) | (6%) | (21%) | (14%) | 3% | (435%) | (96%) | 532% | 144% | 78% | 454% |
| % sales | (3115%) | (239%) | (77%) | (259%) | (118%) | (136%) | 66% | 7% | 32% | 52% | 61% | 84% |
| Income tax | 1,181 | 737 | (0) | - | (0) | 0 | (0) | (0) | - | (1,857) | (6,620) | (55,029) |
| Tax rate | (2%) | (7%) | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 10% | 20% | 30% |
| **Net income/loss** | **(62,015)** | **(9,367)** | **(4,325)** | **(4,317)** | **(8,642)** | **(8,921)** | **29,922** | **1,202** | **7,597** | **16,709** | **26,478** | **128,401** |
| **EPS calculation** | | | | | | | | | | | | |
| **Earnings per Share (Basic)** | **(0.031)** | **(0.005)** | **(0.002)** | **(0.002)** | **(0.003)** | **(0.003)** | **0.010** | **0.000** | **0.003** | **0.006** | **0.009** | **0.042** |
| growth | 52% | (85%) | (5%) | (42%) | (27%) | (11%) | (435%) | (96%) | 532% | 120% | 58% | 385% |
| **Underlying EPS (Basic)** | **(0.007)** | **(0.006)** | **(0.003)** | **(0.002)** | **(0.005)** | **(0.004)** | **0.009** | **(0.001)** | **0.002** | **0.004** | **0.008** | **0.041** |
| **Earnings per Share (Diluted)** | **(0.031)** | **(0.005)** | **(0.002)** | **(0.002)** | **(0.003)** | **(0.003)** | **0.010** | **0.000** | **0.003** | **0.006** | **0.009** | **0.042** |
| growth | 52% | (85%) | (5%) | (42%) | (27%) | (11%) | (435%) | (96%) | 532% | 120% | 58% | 385% |
| **Underlying EPS (Diluted)** | **(0.007)** | **(0.006)** | **(0.003)** | **(0.002)** | **(0.005)** | **(0.004)** | **0.009** | **(0.001)** | **0.002** | **0.004** | **0.008** | **0.041** |
| Number of Shares (basic) | 2,016,566 | 2,072,450 | 2,402,729 | 2,818,298 | 2,610,513 | 3,026,083 | 3,026,083 | 3,026,083 | 3,026,083 | 3,026,083 | 3,026,083 | 3,026,083 |
| Number of Shares (diluted) | 2,016,566 | 2,072,450 | 2,402,729 | 2,818,298 | 2,610,513 | 3,026,083 | 3,026,083 | 3,026,083 | 3,026,083 | 3,026,083 | 3,026,083 | 3,026,083 |

Source: goetzpartners Research estimates. Warning Note: Past performance and forecasts are not a reliable indicator of future results or performance. The return may increase or decrease as a result of currency fluctuations.

