WILSONS

Equity Research

Date
04 November 2021

Theme
Initiating Coverage

Company
Immutep Limited (IMM)

O/W: IMMune to failure

We initiate on Immutep (IMM) with an OVERWEIGHT recommendation and a $0.91 per share risked PT. Immutep is an Australian clinical stage biopharmaceutical company whose clinical assets focus on a new immuno-oncology (IO) target, the immune checkpoint molecule LAG-3. This is the perfect time to engage with LAG-3 directed assets now that Bristol Myers Squibb has filed the first LAG-3 directed drug for FDA & EMA approval. Immutep's clinical programs explore every therapeutic aspect of this multifaceted drug target. IMM's lead product Efti soon advances to Phase IIb & III trials aiming to enhance and extend IO blockbusters including Merck's (MSD) Keytruda. A wealth of pharma partnerships explore utility in oncology and autoimmune disease. We see a valuation disconnect between IMM and their opportunities in these markets with significant TAMs in metastatic cancers (breast $2.3B, head & neck $2.2B, lung $8B) where unmet need is high and partnership with existing blockbusters (Keytruda) sets them up for an immediacy of clinical adoption with future approvals. Our unrisked PT of $2.33/share highlights this.

Recommendation	**OVERWEIGHT**
12-mth target price (AUD)	**$0.91**
Share price @ 02-Nov-21 (AUD)	$0.59
Forecast 12-mth capital return	53.6%
Forecast 12-mth dividend yield	0.0%
12-mth total shareholder return	**53.6%**
Market cap	$504m
Enterprise value	$443m
Shares on issue	854m
Sold short	0.0%
ASX 300 weight	0.0%
Median turnover/day	$0.9m

Key points

Well progressed assets with large TAMs. Immutep's lead asset, Efti, is soon to be placed in its first registration Phase III trial, with other Phase II & IIb's underway. The asset is de-risked to a point given this advanced stage, with solid supporting clinical data thus far.

Established leading pharma partners validates asset quality. Immutep have out-licensed two of their assets to leading pharma partners (Novartis, GSK) with potential for significant future milestone and royalty payments, with no development expense. The long standing collaborative development between IMM and MSD across indications further supports this.

Strong market predicates guide potential value. Numerous recent oncology deals, including ASX-predicate, Viralytics, highlight the potential upside for IMM shareholders given interest from oncology players in Immutep's assets (MSD, GSK, Novartis, Pfizer, Merck). We see opportunity for a >$2B takeout opportunity based on recent deal predicates.

Forecasts. We forecast potential revenue peaks of $950M for Efti in metastatic breast cancer, $720M for Efti in HNSCC and $350M for Efti in NSCLC based on a licensing deal structure (peak royalty revenue $350M, $470M milestones).

Valuation. We value IMM using a SOTP using a real options DCF approach; a) Efti in breast cancer ($0.30/sh); b) Efti in HNSCC ($0.09/sh); c) Efti licensing in NSCLC ($0.53/sh). No other pipeline assets are included in our valuation at this stage. Unrisked PT is $2.33/sh.

Risks and catalysts

Risks: a) adverse clinical trial outcomes; b) negative regulator interactions; c) competitive intensity of immuno-oncology field; d) available capital. **Catalysts:** a) achievement of trial endpoints; b) partnership opportunities; c) regulatory approvals; d) corporate activity.

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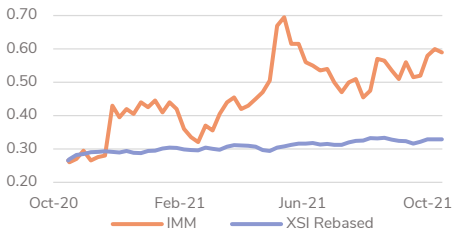
12-mth price performance ($)



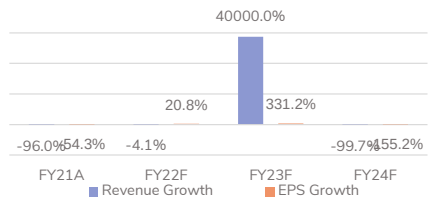
	1-mth	6-mth	12-mth
Abs return (%)	7.3	31.1	122.6
Rel return (%)	5.3	24.3	98.7

Earnings forecasts

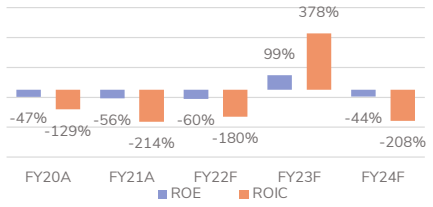
Year-end June (AUD)	FY20A	FY21A	FY22F	FY23F	FY24F
NPAT rep ($m)	-13.4	-30.5	-33.9	78.4	-43.2
NPAT norm ($m)	-13.5	-29.9	-33.9	78.4	-43.2
Consensus NPAT ($m)			-48.2	-6.6	-24.4
EPS norm (cps)	-3.3	-5.0	-4.0	9.2	-5.1
EPS growth (%)	40.5	-54.3	20.8	331.2	-155.2
P/E norm (x)	-18.1	-11.7	-14.8	6.4	-11.6
EV/EBITDA (x)	-38.3	-15.9	-13.8	5.5	-10.7
FCF yield (%)	-2.2	-3.5	-6.9	15.7	-8.7
DPS (cps)	0.0	0.0	0.0	0.0	0.0
Dividend yield (%)	0.0	0.0	0.0	0.0	0.0
Franking (%)	0	0	0	0	0

Source: Company data, Wilsons estimates, Refinitiv

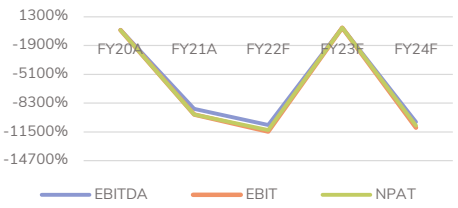
Growth rates



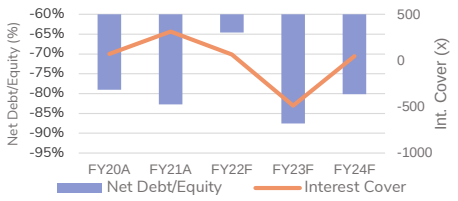
Returns



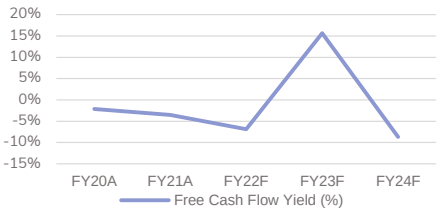
Margin trends



Solvency



Free cash flow yield



Interims ($m)

	1H21A	2H21A	1H22E	2H22E
Sales	0.2	0.1	0.2	0.2
EBITDA	-18.8	-9.1	-15.1	-17.1
EBIT	-19.9	-10.1	-16.2	-18.2
Net profit	**-19.8**	**-10.1**	**-15.9**	**-18.0**
Norm EPS	**-3.8**	**-1.2**	**-1.9**	**-2.1**
EBIT/sales	-	-	-	-
Dividend (c)	0.0	0.0	0.0	0.0
Franking (%)	0.0	0.0	0.0	0.0
Payout ratio	**0.0**	**0.0**	**0.0**	**0.0**
Adj payout	0.0	0.0	0.0	0.0

Key assumptions

	FY18A	FY19A	FY20A	FY21A	FY22F	FY23F	FY24F
Revenue Growth (%)		-64.4	499.8	-96.0	-4.1	40,000.0	-99.7
EBIT Growth (%)	26.6	45.0	-27.1	119.6	14.7	-327.3	-156.5
NPAT Growth (%)	36.1	43.9	-26.6	122.0	13.3	-331.2	-155.2
EPS Growth (%)			**-40.5**	**54.3**	**-20.8**	**-331.2**	**-155.2**
R&D spend	-10.0	-16.6	-20.4	-17.2	-26.0	-33.0	-35.0
ROA (%)	**-31.1**	**-41.9**	**-30.9**	**-46.5**	**-52.7**	**90.8**	**-41.7**
ROE (%)	**-42.4**	**-63.4**	**-46.7**	**-56.1**	**-60.0**	**98.6**	**-44.4**

Financial ratios

	FY18A	FY19A	FY20A	FY21A	FY22F	FY23F	FY24F
PE (x)	-120.4	-10.8	-18.1	-11.7	-14.8	6.4	-11.6
EV/EBITDA (x)	-39.9	-26.3	-38.3	-15.9	-13.8	5.5	-10.7
Dividend yield (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FCF yield (%)	-1.5	-3.0	-2.2	-3.5	-6.9	15.7	-8.7
Payout ratio (%)	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Adj payout (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Profit and loss ($m)

	FY18A	FY19A	FY20A	FY21A	FY22F	FY23F	FY24F
Sales revenue	3.6	1.3	7.8	0.3	0.3	120.3	0.4
EBITDA	-11.1	-16.9	-11.6	-27.9	-32.2	80.6	-41.6
Depn & amort	1.8	1.9	2.1	2.1	2.2	2.4	2.6
EBIT	**-12.9**	**-18.7**	**-13.7**	**-30.0**	**-34.4**	**78.2**	**-44.2**
Net interest expense	-0.2	-0.4	-0.2	-0.1	-0.5	-0.2	-0.9
Tax	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Minorities/pref divs	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Equity accounted NPAT	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit (pre-sig items)	**-12.7**	**-18.3**	**-13.5**	**-29.9**	**-33.9**	**78.4**	**-43.2**
Abns/exts/signif	1.3	0.6	0.1	-0.6	0.0	0.0	0.0
Reported net profit	**-11.4**	**-17.8**	**-13.4**	**-30.5**	**-33.9**	**78.4**	**-43.2**

Cash flow ($m)

	FY18A	FY19A	FY20A	FY21A	FY22F	FY23F	FY24F
EBITDA	-11.1	-16.9	-11.6	-27.9	-32.2	80.6	-41.6
Interest & tax	0.1	0.4	0.2	0.1	0.5	0.2	0.9
Working cap/other	3.2	1.2	0.5	10.2	-2.9	-1.7	-3.1
Operating cash flow	**-7.8**	**-15.3**	**-10.8**	**-17.6**	**-34.6**	**79.0**	**-43.7**
Maintenance capex	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Free cash flow	**-7.8**	**-15.3**	**-10.8**	**-17.6**	**-34.6**	**79.0**	**-43.7**
Dividends paid	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Growth capex	0.0	0.0	0.0	0.0	-0.2	-0.2	-0.2
Invest/disposals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Oth investing/finance flows	-1.3	-0.8	-1.5	-2.1	0.0	0.0	0.0
Cash flow pre-financing	**-9.1**	**-16.1**	**-12.3**	**-19.8**	**-34.8**	**78.8**	**-43.9**
Funded by equity	19.7	8.8	22.0	55.0	0.0	0.0	0.0
Funded by debt	0.0	0.0	-0.1	-0.2	-0.1	-0.1	-0.1
Funded by cash	-10.6	7.3	-9.6	-35.0	34.9	-78.7	44.0

Balance sheet summary ($m)

	FY18A	FY19A	FY20A	FY21A	FY22F	FY23F	FY24F
Cash	23.5	16.6	26.3	60.6	25.7	104.4	60.4
Current receivables	3.4	5.2	3.3	6.1	5.0	5.0	5.0
Current inventories	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net PPE	0.0	0.1	0.0	0.0	0.2	0.3	0.4
Intangibles/capitalised	18.3	16.9	15.2	12.8	13.1	13.1	13.1
Total assets	**47.0**	**40.5**	**46.6**	**82.0**	**46.6**	**126.0**	**81.6**
Current payables	3.7	5.1	2.9	4.8	2.8	3.5	3.0
Total debt	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total liabilities	**13.5**	**16.2**	**13.3**	**8.8**	**6.8**	**6.8**	**6.3**
Shareholder equity	**33.5**	**24.4**	**33.3**	**73.3**	**39.8**	**119.2**	**75.3**
Total funds employed	**33.5**	**24.4**	**33.3**	**73.3**	**39.8**	**119.2**	**75.3**