CHART 64: Immutep Balance Sheet model

| Balance Sheet | 2016A | 2017A | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E |
|---|---|---|---|---|---|---|---|---|---|---|
| Jun YE (A$k) | 30-Jun-16 | 30-Jun-17 | 30-Jun-18 | 30-Jun-19 | 30-Jun-20 | 30-Jun-21 | 30-Jun-22 | 30-Jun-23 | 30-Jun-24 | 30-Jun-25 |
| **ASSETS** | | | | | | | | | | |
| **CURRENT ASSETS** | **21,671** | **15,919** | **26,564** | **82,694** | **107,368** | **103,249** | **105,433** | **116,623** | **137,472** | **242,176** |
| Cash and cash equivalents | 20,880 | 12,237 | 22,808 | 78,863 | 103,460 | 99,263 | 101,367 | 112,476 | 133,243 | 237,862 |
| GST receivable | 74 | 187 | 191 | 195 | 199 | 203 | 207 | 211 | 215 | 219 |
| Grant and other receivables | 95 | 2,007 | 2,047 | 2,088 | 2,130 | 2,172 | 2,216 | 2,260 | 2,305 | 2,351 |
| Other current assets | 623 | 1,488 | 1,518 | 1,548 | 1,579 | 1,611 | 1,643 | 1,676 | 1,710 | 1,744 |
| **FIXED ASSETS** | **20,883** | **19,045** | **17,534** | **16,145** | **14,924** | **13,777** | **12,723** | **11,775** | **10,940** | **10,495** |
| **Tangible assets, net** | 32 | 24 | 19 | 16 | 31 | 49 | 61 | 82 | 118 | 313 |
| Plant & Equipment | 15 | 11 | 9 | 7 | 22 | 41 | 54 | 76 | 114 | 309 |
| Computer | 14 | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 |
| Furniture and fittings | 3 | 1 | - | - | - | - | - | - | - | - |
| Goodwill | 110 | 110 | 110 | 110 | 110 | 110 | 110 | 110 | 110 | 110 |
| **Intangible assets, net** | 20,742 | 18,910 | 17,405 | 16,019 | 14,783 | 13,618 | 12,552 | 11,584 | 10,712 | 10,073 |
| Patents | - | - | - | - | - | - | - | - | - | - |
| Intellectual property | 20,742 | 18,910 | 17,405 | 16,019 | 14,783 | 13,618 | 12,552 | 11,584 | 10,712 | 10,073 |
| **TOTAL ASSETS** | **42,554** | **34,964** | **44,098** | **98,840** | **122,292** | **117,026** | **118,156** | **128,399** | **148,412** | **252,672** |
| **LIABILITIES** | | | | | | | | | | |
| **CURRENT LIABILITIES** | **1,472** | **2,632** | **2,685** | **9,262** | **9,317** | **9,373** | **9,430** | **9,488** | **9,547** | **9,608** |
| Trade payables | 561 | 1,139 | 1,162 | 1,185 | 1,208 | 1,233 | 1,257 | 1,282 | 1,308 | 1,334 |
| Borrowings | - | - | - | - | - | - | - | - | - | - |
| Current tax payable | 22 | - | - | - | - | - | - | - | - | - |
| Employee benefits | 28 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 |
| Other payables | 862 | 1,450 | 1,479 | 1,509 | 1,539 | 1,570 | 1,601 | 1,633 | 1,666 | 1,699 |
| Deferred revenue | - | - | - | 6,524 | 6,524 | 6,524 | 6,524 | 6,524 | 6,524 | 6,524 |
| **NON-CURRENT LIABILITIES** | **5,765** | **5,799** | **6,666** | **64,748** | **59,370** | **54,165** | **49,157** | **44,377** | **39,858** | **17,961** |
| Convertible note liability | 5,027 | 5,779 | 6,646 | 7,643 | 8,789 | 10,107 | 11,624 | 13,367 | 15,372 | - |
| Employee benefits | 43 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Deferred tax liability | 694 | - | - | - | - | - | - | - | - | - |
| Deferred revenue, less of current portion | - | - | - | 57,085 | 50,561 | 44,037 | 37,513 | 30,989 | 24,465 | 17,941 |
| **TOTAL LIABILITIES** | **7,237** | **8,431** | **9,351** | **74,010** | **68,688** | **63,538** | **58,587** | **53,865** | **49,405** | **27,569** |
| **EQUITY** | | | | | | | | | | |
| **SHAREHOLDERS EQUITY** | **35,318** | **26,532** | **34,747** | **24,829** | **53,604** | **53,488** | **59,569** | **74,534** | **99,007** | **225,102** |
| Contributed equity | 194,531 | 195,353 | 212,210 | 211,213 | 210,066 | 208,748 | 207,232 | 205,488 | 203,483 | 201,178 |
| Reserves | 63,258 | 63,019 | 63,019 | 63,019 | 63,019 | 63,019 | 63,019 | 63,019 | 63,019 | 63,019 |
| Accumulated losses | (222,472) | (231,839) | (240,481) | (249,402) | (219,481) | (218,279) | (210,682) | (193,973) | (167,495) | (39,094) |
| **TOTAL LIABILITIES & SHAREHOLDERS' EQUITY** | **42,554** | **34,964** | **44,098** | **98,840** | **122,292** | **117,026** | **118,156** | **128,399** | **148,412** | **252,672** |
| **GEARING** | | | | | | | | | | |
| **Gross debt** | **5,027** | **5,779** | **6,646** | **7,643** | **8,789** | **10,107** | **11,624** | **13,367** | **15,372** | **-** |
| Total ST debt | - | - | - | - | - | - | - | - | - | - |
| Total LT debt | 5,027 | 5,779 | 6,646 | 7,643 | 8,789 | 10,107 | 11,624 | 13,367 | 15,372 | - |
| **Cash and cash equivalents plus investments** | **20,880** | **12,237** | **22,808** | **78,863** | **103,460** | **99,263** | **101,367** | **112,476** | **133,243** | **237,862** |
| **Net debt/(cash)** | **(15,852)** | **(6,458)** | **(16,162)** | **(71,221)** | **(94,671)** | **(89,156)** | **(89,743)** | **(99,109)** | **(117,870)** | **(237,862)** |

Source: goetzpartners Research estimates. Warning Note: Past performance and forecasts are not a reliable indicator of future results or performance. The return may increase or decrease as a result of currency fluctuations.

**CHART 65: Immutep Cash Flow model**

| Cash Flow Statement | 2016A | 2017A | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E |
|---|---|---|---|---|---|---|---|---|---|---|
| Jun YE (A$k) | 30-Jun-16 | 30-Jun-17 | 30-Jun-18 | 30-Jun-19 | 30-Jun-20 | 30-Jun-21 | 30-Jun-22 | 30-Jun-23 | 30-Jun-24 | 30-Jun-25 |
| **OPERATING CASH FLOW** | | | | | | | | | | |
| Payments to suppliers and employees | (13,336) | (10,819) | (14,453) | 49,523 | (20,891) | (21,397) | (21,923) | (22,536) | (27,104) | (40,155) |
| License income | 175 | - | 2,580 | 3,631 | 42,649 | 14,277 | 20,985 | 32,353 | 51,242 | 213,792 |
| License fee received | - | - | - | - | - | - | - | - | - | - |
| Interest received | 264 | 104 | 75 | 76 | 78 | 80 | 81 | 83 | 84 | 86 |
| Tax received / paid | (2) | 22 | (0) | 0 | (0) | (0) | - | (1,857) | (6,620) | (55,029) |
| Miscellaneous income | 703 | 800 | 2,034 | 677 | 691 | 705 | 719 | 733 | 748 | 763 |
| Grant income | 887 | 1,385 | 2,625 | 2,160 | 2,138 | 2,181 | 2,290 | 2,405 | 2,525 | 3,276 |
| **NET CASH USED IN OPERATING ACTIVITIES** | **(11,310)** | **(8,507)** | **(7,138)** | **56,068** | **24,665** | **(4,154)** | **2,152** | **11,180** | **20,876** | **122,733** |
| **CASH FLOW FROM INVESTING** | | | | | | | | | | |
| Payments for held-to-maturity investments | - | - | - | - | - | - | - | - | - | - |
| Proceeds from held-to-maturity investments | - | - | - | - | - | - | - | - | - | - |
| Payments for P&E and intangibles | (27) | (7) | (15) | (13) | (68) | (43) | (48) | (71) | (109) | (436) |
| Proceeds from disposal of P&E | 130 | - | - | - | - | - | - | - | - | - |
| Acquisitions, net of cash acquired | - | - | - | - | - | - | - | - | - | - |
| **Net cash provided by investing activities** | **103** | **(7)** | **(15)** | **(13)** | **(68)** | **(43)** | **(48)** | **(71)** | **(109)** | **(436)** |
| **CASH FLOW FROM FINANCING** | | | | | | | | | | |
| Proceeds from issue of shares and options | 13,761 | 0 | 19,722 | - | - | - | - | - | - | - |
| Proceeds from borrowings | 13,751 | - | - | - | - | - | - | - | - | - |
| Repayment of borrowings | (1,508) | - | - | - | - | - | - | - | - | (17,678) |
| Transaction costs | (283) | (9) | (1,998) | - | - | - | - | - | - | - |
| **Net cash provided by financing activities** | **25,720** | **(9)** | **17,724** | **-** | **-** | **-** | **-** | **-** | **-** | **(17,678)** |
| Net change in cash and cash equivalents | 14,513 | (8,522) | 10,571 | 56,055 | 24,597 | (4,197) | 2,104 | 11,109 | 20,766 | 104,619 |
| Effect of exchange rate on cash and cash equivalents | (393) | (121) | - | - | - | - | - | - | - | - |
| Cash and cash equivalents, beginning of period | 6,760 | 20,880 | 12,237 | 22,808 | 78,863 | 103,460 | 99,263 | 101,367 | 112,476 | 133,243 |
| **Cash and cash equivalents, end of period** | **20,880** | **12,237** | **22,808** | **78,863** | **103,460** | **99,263** | **101,367** | **112,476** | **133,243** | **237,862** |
| **Cash burn/(generation)** | **(11,207)** | **(8,513)** | **(7,153)** | **56,055** | **24,597** | **(4,197)** | **2,104** | **11,109** | **20,766** | **122,297** |