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Glossary

Efti	Eftilagimod alpha (Efti) is Immutep's lead asset. It is a soluble fusion protein containing LAG-3 that can stimulate the immune system to help fight cancer. Efti is also referred to IMP321 in some circumstances.
LAG-3	Lymphocyte Activator Gene 3 (LAG-3) is a key checkpoint within the immune system that can function to supress or activate immune response (via T cell activation) depending on how it is modulated.
IO	Immuno-oncology (IO) is an area of cancer treatment that focuses on targeting the body's own immune system in order to fight tumours/cancer. IO drugs have become a major component of the oncology landscape since introduction a decade ago and target different immune checkpoints (including PD-1, CTLA-4, PD-L1). The first IO drug was approved in 2011 (Yervoy for melanoma) with a swathe of other IOs to follow; Keytruda being the highest selling current IO drug (US$14B sales in 2020) for a multitude of cancer indications.
ICI	Immune checkpoint inhibitors are typically antagonist antibodies that block a key immune checkpoint involved in immune response and tumour growth such as PD-1. Pembrolizumab and ipilimumab are examples of ICIs.
PD-1/PD-L1	Programmed cell death receptor 1 (PD-1) and its ligand (PD-L1) are key targets within immuno-oncology. Blocking these molecules induces anti-tumour responses. They are the target of many ICIs, including pembrolizumab.
APC	Antigen presenting cells (APCs) are a key part of the innate immune system and responsible for moderating immune response to antigen stimulus. A specific class of APCs are the target of Efti.
T Cell	T cells are a type of immune cell within that body whose primary role is to eliminate cells infected by pathogens or that have undergone malignant transformation (cancer).
BLA	A Biologics License Application (BLA) is a type of FDA drug submission required to grant marketing authorisation for drugs that are biologic in nature, i.e. Antibody or protein-based drugs, such as Eftilagimod Alpha.
Hazard Ratio (HR)	Hazard ratio (HR) is a statistical measure used to define the benefit of one treatment over another. A HR <1 indicates less risk of death or disease progression compared to the other treatment of interest.
DCR	Disease control rate (DCR) represents the complete, partial and stable responses to a cancer drug. It shows the proportion of patients where the drug treatment has 'stalled' or controlled their cancer.
ORR	Overall response rate (ORR) represents the complete and partial responses to a drug. It is a typical primary endpoint and represents the proportion of patients within a treatment group that had benefit (reduced tumour size) from the drug.
PFS	Progression free survival (PFS) measures the period of time that a patient is able to live without their cancer progressing (i.e. stable or improving) after they have initiated a treatment regimen. It is a common primary endpoint measure.
OS	Overall survival (OS) measures how long a patient survives before death after starting a therapeutic treatment. It is a common primary endpoint measure in cancer clinical trials that is an approvable endpoint.
NSCLC	Non-small cell lung cancer is the type of lung cancer that accounts for ~80-85% of all lung cancers.
HNSCC	Head and neck squamous cell carcinoma is a common form of cancer affecting areas in the head and neck.
Metastatic cancer	Metastatic cancers are those that have spread beyond the primary organ/site of the cancer into other areas of the body. Metastatic cancer has a higher associated mortality rate and is often more challenging to treat.
Unresectable cancer	Unresectable refers to cancerous tumours that are not able to be surgically removed, typically due to there not being clear margins around the tumour, it being located in an area that cannot be removed and/or the tumour having spread into other surrounding tissues and organs. Surgical resection is a typical first line therapy for solid tumours.
HR status (+ or -)	Hormone receptor (HR) status is used to categorise breast cancer types as it guides treatment decisions. HR status includes expression of both estrogen receptors (ER) and progesterone receptors (PR). Cancers that are positive for one or both (ER/PR) are defined as HR^+. Only cancers that are ER- and PR- are classified as HR-.
HER2 status (+ or -)	Human epithelial growth factor receptor 2 (HER2) status is used to categorise breast cancer types as it guides treatment decisions. Patients with HER2+ cancer types are often amenable to targeted HER2 therapies not useful in HER2- patients
TNBC	Triple negative breast cancer (TNBC) is a subtype where the cancer is negative for all three key receptors (HER2, ER, PR).

Investment thesis

We initiate coverage on Immutep with an OVERWEIGHT rating and risked price target of $0.91 per share. Immutep is an Australian clinical stage biopharmaceutical company whose clinical assets focus on a new immuno-oncology (IO) target, the immune checkpoint molecule LAG-3. This is the perfect time to engage with LAG-3 directed assets now that Bristol Myers Squibb has filed the first LAG-3 directed drug for FDA and EMA approval. Immutep's clinical programs explore every therapeutic aspect of this multifaceted drug target. IMM's lead product Efti soon advances to Phase IIb & III trials aiming to enhance and extend IO blockbusters including Merck's (MSD) Keytruda. A wealth of pharma partnerships explore utility in oncology and autoimmune disease. We see a valuation disconnect between IMM and their opportunities in these markets with significant TAMs in metastatic cancers (breast $2.3B, head & neck $2.2B, lung $8B) where unmet need is high and partnership with existing blockbusters (Keytruda) sets them up for an immediacy of clinical adoption with future approvals.

The four key points we would emphasise in supporting our investment thesis are as follows;

1. Clinical data supports progression of Efti in 3 key indications with large TAMs. Immutep have standout data in HNSCC, an indication where they also have Fast Track Designation. They also have data to support expansion of current anti-PD-1 therapies in a broader patient population including positive efficacy in refractory patient subsets. Finally, whilst less straightforward, they have clear efficacy advantages over the current mBC standard of care in a patient subtype (HR+/HER2-) with limited treatment options.
2. Unique and scientifically valid approach to emerging IO field. Immutep represent the only LAG-3 focused 'pure-play' biotech on the market (ASX or NASDAQ). They have a strong R&D pipeline with unique assets (4 different mechanistic approaches to LAG-3 modulation) and very strong scientific expertise to support their continued innovation in the space. LAG-3 is the newest checkpoint inhibitor close to first market approval, setting it up to be a hot space in the near term.
3. Proven engagement with several oncology leaders in market positions IMM well for acquisition. Immutep have broad ranging partnerships (in the form of collaborations and licensing deals) with a large number of oncology heavy hitters (MSD, GSK, Merck KGaA, Pfizer, Novartis). Engagement by these oncology powerhouses validates the assets and approach Immutep are taking to their clinical development programs. Further, their pairing of Efti to the market leading IO drug, Keytruda (MSD) positions them well for future market entry.
4. Timing is right – valuation discount present whilst field awaiting regulator validation. The likely and impending FDA approval of BMS' relatlimab in melanoma represents the first regulatory validation of LAG-3 as a relevant anti-tumour immune checkpoint. This brings broad validation to the field of LAG-3 targeted assets, with Immutep being the forefront player given their unique pipeline of four assets, each with unique mechanisms of action. The significant valuation discount we see in Immutep will be moderated following regulator validation of LAG-3 as a target in early CY22.

Investment merits

Diversified portfolio of assets with large addressable market opportunities. Immutep has four assets in clinical development (two out-licensed and two kept in house) which provide them multiple opportunities for future commercial revenues and cover a broad array of indications across oncology and autoimmune disease. Whilst our valuation rests currently on the Efti asset we note the future potential for other assets to contribute to valuation, notably IMP761 given its disease modifying potential in poorly treated (large) indications such as IBD and rheumatoid arthritis. Several assets de-risks the IMM investment case to some extent.

Provides exposure to LAG-3 as a new and exciting IO target that is clinically de-risked. Immutep is the only LAG-3 pure play biotech in the IO market with four different assets approaching LAG-3 modulation via different mechanisms. This sets them apart from others players which thus far have antagonist-only approaches (via monoclonal or bi-specific antibodies). Given the increasing interest and potential importance of LAG-3 in the IO landscape, we view Immutep as a unique opportunity for exposure to a new checkpoint that could bring in the next IO revolution (akin to PD-1). Given the imminent approval of the first LAG-3 targeted therapy (BMS' relatlimab) in CY22, this is the perfect time to engage with LAG-3 directed assets.

Strength of Efti clinical data to date supported by a favourable toxicity profile. Efti clinical programs AIPAC and TACTI-002 exhibit incremental efficacy improvements over and above current treatment options without the addition of toxicity. Of particular interest is their 2nd line HNSCC data (TACTI-002 Part C) where we see superior overall survival and response rates for Efti + pembrolizumab when compared to approved anti-PD-1 monotherapies (nivolumab, pembrolizumab) in both the 2nd (and impressively) 1st line settings. This supports our confidence in the TACTI-003 program in 1st line HNSCC. The data derived from the AIPAC breast cancer program, whilst less obviously positive (given the primary endpoint miss), does show stellar survival improvements in patients subsets, several of which we see as relevant to progress in this indication with a meaningful TAM. Finally, the ongoing TACTI-002 NSCLC indication data continues to excite, more so in the patient cohorts with nil-low PD-L1 expression and those that have failed 1st line anti-PD-L1 therapies. The ability for Efti to 'boost' pembrolizumab efficacy in these difficult to treat cohorts is a key opportunity to expand anti-PD-1 therapy applicability in this indication addressing a greater proportion of the unmet need.

Attractive valuation versus listed peers in oncology space. The recent ASX-300 addition, Imugene (ASX:IMU) is listed peer to Immutep also with several pipeline assets focused in oncology. On a valuation relativity basis, we view Immutep as markedly more attractive given its market capitalisation which is ~5 fold lower than Imugene despite it having more advanced clinical assets and broader indication applicability. When comparing to NASDAQ-listed biotech peers in the IO space such as Cue Biopharma (CUE), Zymeworks (ZYME) and iTeos Therapeutics (ITOS) we also see valuation discounts in the 20% to 75% range (despite Immutep being further progressed in some cases) suggesting the market has not yet digested the full potential and development status of Immutep in our view. The complexity associated with the immunotherapy space and the specific mechanism and indication subset nuance are likely barriers for some potential investors in understanding IMM's potential in this market hence the valuation discount to date.

Strong collaborative development partnerships with big pharma validate their science. Not only do the license deals and collaborative partnership with big pharma provide diversified revenue opportunities (in the form of milestone/royalty payments) but they also provide a degree of validation with regards to Immutep's drug assets and their scientific strength. These collaborations are a typical precursor step for pharma when looking to evaluate assets for licensing or acquisition. Efti is well positioned in this sense.

Sector leading in-house expertise. Immutep have significant inhouse knowledge and expertise when it comes to understanding LAG-3 and its function with respect to immune activation and oncology. Immutep's CSO and CMO is the original scientist who discovered LAG-3 as an immune checkpoint and identified its potential immunomodulatory actions which could be used in tumour suppression. The scientific team at Immutep have largely retained many of the core scientists involved in these early LAG-3 discoveries. Immutep continues to be a scientifically-driven biotech with consistent and impactful scientific outputs as evidenced by their consistent peer-reviewed publication history. We note the expertise of Immutep's scientific team have been sought out specifically in the case of LabCorp to help in the development of LAG-3 diagnostics; LabCorp being a significant player in the diagnostics space with many

other large pharma collaborations. It is clear from Immutep's asset pipeline and in-house expertise they are leaders in the LAG-3 field.

High level manufacturing investment ahead of peers. Immutep have invested significantly over the past 3-5 years (~$14M) in establishing GMP manufacturing processes for their lead asset, Efti. Manufacture of biologics is more challenging that other drug products and the manufacturing processes and controls form a significant part of a BLA submission. Immutep have partnered with Wu Xi Biologics, a respected global CDMO, to optimise manufacturing processes and scale up batches to commercial volume runs. Immutep are now well positioned for commercial scale manufacture of Efti for large upcoming Phase III trials. They have invested ahead of potential BLA submissions for Efti knowing that manufacture is a key hurdle to approval and is often left behind in late stage development planning by biotech companies. Phase III drug materials need to be the same as what one intends to go to market with; Immutep are preparing for this.

Successful ASX acquisition predicates in market. The immuno-oncology space is busy in terms of deals, with big pharma looking to fill their pipelines with new IO assets that could expand or completement their existing IO franchises. We note that Viralytics (ASX:VLA) is an ASX predicate in the IO space acquired by MSD in early 2018 that potential IMM shareholders should be aware of. We look to this example to highlight the similarities in terms of indications (i.e. NSCLC) but also long-standing development agreements (with MSD) and use of their lead asset in combination with MSD's pembrolizumab (akin to Efti). Immutep has the potential to be a VLA 2.0 story albeit we expect at a far higher valuation given its breadth of assets, furthered clinical development stage and increased TAM opportunities. We assess potential for a >$2B takeout of Immutep by an interested IO pharma leader delivering shareholder value and better supporting the commercial potential of Immutep's assets.

Considered management approach to trial design and optimisation of lead programs. We assess management are taking a well thought out approach to trial design generally, ensuring there is input from all relevant parties, including trial design experts. This may not seem to be a differentiator however we note that trial design is often not adequately invested in by small biotech and can and has been a source of many missteps ultimately costing shareholders significant value and time to return on their investment. We are reassured by the fact that Immutep are investing in their trial design processes, in particular for their upcoming Phase III in metastatic breast cancer which is a lead program for Efti. Immutep are seeking input from regulators (US & EU) as well as health economics experts and reimbursement specialists to ensure the trial design satisfies relevant and necessary data endpoints for all parties involved to optimise the likelihood of commercial success should clinical endpoints be met.

Broad KOL collaborations to extend and expand understanding and reach of LAG-3. Immutep have a number of quality investigator led studies underway, most notably the INSIGHT program, which is focused on evaluation of Efti in a range of scenarios including via different administration routes (e.g. intra-tumoural) as well as in combination with or without several standard of care therapies and novel drug assets (avelumab, bintrafusp alfa) in different solid tumours. This alongside several other investigator led studies highlights the keen level of interest in IMM's assets from KOLs in the IO field. This also provides a platform for advancing Immutep's R&D pipeline with minimal expense whilst further expanding the clinical understanding of LAG-3 within the oncology community.

Catalyst rich period for stock. Given the breadth of clinical activity being undertaken by Immutep and its development partners we assess there will a significant number of catalysts for the stock in the near to medium term (6-24 months). Several key programs are set to deliver data readouts (TACTI-002 Part A & B, AIPAC final OS data) in the next ~1-6 months. Other catalysts include new program starts (i.e. AIPAC Phase III) and regulatory milestones.

Investment risks

Competitive technology risk. The world of IO and immune checkpoint inhibitors is increasingly competitive with several large players working on competitive LAG-3 directed assets (15+ in clinical development). Further to this, advances in the IO field can be swift and given the timelines required to undertake clinical trial programs with Efti there may be changes to the SOC treatment landscape that affect how Efti is to be evaluated. ICI development, including for LAG-3, is a highly competitive area and there are large players with significantly more resources that can accelerate development of competitive technologies. Immutep have partnered with many of these pharma players across their asset portfolio which insulates them from some of this risk, yet it must be acknowledged.

LAG-3 is yet to be validated as an approved IO target. Despite supportive Phase III data (from BMS' relatlimab) demonstrating a benefit from antagonising LAG-3 in oncology, the LAG-3 target is yet to be validated commercially by a major market approval. We understand that this could be as early as CY22.

Have IMM wed themselves to MSD limiting other big pharma interest? Whilst the collaborations with MSD (i.e. TACTI) validate the Efti asset, there is a risk that Immutep have progressed along a path with this big pharma partner too far, thus making them unattractive/a deprioritised target for other large pharma players. The use of the Efti – pembrolizumab combination in their Phase II and now Phase IIb TACTI program runs the risk of MSD being the only interested partner and thus potentially lowering deal making outcomes (with limited competition to elevate deal valuation). Industry channel checks have suggested that Phase II is not yet too late, should the asset be interesting to a third party, however it is nearing a point of no return. We draw to remind readers of the Viralytics (VLA) predicate that was acquired by MSD for a third of Wilsons' unrisked valuation (note here).

Clinical trial and regulatory risk. As with any clinical development stage biopharmaceutical company, there are inherent investment risks associated with the outcomes of clinical trials and subsequent regulatory marketing authorisation decisions outside the control of the company. The clinical data thus far to support Immutep's clinical programs in metastatic breast cancer, head and neck cancer and non-small cell lung cancer has been gained in Phase II studies, however in some cases was there a lack of blinded randomised control group (i.e. TACTI-002) and therefore cross trial comparisons must be relied upon to gauge the extent of efficacy. In this sense there is elevated risk entering further Phase IIb and III trials that the efficacy seen thus far with Efti is not significant when compared in a controlled trial setting. As a reminder, on average 40% of drug assets fail at the Phase IIb/III trial stage never making it to a market approval. Investment by pharma into further development of these programs (i.e. MSD with TACTI-003) does however support the notion that the data thus far is convincing enough for continued involvement.

Intellectual property risk. Despite having an extensive patent portfolio comprising of twelve patent families that protect the four assets within Immutep's portfolio there are risks that these patents are not enforceable or encroach upon other competitive technologies. We have not conducted any explicit analysis of patent validity or freedom to operate. Given how busy the LAG-3 landscape is, there is increased risk that Immutep's IP may be infringed upon, at which time their IP is only as valuable as their ability to enforce it, requiring capital investment. We take confidence that Immutep's management team includes a director of IP with extensive experience in the pharma area, and that this is a focus of the business (which is not seen with many ASX-listed peers). The foundation IP that supports Efti (i.e. composition of matter) is managed via a know-how license from Merck Serono and INSERM given the original patents have now expired. Further, our understanding of the IP supporting the out-licensed asset, IMP731 to GSK, highlights that IMM's patent claims are broader than GSK's surrounding this LAG-3 depleting antibody and therefore, despite GSK's modifications to the original asset, it is still covered under IMM's IP with attached royalties and milestones.

Financial risk. As with most pre-commercialisation biotech, Immutep require continued capital investment to support their clinical development programs with no revenues to support these costs for at least 3-4 years. Lack of available capital to fund clinical development programs and/or commercialisation of their assets is a risk given the changes in market conditions that may occur which could be unfavourable with regards to capital availability. Immutep have somewhat mitigated this risk with their dual NASDAQ listing allowing capital to be sourced from two markets, in addition to future potential milestone payments and royalties from their out-licensed assets, however it is an inherent risk that must be appreciated.

Valuation risk. Our SOTP valuation is premised on successful clinical and commercial development of the Efti asset in mBC, HNSCC and NSCLC indications. Our risked valuation is premised on a 39% chance of success of Efti in these indications as we model them (when factoring in all clinical development stages and risks). Should Efti fail to show clinical efficacy in one or more of these indications there is significant downside risk to our valuation, notwithstanding potential future revenues/royalties for other assets (two out-licensed assets plus IMP761) that do not factor into our valuation at this time.

Company overview and background

Immutep Ltd comprises six wholly owned subsidiaries (2x AUS, GER, FRA, USA, UAE).

Name changes and divestments pave the way. Immutep SAS was founded in 2001 by the now Immutep Limited CSO/CMO Dr Frederic Triebel in France as an academic institute spin-out. It was subsequently acquired in 2014 by ASX-listed Prima Biomed (PRR.ASX) for a total of ~US$21M (upfront + milestones+ PRR shares). Prima Biomed first listed on the ASX in July 2001 (previously Prima resources est. 1988) following the acquisition of rights to develop Burnet Institute technology; primarily their cancer vaccine candidate CVac. In late 2014 Prima acquired French biotech Immutep SA for a total consideration of US$28M (comprised of US$18M cash pending milestones, US$3M PRR shares. US$7M warrants)[1]. This acquisition included the four key LAG-3 directed assets within Immutep's current pipeline (**Table 1**).

In mid-2016 Prima divested their forefront asset, CVac, to a now private US entity (Sydys Corp; SYYC) for ~10% stake in Sydys Corp and the potential for up to $400M in future milestone and royalty payments. From our best assessment Sydys deregistered in 2019 and no longer has an active presence in the space. We no longer see any potential value for Immutep from this transaction.

LAG-3 becomes the focus of the company. Following this divestment Prima Biomed (PRR) was changed in name to Immutep (IMM) (2017) to accurately reflect the company's assets (only held Immutep SA assets). Immutep's current management team including the CEO and COO were both employed by Prima prior to the Immutep SA acquisition. Immutep's current CEO, Marc Voigt, joined Prima in 2012 as CFO and Chief Business officer before being made CEO in mid-2014.

Table 1. Immutep's pipeline of assets

Asset	MOA	Indication	Status	Partner
Eftilagimod Alpha (Efti or IMP321)	Soluble LAG-3, APC activator	Metastatic breast cancer (HR+)	Phase III planning	EOC Pharma for China only
		NSCLC	Phase II	MSD
		HNSCC	Phase IIb	MSD
		Solid Tumours	Various Phase I/II	IKF, Merck KGaA, GSK Pfizer, Cytlimic
IMP761	LAG-3 agonist antibody	Autoimmune conditions	Preclinical	NA
IMP701 (LAG525)	LAG-3 antagonist antibody	Triple Negative Breast cancer	Phase II/IIb	Out-licensed to Novartis
		Melanoma	Phase II	
		Solid Tumours & Haematological cancers	Phase II	
IMP731 (GSK2831781)	LAG-3 depleting antibody	Ulcerative Colitis	Phase II terminated	Out-licensed to GSK
		Psoriasis	Phase I complete	

Source: Wilsons, Immutep

NASDAQ listing in 2012 too early. Immutep listed on the NASDAQ (IMMP) in April 2012 (pre-acquisition) with an opening market capitalisation of ~US$427M which quickly proceeded to decline in the subsequent 2 years of trading (**Figure 1**). In early 2016 (post-acquisition) Prima were issued with a notification from the NASDAQ given the IMMP share price had slipped below the US$1 minimum bid price which if not rectified would see them removed from the NASDAQ. Needless to say, the early NASDAQ listing of Immutep was not beneficial in our view. Today, following a 3x share consolidation, each IMMP ADS represents 10 ordinary ASX shares.

Figure 1. IMMP trading on NASDAQ (2012-2014)

Source: Refinitiv

[1] Prima BioMed announcement; 2 Oct 2014. https://www.globenewswire.com/news-release/2014/10/02/947801/0/en/Prima-BioMed-Announces-Strategic-Acquisition-of-Immutep-SA.html

Viralytics (VLA) an interesting ASX predicate. The acquisition of Viralytics in early 2018 by MSD for $502M is an interesting predicate given the similarity in approach between Immutep and Viralytics. Voracious partnering with pharma development partners is a common theme and saw Viralytics be acquired for a significant (160%) premium. Akin to Viralytics, Immutep have also combined their forefront asset, Efti, with Keytruda in a range of clinical studies currently in Phase II/IIb (Viralytics' CAVATAK asset was in clinical development in combination studies with MSD's Keytruda also at the time of acquisition). The VLA acquisition was announced when VLA had a market cap of ~$140M. The transaction represented a significant return for shareholders. Given the heightened interest in LAG-3 as the next checkpoint inhibitor we assess significant interest in IMM is likely from large players lacking any assets in this space (i.e. Pfizer, Roche, AstraZeneca) or from MSD looking to further optimise Keytruda's portfolio prospects.