Source: goetzpartners Research estimates. Warning Note: Past performance and forecasts are not a reliable indicator of future results or performance. The return may increase or decrease as a result of currency fluctuations.

# Charts

## COMPANY DESCRIPTION

Immutep (known as Prima BioMed until November 2017) is an Australian clinical-stage biotechnology company that develops immunotherapies for cancer and autoimmune diseases. Immutep is the global leader in the understanding of and in developing therapeutics that modulate Lymphocyte Activation Gene-3 (“LAG-3”). LAG-3 was discovered in 1990 at the Institut Gustave Roussy by Dr Frédéric Triebel, Immutep's Chief Scientific Officer and Chief Medical Officer. The company has three assets in clinical and one asset in preclinical development. The lead product candidate is eftilagimod alpha, a first-in-class antigen presenting cell ("APC") activator being investigated in combination with chemotherapy or immune therapy for advanced breast cancer and melanoma. Immutep is dual-listed on the Australian Stock Exchange (“IMM”) and on the NASDAQ Global Market (“IMMP”) in the US (American Depository Receipts), and has operations in Europe, Australia, and the US.

## SCENARIOS

### Base Case - GP Investment Case

Eftilagimod alpha completes the Phase IIb AIPAC trial in mBC in 2019, Immutep signs a $1bn licensing deal with a large pharma partner in H2/2019, and efti receives conditional approval in 2020E in Europe. US launch follows one year later. Immutep has sufficient cash to fund operations until Q4/2019. Revenue from the expected efti licensing deal means that Immutep does not need to raise further funds.

### Bluesky Scenario

Immutep signs a more lucrative licensing deal for efti than the $1bn reflected in our forecasts, including a substantially larger upfront payment (we model $50m).

### Downside risk

Efti fails to shows a benefit in the Phase IIb AIPAC trial. Conditional approval is not granted based on Phase IIb data. Immutep is unable to sign a licensing deal for efti by Q4/2019.

## Peer Group Analysis

### Peer Group - Grid 1

Merck & Co., Bristol-Myers Squibb, Roche, AstraZeneca, Pfizer, Merck KGaA, Novartis, GSK, Boehringer Ingelheim, Sanofi, Regeneron, Eli Lilly

### Peer Group - Grid 2

Macrogenics, Tesaro, F-Star, Symphogen, Incyte

## SWOT

**Strengths:** Leader in the understanding of LAG-3; broadest LAG-3 focused pipeline; validation from large pharma partners (Novartis, GSK, Merck & Co.); funded for >12 months.