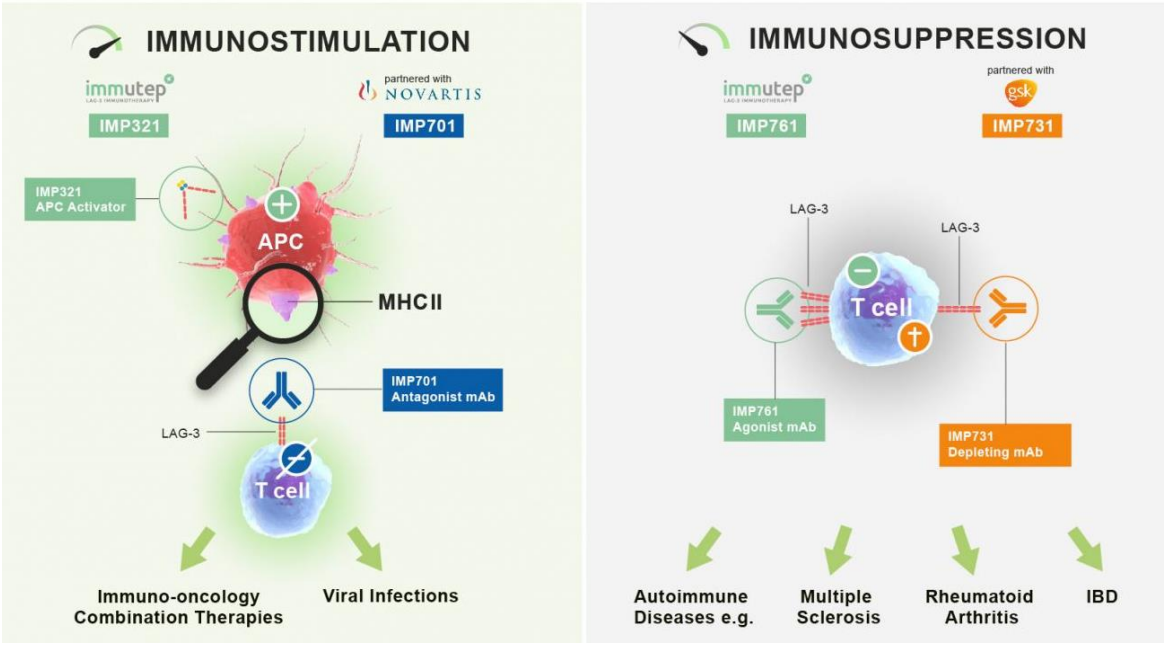
A portfolio of two halves. When thinking about the four assets within Immutep's portfolio (Efti, IMP761, IMP701 and IMP731) its best to think of them as two pairs of assets that have opposing actions in terms of the immune system, which lends them to different indication areas (**Figure 2**).

NOTE: Antagonist drugs block or inhibit a target; agonist drugs stimulate or activate a target.

a) **Immune stimulation**. Efti, and IMP701 (out-licensed Novartis) both act to stimulate the immune system but via different mechanisms. IMP701, referred to as LAG525, is a monoclonal antibody that antagonises LAG-3 directly, thus inhibiting its natural checkpoint activity (i.e. inhibits suppression and thereby stimulates immune pathways). Efti is a soluble version of LAG-3, formulated as a drug to exploit its natural role in stimulating MHC II antigen presenting cells. Immune system activation lends itself to therapeutic outcomes in oncology indications where the body has lost the ability to fight tumour cells. In cancer, immune-stimulation can help fortify the body's own immune system to fight the foreign body (cancer) with beneficial outcomes.

b) **Immune suppression**. Opposing this is the idea of suppressing an over active immune system that is the source of the disease pathogenesis. This is the case in autoimmune disorders where the body's immune system is overactive and begins to attack itself (i.e. healthy cells) leading to inflammation and disease outcomes such as in Inflammatory bowel disease (IBD) or rheumatoid arthritis. In these indications, suppression of the immune system is required to allow the body to return to homeostasis and prevent the autoimmune attack on itself. Agonism or depletion of LAG-3 are mechanisms to do this. This is what the IMP761 and IMP731 (asset out-licensed to GSK) aim to do via different mechanisms; IMP761 in a disease-modifying capacity which differentiates it from current approaches in AID which provide symptom control only (i.e. Humira).

Figure 2. Immutep's four assets are divided across their ability to modulate the immune system via either stimulation or suppression which confers different disease indication targets.



**IMP321 is another reference to Efti. IMP701 program referred to as LAG525. IMP731 program referred to as GSK2831781.*
Source: Immutep.

Valuation

Risked price target = $0.91 per share

Unrisked PT = $2.33 per share

We have used a sum-of-the-parts (SOTP) real options valuation (ROV) approach to value Immutep with their Efti asset as a predominant driver of valuation (**Table 2**). We also include a partner licensee modelling valuation to highlight the opportunity for Efti in non-small cell lung cancer (NSCLC).

Table 2. SOTP valuation for Immutep includes three key therapeutic programs

Valuation (SOTP)	Risked valuation (A$m)	Comments / methodology	Un-risked valuation (A$m)
Efti mBC	257	Real options valuation for EU and US market	897
Efti HNSCC	79	Real options valuation for EU and US market	414
Efti NSCLC	456	License deal to pharma based on upfront, milestone and royalty payments.	702
IMP761	-		-
LAG525	-		-
GSK781	-		-
Equity value ($M)	792		2013
Price per share (A$)	**0.91**	**Unrisked price per share (A$)**	**2.33**

Source: Wilsons

Our SOTP valuation comprises:

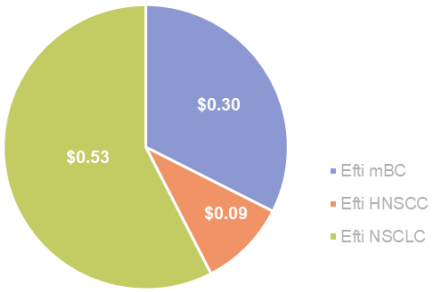
- Efti as an adjunct 1st line treatment for HR+/HER2- metastatic breast cancer (mBC) in combination with paclitaxel (**Figure 4**)
- Efti as a 1st line adjunct treatment for metastatic head and neck squamous cell carcinoma (HNSCC) in combination with pembrolizumab (**Figure 5**)
- Efti as a 1st line adjunct treatment for metastatic non-small-cell lung carcinoma (NSCLC) in combination with pembrolizumab (**Table 3**)

Our current valuation does not provide any attribution for:

- IMP761 given its early stage of development and lack of clinical efficacy data to support an indication approval thesis;
- the out-licensed Novartis (LAG525/IMP701) and GSK (GSK'781/IMP731) assets given the lack of detail regarding license agreements (milestone timing, structure, value etc).

We view these three programs as potential upside to our core Efti SOTP valuation of Immutep.

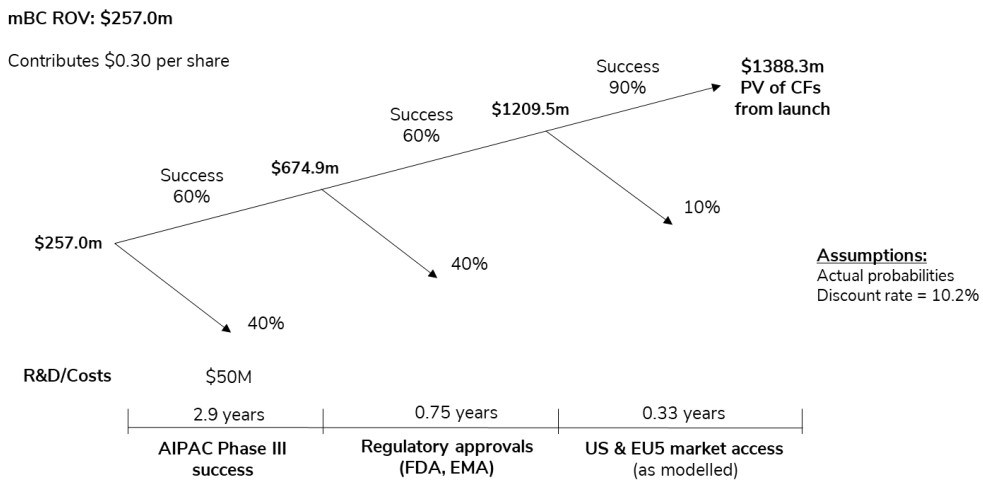
Figure 3. Relative contributions of each Efti program to $0.91 per share price target



Source: Wilsons

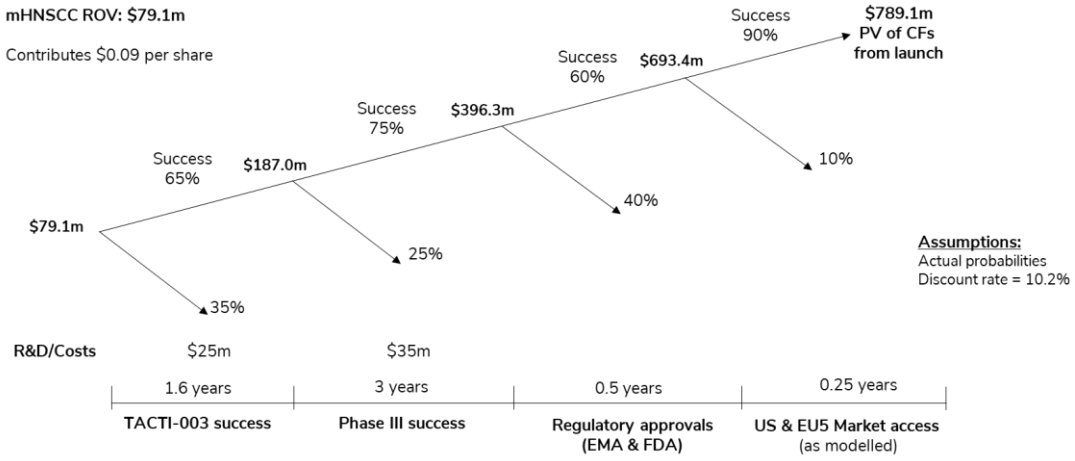
Figure 4. Real options valuation (ROV) decision tree for Efti in 2nd line HR+/HER2- mBC

See section A.2.3 for further detail on Efti in mBC indication.



Source: Wilsons

Figure 5. Real options valuation (ROV) decision tree for Efti in 1st line mHNSCC



Source: Wilsons

See section A.2.4 for further detail on Efti in HNSCC indication.

Licensing of Efti in NSCLC indication. Our SOTP valuation (**Table 2**) includes a $456M valuation for the use of Efti in metastatic NSCLC, as an adjunct to pembrolizumab. We view a significant opportunity for MSD (the developer of pembrolizumab) to license Efti in this indication given the potential synergies and increased market applicability it could bring their pembrolizumab asset in NSCLC. The clear opportunity for MSD is the ability for Efti to expand their addressable markets in both US and EU by 35% and 65% respectively by allowing them to seek a label not bound by PD-L1 tumour expression levels. Further, we view an opportunity for Efti to enhance pembrolizumab response rates and counter acquired resistance in the ~30-50% of patients with PD-L1 expression that do not respond to pembrolizumab alone.

See section A.2.5 for further detail on Efti in NSCLC indication.

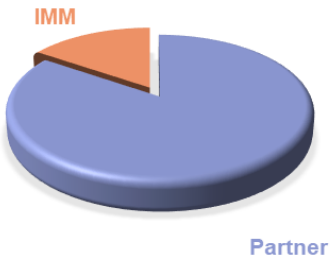
Given the compelling nature of this offering (that is specific thus far to pembrolizumab) we view MSD as the natural licensee of Efti in this indication. We apply a 65% probability to this licensing deal. Summary of deal metrics in **Table 3** below. Based on 2H FY23 deal timing we see a Partner:IMM deal share split of ~84:16 which accounts for the significant R&D investment ($ and time) required to progress Efti in this indication to a market approval stage. (**Figure 6**).

Table 3. NSCLC licensing deal outline – key metrics

Timing	Deal term	Value (A$)
FY23 (2H23)	Licensing of exclusive global rights for Efti in NSCLC indication. Supported by TACTI-002 Part A extension data.	Upfront payment; $120M
FY26 (1H26)	FDA/EMA approvals for Efti in 1st line NSCLC.	Milestone payment 1: $150M
FY27 onwards	12% royalty on net sales revenues.	Royalty: 12% (up to $2.8B across FY27-39 in our model)
FY30 (1H30)	Efti reaches $1B in cumulative global sales in NSCLC indication.	Milestone payment 2: $100M
FY33 (2H33)	Efti reaches $2B in cumulative global sales in NSCLC indication.	Milestone payment 3: $100M
TOTAL	**Upfront + milestones (incl royalties)**	**$470M ($3.3B)**

Source: Wilsons

Figure 6. Licensing deal share distribution (NSCLC)



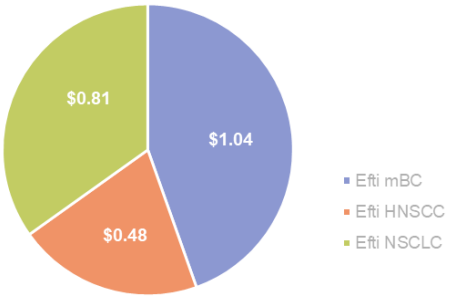
Source: Wilsons.

Standard valuation assumptions. In the three parts that comprise our SOTP valuation we use a common set of assumptions with regard to cost of equity (WACC) that is applied to our post-tax, free cash flows in order to generate our real-options valuations (mBC, HNSCC) or licensing deal model (NSCLC). We assume a market beta of 1.2 broadly in line with other small-mid biotech under our coverage (TLX, CUV). Our assumed risk-free rate (3%) and market risk premium (6%) are consistent across all of Wilsons' coverage.

Clinical risk. We do not apply an explicit clinical risk value to the NSCLC program however capture this within the 65% deal probability assessment. The total probability of success in our ROV models for mBC and HNSCC indications are 32% and 26% respectively factoring in clinical risk associated with clinical trial milestones and regulatory approvals.

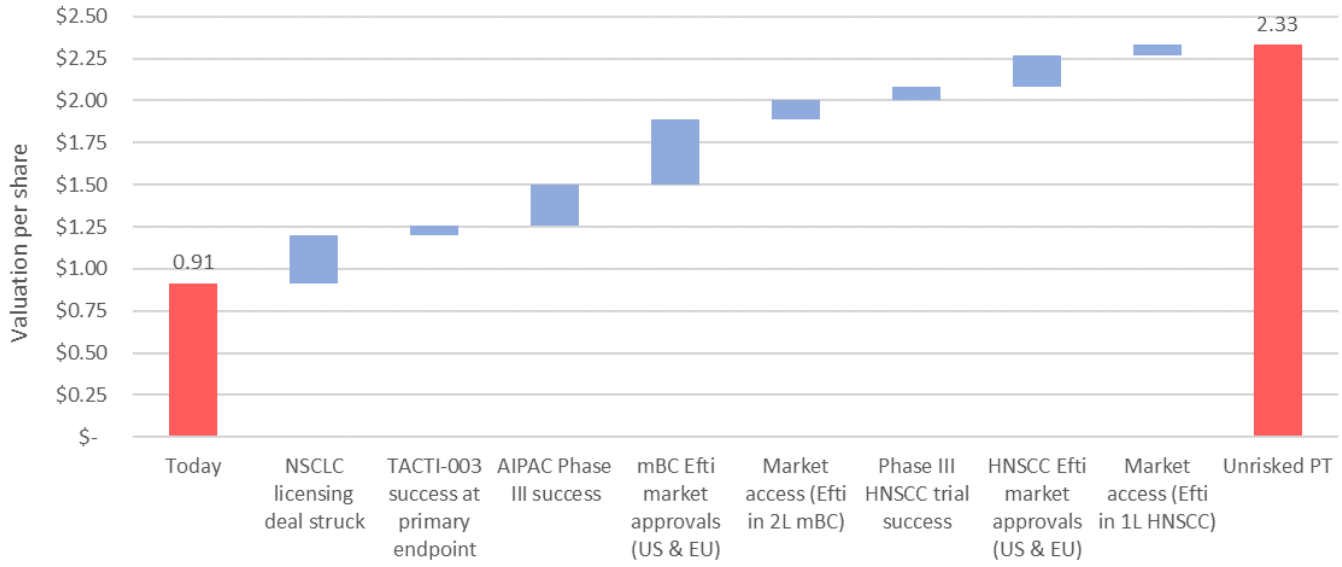
Figure 8 below outlines the bridge between our risked and unrisked price targets based on achievement of clinical and development milestones for Immutep across the three indications of interest (mBC, HNSCC, NSCLC).

Figure 7. Relative contributions of each Efti program when we de-risk each program to achieve our unrisked $2.33 per share price target



Source: Wilsons

Figure 8. Waterfall with de-risking events to our unrisked $2.33 PT.



Source: Wilsons.

M&A modelling valuation

Here we look to provide a valuation of Immutep based on a potential strategic acquisition by a large pharma with an established presence in the oncology space. We assess an attractive proposition based on our current risked valuation ($0.91 per share; Enterprise value = $724M).

We look to recent deals within the IO space by large oncology players to support what a potential IMM takeout could be valued at (**Table 4** overleaf). We assess >$2B is not an unreasonable expectation when evaluating recent deals with clinical pipelines akin to Immutep's.

Efti the key asset driving acquisition. Immutep lack the infrastructure and means to commercialise Efti alone in the highly competitive oncology marketplace. Partnering on the basis of the Efti asset we assess as the most likely outcome for Immutep to optimise commercial outcomes for this drug across a range of indications. Successful pivotal stage evidence development, approval and commercial launch requires a large dominant oncology player to leverage its expertise, sales channels and market positioning.

Potential acquirers. Given the extensive clinical work that has been undertaken with MSD's pembrolizumab, we assess they are a natural potential acquirer, however noting that MSD do have another LAG-3 asset under development, albeit an anti-LAG-3 mAb. The existing clinical data supporting this asset does not crossover with the Efti/pembrolizumab clinical program indications (HNSCC, NSCLC). Efti could be a great fit for MSD looking to extend their pembrolizumab franchise patent term.

Timing of an acquisition. We appreciate that a likely acquirer would want to see further data in larger patient cohorts to support Efti in key indications (i.e. TACTI-003 or TACTI-002 expanded Part A). We assess an acquisition may likely be timed prior to the final Phase III AIPAC readout, potentially after TACTI-003 first interim data readout (~2H CY22 to early CY23).

Recent M&A examples within the oncology space; supports >$2B takeout valuation. In **Table 4** overleaf we summarise selected deals within the IO and autoimmune space in the past 2- 3years that are relevant when thinking about the potential future acquisition value of Immutep. We note the recent Amgen acquisition of Five Prime Therapeutics (NASDAQ:FPRX) as an interesting predicate given the similarity in terms of assets, partnership with other pharma (Opdivo combo trials) and pipeline progression, noting that Efti is further developed than Five Prime given it is heading into a Phase III study and therefore further value could be attributed to an Immutep takeover valuation.

Based on the deals noted in **Table 4**, we see a range of $2B to $3B as a potential acquisition transaction value for Immutep given their pipeline and development stage. This range reflects the potential timing differences and level of progression of their clinical programs (including IND-readiness of IMP761) at the time of possible acquisition.

Table 4. Selected recent (2018-2021) transactions within oncology & autoimmune space

Acquired target	Buyer	Date	Transaction value (A$)^	Deal notes	Clinical phase of lead asset/s at time of deal
Trillium Therapeutics (NASDAQ:TRIL)	**Pfizer** (NYSE:PFE)	23 Aug 2021	$2.92B* announced not closed	Clinical stage immuno-oncology company with two lead assets TTI-662 and TTI-661; both IgG fusion proteins that block CD47 signalling, in Phase I trials for a range of advanced cancers.	Phase I
Five Prime Therapeutics (NASDAQ:FPRX)	**Amgen** (NASDAQ:AMGN)	4 Mar 2021	$2.49B	Clinical stage biopharma focused on immuno-oncology and targeted cancer therapies. It has 3 clinical stage assets including FPT155, a soluble CD80 fusion protein that enhances T cell stimulation in Phase I for solid tumours (similar to Efti) and an anti-T-cell antibody in Phase I/II with Opdivo in advanced malignant tumours. Their preclinical pipeline also includes an anti-CCR8 depleting antibody that target CCR8 expressing T cells for use in solid tumours. They have licensing and collaboration agreements with BMS among others.	Phase I/II
NBE Therapeutics (Private)	**Boehringer Ingelheim** (Private)	10 Dec 2020	$1.9B* announced not closed	Clinical stage biopharma focused on development of antibody-drug-conjugates in oncology space. NBE-002 lead candidate (anti-ROR1 ADC) in first in human Phase I/II in advanced solid tumours.	Phase I/II
Immunomedics (NASDAQ:IMMU)	**Gilead Sciences** (NASDAQ:GILD)	13 Sept 2020	$28.7B	Clinical stage biopharma focused on monoclonal antibody drugs (mAbs) to treat cancer. Deal focused on sacituzumab govitecan (new mAb in breast cancer). Have an ongoing collaboration between with Roche using atezolizumab in mBC. See **Section A2.3** for more info.	Phase IIb
OncoImmune (Private)	**MSD** (NYSE: MRK)	23 Nov 2020	$581M	Clinical-stage company involved in development of biopharmaceuticals for the treatment of cancer and autoimmune disease. Three key assets under development including ONC-392 (anti-CTLA4 mAb) currently in Phase I for NSCLC and solid tumours (in combo with pembrolizumab).	Phase I
VelosBio (Private)	**MSD** (NYSE: MRK)	5 Nov 2020	$3.71B	Clinical stage biopharma developing portfolio of antibody-drug-conjugates (ADCs) focused on haematological cancers and solid tumours. VLS-101 is their lead asset (targeting ROR1) currently in Phase I and Phase II studies for hematologic cancers and solid tumours.	Phase II
Forty Seven (NASDAQ:FTSV)	**Gilead Sciences** (NASDAQ:GILD)	2 Mar 2020	$7.59B	Clinical stage biopharma with several key assets. Magrolimab is lead (anti-CD47 mAb) current in Phase Ib/II oncology trials. Existing agreement with Genentech for clinical trial in Non-Hodgkin's Lymphoma plus other collaborations focused on IO triple combination approaches.	Phase III ready
Sythorx (NASDAQ:THOR)	**Sanofi** (NYSE:SNY)	9 Dec 2019	$3.6B	Clinical stage biopharma focused on modulation of Synthorin (a cytokine) in oncology and autoimmune indications. THOR-707 lead candidate in solid tumour studies in combo with an ICI; also in autoimmune indication studies.	Phase II
Peloton Therapeutics (Private)	**MSD** (NYSE: MRK)	21 May 2019	$3.2B	Clinical stage biopharma with two key assets. Lead asset PT2977 (anti-HIF2a inhibitor) is oncology focused and is in phase IIs for metastatic renal cell carcinoma (several programs), and glioblastoma multiforme.	Phase II
Potenza Therapeutics (Private)	**Astellas Pharma** (TSE:4503)	14 Dec 2018	$564M	Immuno-oncology focused biopharma with anti-TIGIT mAb as lead asset (2 other novel assets). Had been strategic collaboration with acquirer since 2015 to develop these assets prior to takeover.	IND/Phase I
Tesaro (NASDAQ:TSRO)	**GSK** (LSE/NYSE:GSK)	3 Dec 2018	$7.42B	Oncology pathway focused biopharma; with two approved products (rolapitant, niraparib) plus three IO mAb candidates in Phase I trials including TSR-033 (anti LAG-3 mAb). Tesaro has numerous license and collaboration agreements with other Pharma including Janssen, MSD, Genentech and several Chinese pharma players.	Approved products plus Phase I pipeline
Endocyte (NASDAQ:ECYT)	**Novartis** (NYSE:NVS)	18 Oct 2018	$2.95B	Developer of small molecule drug conjugates with associated imaging agents (theranostics focus). Most progressed asset, vintafolide, in Phase IIb in NSCLC. >3 other pipeline assets in Phase I trials.	Phase IIb
ARMO Biosciences (NASDAQ:ARMO)	**Eli Lilly** (NYSE:LLY)	10 May 2018	$2.17B	Clinical stage immuno-oncology company. Lead asset (AM0010) is a form of the immune growth factor IL-10 focused in NSCLC initially. Four other related assets in pipeline.	Phase II
Viralytics (ASX:VLA)	**MSD** (NYSE:MRK)	21 Feb 2018	$502M	Clinical stage cancer vaccine company with lead asset CAVATAK, an oncolytic immunotherapy. Asset in Phase I and II trials in combination with pembrolizumab. Existing collaboration agreement with MSD since 2015 investigating melanoma, lung and bladder cancers.	Phase II
Ablynx NV (NASDAQ:ABLX)	**Sanofi** (NYSE:SNY)	29 Jan 2018	$5.9B	Late stage clinical biopharma with broad focus (including oncology and inflammation). Large range of assets in development including in autoimmune conditions using their nanobody technology. Large number of collaborations with pharma for development of their pipeline assets.	Completed Phase III. Other assets in Phase IIb.
MEDIAN			**$2.95B**		
AVERAGE			**$4.95B***	***skewed by Immunomedics deal. Ex-Immunomedics average $3.25B.**	