**Weaknesses:** One single asset (eftilagimod alpha) accounts for the lion share of value; efti has not demonstrated convincing efficacy in monotherapy settings; efti is protected mainly by use and formulation patents, as the composition of matter patent has already expired.

**Opportunities:** LAG-3 could become the third pillar in immune checkpoint therapy and efti is the most advanced LAG-3 focused asset; efti could be the first immuno-oncology drug to be approved for metastatic breast cancer; oncology drugs addressing high unmet needs often enjoy shorter development and approval timelines than therapeutics in other disease areas; significant M&A activity in the immuno-oncology space.

**Threats:** EMA and FDA raise the hurdles for immunotherapy drugs.

## INDUSTRY EXPECTATIONS

Immutep is developing immunotherapies for cancer, with a focus on the immune checkpoint LAG-3. The immune checkpoint inhibitor ("ICI") class has experienced rapid adoption since the launch of BMS's Yervoy (ipilimumab) in 2011, owing to their ability to elicit durable responses in 20 - 50% of patients for up to 10 years. The global ICI market was worth $10.5bn in 2017 and is expected to nearly triple by 2022E, driven largely by expanding use of existing therapies both in approved and new indications. The race is on to develop novel compounds with complementary mechanisms of action for combination therapy able to augment response rate without increasing toxicity, which, if successful, are expected to enjoy rapid uptake.

# Important Disclosures: Non-Independent Research

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I, Brigitte de Lima, PhD, CFA, hereby certify that the views regarding the companies and their securities expressed in this research report are accurate and are truly held. I have not received and will not receive direct or indirect compensation in exchange for expressing specific recommendations or views in this research report.

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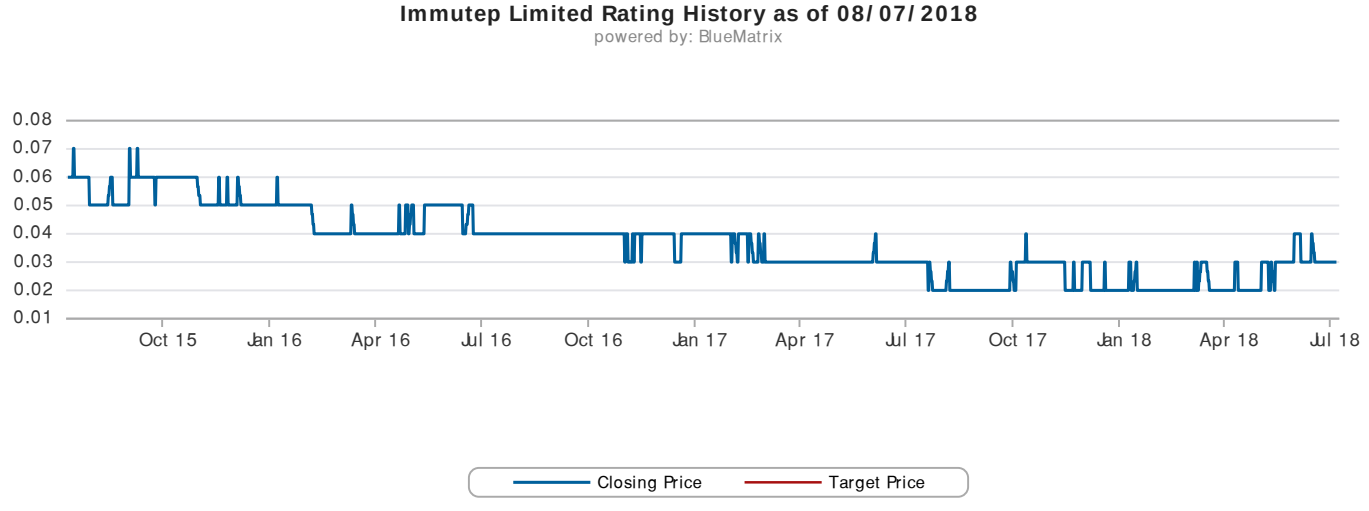


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