^The total transaction value given represents the approx. total cash consideration for acquisition of each target. In some cases this value represents upfront payment + conditional milestone payments.

Source: S&P Capital IQ, Wilsons.

Valuation sensitivities

We have modelled key sensitivities to our valuation which are summarised in **Table 5** below.

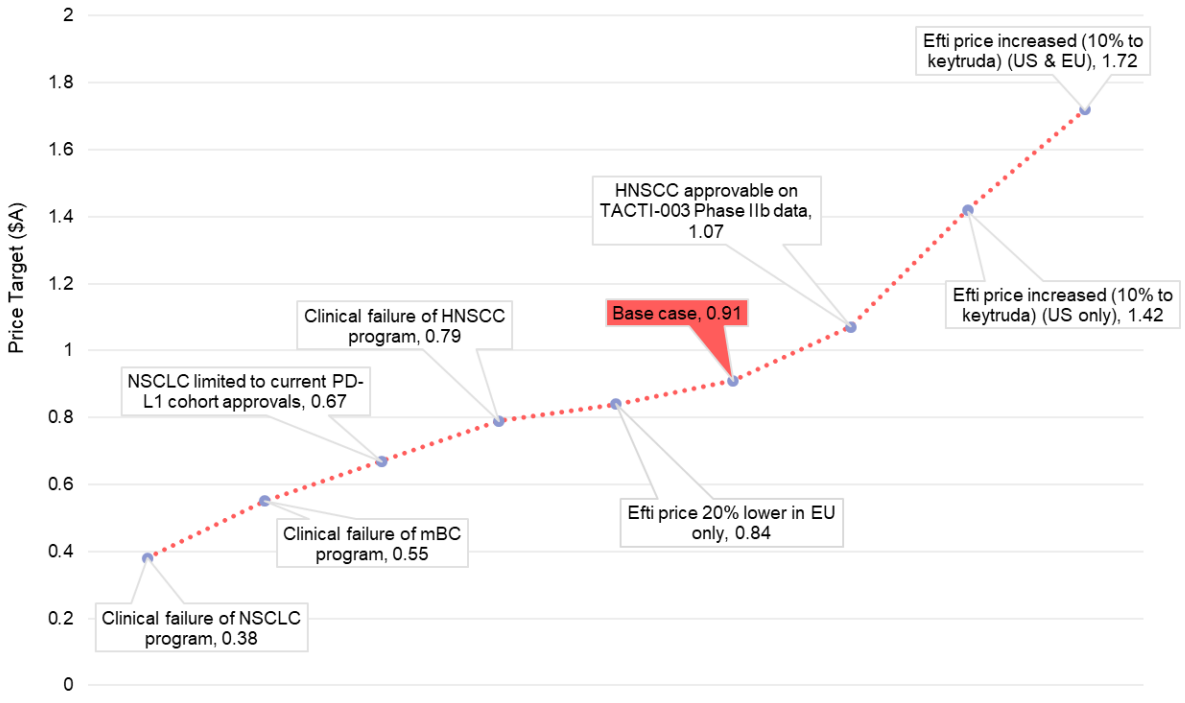
Key sensitivities relate to: a) the net pricing of Efti per dose across indications, b) the ability to progress Efti in HNSCC to a BLA based on TACTI-003 Phase IIb data alone; and c) clinical failure of any of the key programs.

Table 5. Drivers of valuation sensitivity

Sensitivity	Assumption *(deviation from base case)*	ΔPT	Revised PT
Market penetration			
Efti pricing	Increased pricing representing ~10% discount to current Keytruda pricing in US market (US$9,000 per dose vs base assumption of US$5,000 per dose in US). EU5 ASP assumption unchanged at US$3,000 per dose.	+56%	$1.42
	Increased pricing representing ~10% discount to current Keytruda across US and EU5. (EU5 pricing increased to US$5,400 per dose from US$3,000 gross price).	+89%	$1.72
	20% lower Efti pricing in EU5 markets, reflecting potential challenges with payer support and reimbursement in this market for IO drugs. (US$2,400 per dose). US remains base.	-8%	$0.84
Indication limited in NSCLC	Addressable market in NSCLC restricted to PD-L1 cohorts amendable to current approved pembrolizumab monotherapy (≥1% CPS in US; ≥50% TPS in EU5). Not an all-comers approach as per the efficacy seen with Efti thus far in TACTI-002 program.	-26%	$0.67
R&D timelines and spend in HNSCC	TACTI-003 Phase IIb is adequate to support BLA. No Phase III required as in base case modelling. Brings forward approval ~3 years with first revenues FY25e.	+18%	$1.07
Clinical failure of key programs	Failure of HNSCC program (i.e. TACTI-003 Phase IIb misses primary endpoint)	-13%	$0.79
	Failure of mBC program (i.e. AIPAC Phase III misses primary endpoint)	-40%	$0.55
	Failure of NSCLC program (i.e. future royalty and milestone revenues removed)	-58%	$0.38

Source: Wilsons.

Figure 9. Valuation range based on sensitivity analysis in Table 5.



Source: Wilsons.

Upside risk to Efti pricing. We assess upside risk to our revenue forecasts for Efti based on higher net pricing, which we currently forecast at a conservative ~50% discount to current estimated Keytruda net pricing. Based on the premise of pricing at a slight discount (i.e. 10%) to Keytruda or Opdivo we see significant upside to our valuation (+56%-89%). We maintain our conservatism regarding pricing in our base case scenario to accommodate for reductions in peer pricing by the time of Efti market entry. A test case for further reduced pricing in Europe (20% lower than our base case) highlights it has modest impact to our valuation (-8%). This we would expect to be the worst-case scenario in Europe with regards to Efti pricing should payer and reimbursement appetite be low to support IO-IO combo therapies.

Fast track designation status in mHNSCC could support valuation upside. We model a conservative scenario in HNSCC where the current Phase IIb trial (TACTI-003) is successful and supports a follow-on registration Phase III trial (ending mid CY26e). Immutep have already been granted Fast Track designation by the FDA for Efti in this indication, which is given to programs the regulator is keen to aid in progressing given the dire unmet clinical need. There is a scenario in which quality data from the TACTI-003 trial (end CY23e) could be adequate to support a BLA filing in FY24 (3 years earlier than our modelling). In this event significant R&D cost (>$35M) and time savings could see 18% upside to our current valuation.

Downside risk to NSCLC addressable market. We assess a 26% downside impact to valuation should Efti be restricted to the NSCLC patient cohorts in which pembrolizumab monotherapy is currently approved, and it not be a PD-L1 all-comers approach (based on the roll-on effects of this to future royalties in a licensing scenario). This scenario implies only 30% of the EU market is addressable, and 65% of US market is addressable. Based on the efficacy observed thus far with Efti in PD-L1 all comers and PD-L1 negative/refractory cohorts in TACTI-002 trial we do expect this to be a likely scenario.

Failure of any key clinical program poses significant downside risk to PT. We highlight the downside to our PT should any of the three key clinical programs with Efti (mBC, HNSCC, NSCLC) fail clinically, meaning they fail to meet primary efficacy endpoints or a significant safety concern eventuates. We highlight the downside to our SOTP PT that ranges from 13% to 58% downside depending on the program importance with regard to valuation (i.e. HNSCC<mBC<NSCLC).

Catalysts

In Table 6 below we summarise key catalysts and relevant news flow expected for Immutep and their relevant peer set over the next 12-18 months. Timing estimates provided.

Table 6. Near term catalysts and expected news flow relevant to Immutep

Date (CY)	Company	Event	Significance
10-14 Nov 2021	IMM	SITC conference	AIPAC OS final data readout for Efti + chemo combination in mBC.
26 Nov 2021	IMM	Virtual AGM	CEO presentation on year overview, future plans for CY22.
4Q21	Novartis	LAG525 melanoma trial primary completion	Primary readout data from the Phase II of LAG525 in previously treated melanoma (NCT03484923)
4Q21	Tesaro	Anti-LAG3/PD-1 combo trial readout	Initial primary readout from Tesaro/GSK trial focused on their anti-LAG-3 TSR-033 or in combo with anti-PD-1 dostarlimab in advanced cancers. (NCT03250832)
4Q21	Various	4Q21 earnings releases for listed US and EU peers	Update on market growth, competitive positioning
1Q22	IMM	Manufacturing scale up complete	We expect to see successful completed scale up of Efti manufacturing ready for supporting AIPAC-003 Phase III study.
1Q22	Novartis	LAG525 readout from TNBC trial	Primary readout noted for Phase I study of LAG525 in triple negative breast cancer. (NCT03742349)
1H22	IMM	TACTI-002 Part A update	Update on completion of recruitment of extension cohort (n=74) – if not earlier (i.e. 4Q21).
19 March 2022	**BMS**	**Relatlimab PDUFA date**	**FDA decision due on approval of BMS' anti-LAG-3 relatlimab in metastatic melanoma. This represents the first approval event for a LAG-3 targeted drug.**
1Q22	Various	1Q22 earnings for US and EU peers	Update on market growth, competitive positioning
1H22	**IMM**	**IND approval AIPAC-003 trial**	**FDA approval to start US sites of AIPAC-II Phase III registration trial in mBC. (estimated)**
9-13 April 2022	Various	AACR annual meeting	Large US oncology conference; many clinical pipeline updates expected. Key forum for IMM to share trial program updates.
1H22	**IMM**	**Readout TACTI-002 Part B**	**Updated results for Part B (PD-X refractory) NSCLC data TACTI-002**
2-7 June 2022	Various	ASCO Annual meeting	Large US oncology conference; many clinical pipeline updates expected. Key forum for IMM to share trial program updates.
1H22	IMM	INSIGHT-003 update	Expect some interim data for INSIGHT-003 triple combo trial program. (estimated)
1H22	EOC	Phase II mBC ECO trial	We could expect EOC pharma to initiate on their Phase II program of Efti in Chinese mBC patients.
1H22	IMM	TACTI-002 Part A update	Update on completion of recruitment (expected early CY22)
1H22	**IMM**	**TACTI-003 readout**	**We may expect a first interim readout from TACTI-003 in HNSCC with Efti. This may align with ASCO where IMM could look to present first data.**
2Q22	Various	2Q22 earnings releases for listed US and EU peers	Update on market growth, competitive positioning
2H22	IMM	TACTI-002 Part A update	Updated data readout for TACTI-002 Part A in 1st line NSCLC including for extension cohort.
9-13 Sept 2022	Various	ESMO Congress	Large EU oncology conference; many clinical pipeline updates expected. Key forum for IMM to share trial program updates.
3Q22	IMM	AIPAC-003 trial start	Estimated initiation of Phase III registration study of Efti in mBC.
2H22	IMM	Completion of GMP/tox studies to support IMP761	Finalised data package to support IMP761 IND approval for a Phase I first in human trial.
3Q22	Various	3Q22 earnings releases for listed US and EU peers	Update on market growth, competitive positioning
2H22	IMM	INSIGHT-005 update	Expect interim data from INSIGHT-005 trial program with bintrafusp alfa.
4Q22	IMM	IND approval for IMP761 trial	Approval to commence Phase I FIH study of IMP761 in autoimmune disease.
4Q22	Various	4Q22 earnings releases for listed US and EU peers	Update on market growth, competitive positioning

Source: Wilsons, Immutep, Company data

Forecasts

Our revenue and expense forecasts are generated from three market models for the respective cancer indications in which Immutep's key asset, Eftilagimod alpha, is being assessed:

- Metastatic Breast Cancer (mBC)
- Head and Neck Squamous Cell Carcinoma (HNSCC)
- Non-small cell lung carcinoma (NSCLC)

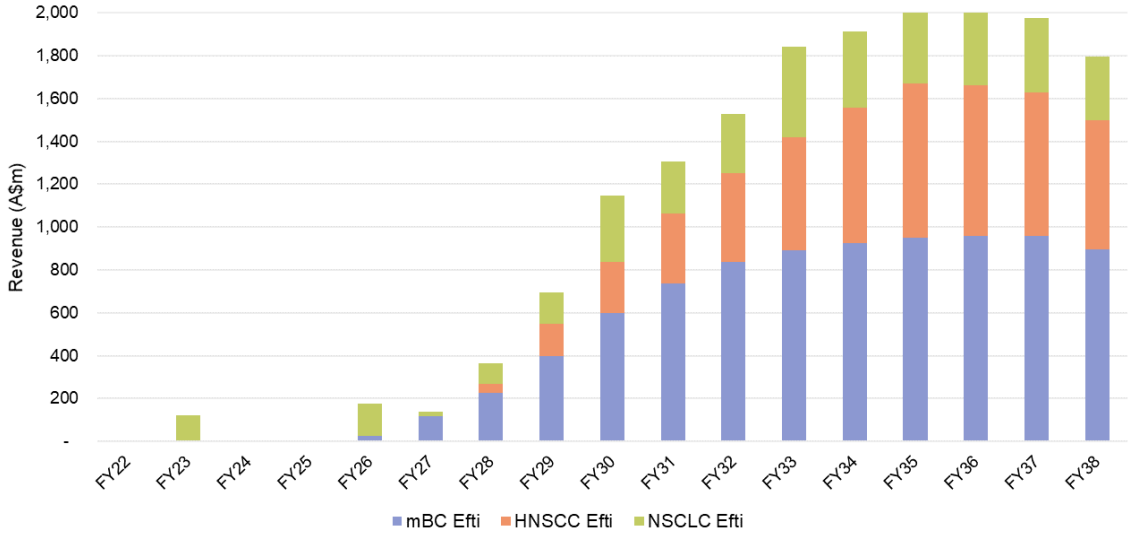
Our revenue and expense forecasts are premised on the assumption that Immutep commercialise Efti for both mBC and HNSCC (with associated expenses for R&D/commercialisation factored in) and that the NSCLC indication is out-licensed in late FY23. The revenues incorporated for NSCLC are in the form of upfront and milestone payments and royalties from their licensee (i.e. MSD as an example).

We model the potential economic value of Immutep using these assumptions but appreciate there are a number of scenarios in which this value could be realised (i.e. via their own commercialisation, via commercialisation with a partner, or via an acquisition ahead of commercialisation phase).

We do not incorporate revenue from licensing agreements that Immutep have in place given the lack of disclosure regarding the timing and value of each agreement. We summarise these in **Table 11** for reference. Further, we do not explicitly forecast sales revenues for IMP761 or any other pipeline assets.

Revenue Model

Figure 10. Efti revenue forecast split by indication



Source: Wilsons.

Table 7. Key Revenue Assumptions HR+/HER2- mBC

Efti	US	EU5
Launch year	FY26	FY26
Exclusivity period ends	FY38	FY36
Peak sales (A$)	$700M	$290M
Total addressable population	29,000	16,500
Maximum patient penetration of addressable cohort (of total $HR^+/HER2^-$ mBC patients)	42% (15%)	42% (17%)
Average net annual price/patient^ (USD)	$51,000	$35,700
TAM (A$)	$1.67B	$660M

Source: Wilsons

Table 8. Key Revenue Assumptions mHNSCC

Efti	US	EU5
Launch year	FY27	FY27
Exclusivity period ends	FY38	FY36
Peak sales (A$)	$310M	$430M
Total addressable population	11,000	22,000
Peak market share of addressable cohort (as % of total mHNSCC cohort)	33% (14%)	33% (13%)
Average net annual price/patient^ (USD)	$63,000	$44,100
TAM (A$)	$1.0B	$1.3B

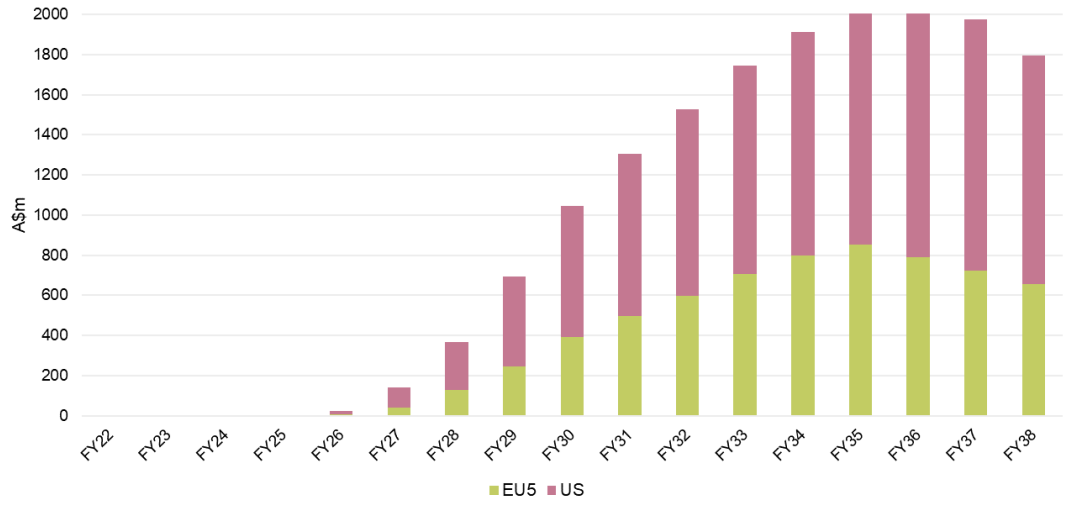
Source: Wilsons

Table 9. Key Revenue Assumptions NSCLC
(to support licensing deal outlined in Table 3)

Efti	US	EU5
Anticipated launch year	FY27	FY27
Exclusivity period ends	FY38	FY36
Peak sales (A$)	$1.95B	$1.24B
Total addressable population	67,000	64,000
Peak market share of addressable cohort (% of total NSCLC)	35% (35%)	33% (33%)
TAM (A$)	$5.6B	$3.7B
Licensing deal timing	2H23	
Upfront + milestone payments	$470M	
Royalty assumption	12%	

Source: Wilsons.

Figure 11. Efti revenue forecasts split by geographic market^



^Excludes NSCLC upfront and milestone payments (only royalty revenues)
Source: Wilsons

Biosimilars and market exclusivity for biologics. We factor in both EMA and FDA market exclusivities for newly approved biologics into our Efti market models, with the first potential approval in breast cancer setting (FY26) the starting point for market exclusivity periods.

EU: EMA new Biologics exclusivity of 8 years data exclusivity plus 2 years market exclusivity (10-year total). This is same as for new chemical entities (NCEs) in Europe.
US: FDA Biologics exclusivity guarantees 12 years of market exclusivity prior to allowing biosimilar entry.
We anticipate revenue degradation once exclusivity is lost however the magnitude of this is challenging to understand given that we have yet to see any immune checkpoint inhibitor (ICI) biosimilars enter major markets to gauge their uptake and impact to originator revenues. Ipilimumab is the first ICI vulnerable to biosimilar entry with its loss of EU exclusivity this year (2021) and US market exclusivity in 2023. See other relevant ICI expiry dates in **Table 10**. We model ~9% average annual loss in our Efti market models at the time of lost exclusivity to factor in this eventuality (~4-5 year period).

Table 10. Market exclusivity expiry dates for monoclonal antibody drugs including blockbuster ICIs.

	Europe	US
Immune checkpoint inhibitors (ICIs)		
Ipilimumab	2021	2023
Nivolumab	May 2026	June 2027
Atezolizumab	Sept 2027	May 2028
Pembrolizumab	June 2028	Nov 2036
Other blockbuster monoclonal antibodies used in oncology		
Cetuximab	June 2014	Feb 2016
Trastuzumab	Aug 2015	June 2019
Panitumumab	2018	April 2020
Pertuzumab	May 2023	June 2024

Source: Wilsons, Busse & Luftner (2019).[2]

[2] Busse A & Luftner D. 2019. What does the pipeline promise about upcoming biosimilar antibodies in oncology? *Breast Care.* 14: 10-16.

Pharma partnerships with development milestone payments and future royalty potential. In **Table 11** we summarise the existing licensing agreements and partnerships that Immutep are party to. Given the limited visibility on deal terms we do not attempt to model out milestone payments in our revenue model. In addition to the below Immutep is engaged in academic research collaborations that may provide grant income (i.e. Monash University).

Table 11. Pharmaceutical licensing agreements & collaborative partnerships of Immutep assets

Licensee	Date entered into	Asset	Exclusivity	Milestone payments (including upfront)	Commercial royalties	Terms
Novartis (CoStim)	Sept 2012	IMP701 (LAG525)	Exclusive global rights	Undisclosed	Undisclosed	CoStim funds all development costs for humanized antagonist antibodies of LAG-3.
GSK	Dec 2010	IMP731	Exclusive global rights	£64M (A$115M)	Single digit tiered	GSK funds all development costs. First milestone paid Jan 2015 (≤US$9M)
EOC Pharma	Pre 2014	Efti	Exclusive rights to Efti (EOC202) in China, HK, Macau & Taiwan	US$1M milestone paid Feb 2018. Total undisclosed.	Undisclosed	EOC Pharma funds all development of EOC202 (Efti) for Chinese markets and commercialisation. Immutep eligible for milestone and royalty payments.
Cytlimic	Jan 2019	Efti (with CYT001 in vaccine)	3 agreements	US$5M^	NA	Clinical trial collaboration, service and supply agreements to support trial programs of CYT001 vaccine program. CYT conducts and funds all trial development.
Sydys Corp.	May 2016	CVac vaccine	Exclusive global rights	Up to total of US$400M.	Undisclosed	Potential for up to US$400M in milestones and royalty payments premised on the successful clinical development of CVac. We note that Sydys Corp no longer appear active in the space and do not expect any future payments from this agreement.
LabCorp	Oct 2020	Nil. Immutep's expertise and know-how of LAG-3 to aid in development of LAG-3 diagnostics.	NA	US$125,000 upfront.	Undisclosed	Eligible for up to three milestone payments tied to the commercialisation of new drugs/indication expansion requiring a LabCorp developed IO diagnostic.
MSD	Mar 2018 Mar 2021	Efti	Partnership on TACTI-002 trial. IMM retains exclusivity. Partnership on TACTI-003 trial. IMM retains exclusivity.	NA	MSD eligible for commercial royalties.	Clinical trial collaboration and supply agreements. Immutep funds development of the programs with contribution from MSD. Exclusive global rights for Efti maintained by IMM.
Pfizer & Merck KGaA	Sept 2018	Efti	Partnership on INSIGHT-004 program with their asset avelumab.	Undisclosed.	Undisclosed.	Clinical trial collaboration and supply agreement specific to exploration of avelumab + efti combination.

^US$0.5M upfront payment made FY19.
Source: Wilsons, Immutep.

Table 12. Extended forecast snapshot (FY20a – FY30e)

	FY20a	FY21a	FY22e	FY23e	FY24e	FY25e	FY26e	FY27e	FY28e	FY29e	FY30e
Income statement											
Revenues											
Product sales	-	-	-	-	-	-	26.1	118.2	268.7	548.7	839.0
License revenue/royalties/milestones	7.5	-	-	120.0	-	-	150.0	21.4	96.8	144.9	306.9
Research material sales	0.3	0.3	0.3	0.3	0.4	0.4	0.5	-	-	-	-
Total revenue	**7.8**	**0.3**	**0.3**	**120.3**	**0.4**	**0.4**	**176.6**	**139.5**	**365.5**	**693.5**	**1,145.8**
Gross Profit	**7.8**	**0.3**	**0.3**	**120.3**	**0.3**	**0.3**	**172.6**	**121.8**	**325.2**	**611.2**	**1020.0**
Operating Expenses											
SG&A	(6.3)	(6.3)	(6.5)	(6.7)	(6.9)	(7.1)	(42.9)	(42.6)	(90.3)	(179.1)	(282.4)
R&D	(20.4)	(17.2)	(26.0)	(33.0)	(35.0)	(20.0)	(14.1)	(11.2)	(29.2)	(55.5)	(63.8)
D&A	(2.08)	(2.1)	(2.2)	(2.4)	(2.6)	(2.9)	(3.2)	(3.5)	(3.8)	(4.2)	(4.7)
EBIT	(15.1)	(19.7)	(34.4)	78.2	(44.2)	(29.6)	112.4	64.6	201.8	372.4	669.1
EBITDA underlying	**(13.0)**	**(21.8)**	**(32.2)**	**80.6**	**(41.6)**	**(26.8)**	**115.6**	**68.1**	**205.7**	**376.7**	**673.8**
Net interest expense/finance costs	0.2	0.1	0.5	0.2	0.9	0.5	0.5	1.1	1.5	2.7	5.2
Profit (Loss) before tax (EBT)	**(13.5)**	**(29.9)**	**(33.9)**	**78.4**	**(43.2)**	**(29.1)**	**112.9**	**65.7**	**203.3**	**375.2**	**674.3**
Tax (expense)/credit	(0.0)	(0.0)	-	-	-	-	(33.9)	(19.7)	(61.0)	(112.5)	(202.3)
NPAT	**(13.5)**	**(29.9)**	**(33.9)**	**78.4**	**(43.2)**	**(29.1)**	**79.0**	**46.0**	**142.3**	**262.6**	**472.0**
Condensed cash flow snapshot											
Net cash flow from operations	(10.8)	(17.6)	(34.6)	79.0	(43.7)	(29.9)	77.1	24.8	99.2	200.1	383.0
Net cash flow s from investing activities	(0.0)	(0.0)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)
Net cash flow from financing activity	20.48	52.7	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)
Cash at End of period	**26.3**	**60.6**	**25.7**	**104.4**	**60.4**	**30.2**	**107.0**	**131.5**	**230.4**	**430.3**	**813.0**

Source: Wilsons.

Investment and Expense Assumptions

Cash. Immutep had $60.6M in cash as at 30 June 2021 following two recent equity raises ($67.2M in June '21, $29.6M in Nov '20) which were noted to fund Immutep into CY23. They are currently running at a cash burn rate of ~$6M per HY, noting we expect an uptick in R&D spend. We assess Immutep are funded into late FY23e.

Balance Sheet. Immutep do not have any debt to service, with the majority of their assets captured at the intangibles line representing their drug IP, know-how and associated patent families. We do not assess a need for future capital raises in our current modelling, however this assumption is premised on a potential 2H23 licensing deal (NSCLC) in which an upfront payment (c$120M) would support continued clinical trial program efforts. FY22 and FY23 are anticipated to be high cash burn years given the significant R&D expenses that will be incurred for the TACTI-003 and AIPAC Phase III programs.

Expense assumptions include the following:

COGS and gross profit margin. We understand that Efti manufacturing following recent scale up work by Immutep is now relatively cost efficient. We assume COGS of ~15% assuming a final net ASP to Immutep of US$3,000 per dose (in US) (annual costs per indication summarised in **Table 13** below). We price Efti at a 50% discount to pembrolizumab noting that Efti is being trialled always as an adjunct to other treatments (chemotherapy, pembrolizumab etc) and therefore the value ascribed by value assessment committees is likely reduced. Further, the financial cost of an IO-IO combination treatment (such as Efti + pembrolizumab) is likely to be significant. We ensure Efti is priced at a level that does not prevent its use in such combination due to caps on treatment spending.

ASP. The gross price of current checkpoint inhibitors in the US market is ~US$100K per patient treatment course (Opdivo, Keytruda). Current pricing of pembrolizumab and nivolumab in both US and EU markets suggests a 30-40% discount to US gross pricing. Our pricing assumptions for Efti are summarised in **Table 13**.

We assume a consistent pricing of Efti per dose (30mg) across all potential approved indications. We look to price Efti at a discount (-50%) to other ICIs (i.e. pembrolizumab, nivolumab) given that Efti is being evaluated (thus far) in adjunct and is not a monotherapy and therefore cost evaluations could be lower than for some of the other approved IOs (in terms of reimbursement & payer support).

We base our "annual treatment cost" per patient assumptions for each market model on the dosing regimens employed in IMM's respective clinical trial programs; i.e. AIPAC for mBC, TACTI-002 Part A/B for NSCLC and TACTI-003 for HSNCC.

Gross to net discount. We look to MSD's published gross to net discount rates (as referenced) to inform the rebates and wholesaler/PBM discount that is taken from the gross drug price. We assume a 40% discount for the US market, and a lower 30% discount in the EU market given reduced third-party rebates.

Table 13. Efti pricing assumptions

(all USD)	US	EU5
Eftilagimod Alpha		
Price per 30mg dose (~Q2-3W)	$5000	$3000
COGS assumption (~15%)	$350	
Doses per '12 month' regimen		
mBC (per AIPAC)	~17 doses	
NSCLC (per TACTI-002)	~21 doses	
HNSCC (per TACTI-003)	~21 doses	
Gross to net discount (%)	40%	30%
Gross price per dose (WAC)	$3000	$2100
Net price per '12 month' regimen		
mBC (per AIPAC)	$51,000	$35,700
NSCLC (per TACTI-002)	$63,000	$44,100
HNSCC (per TACTI-003)	$63,000	$44,100
Keytruda reference example	**US**	**UK**
Price per Q3W dose (200mg) WAC	$10,067	$7188 (£5260)
Gross to net discount	~40% [3]	~30%
Net price per '12 month' regimen		
NSCLC/HNSCC (per TACTI-002)	$102,683	$85,750
Efti discount to Keytruda pricing	*~50%*	

Source: Wilsons, MSD.

R&D expense. Immutep's historical R&D expense has been relatively high, however is aligned with the vast number of programs they are running. They have in fact leveraged their R&D spend well given the number of investigator-led studies ongoing with Immutep assets which are funded by institutions with IMM only supplying drug product for the trial.

[3] Merck & Co. 2020. US Pricing transparency report. Accessed at: https://www.merck.com/wp-content/uploads/sites/5/2021/07/2020-US-PRICING-TRANSPARENCY-REPORT.pdf

In addition, their development partnerships of out-licensed products lessen the R&D burden on Immutep whilst still keeping future revenue (milestone, royalty revenue) optionality.

Immutep currently expense 100% of their R&D with no portion capitalised. We forecast based on the assumption this R&D treatment remains consistent moving forward.

SG&A expense. Immutep have had relatively flat G&A expense (~$3M per HY) since ~2018. We do not see a reason for material increases in G&A spend in the next 3-4 year period given the clinical development stage of their drug assets. We note there has been no sales and marketing expense to date given their lack of approved drug products.

In outer forecast years we look to add sales and marketing expense (FY26-) in line with relevant market approval timelines for HNSCC and mBC indications. We assume total SG&A expense as 30% of total revenues from FY26e onwards, noting that sales and marketing expense associated with Efti in NSCLC is deferred to the potential licensee in our modelling. Ultimately, we view Immutep as an acquisition asset with a low likelihood they would commercialise Efti for any indication independent of a large pharmaceutical partner.

We do not explicitly forecast any "Other" income or expenses for Immutep, noting that we classify grant income under this line item. Given the uncertainty and lack of detail regarding future grant income payments we omit this potential additional income from our forecasts.

Tax. We forecast Immutep incurring first material tax expense in 1H26e at a standard 30% corporate rate. We note the possibility of receipt of R&D tax refunds for a period of time however the R&D spend is unlikely to be incurred in Australia predominantly and therefore we do not explicitly forecast R&D refunds in our model.

Capex. Immutep is an infrastructure light business with minimal capex requirements. We do not forecast any substantive capex investments for Immutep in our forecast period.

Appendix

Appendix I: Industry and competitive positioning

A1.1 Immuno-oncology (IO) landscape

Weaponizing the body's own systems to fight cancer. Immuno-oncology is premised on treatments that are targeted toward the body's own immune system in order to fight cancer. The immune system's key role is to protect the body from foreign pathogens and insults. In certain cancers the immune system is either shut off from this function or changed in a way that it prevents the body from recognising and attacking the insult (being cancer).

IO drugs focus on stimulating or blocking different immune targets (proteins/cell types) to a) restore immune function to fight cancer cells; and/or b) block pathogenic immune signalling that is aiding the cancer in evading immune response. Typically, IO drugs are most useful in cancer types that are "immunogenic" meaning they are expressing and respond to different immune proteins or signals. This makes these tumours/cells susceptible to immune modulation. Melanoma and NSCLC are well known "immunogenic" cancer types. Other cancers, often referred to as "cold" tumours can lack immune signalling components making them less responsive to IO therapies. There are strategies underdevelopment now (i.e. oncolytic viruses) that attempt to make these "cold" tumours into immune-expressing cancers making them susceptible to IO drug effects.

The IO landscape is comprised of:

- targeted antibody therapies (including T-cell targeted checkpoint inhibitors),
- cell therapies (i.e. CAR T),
- cancer vaccines,
- oncolytic viruses,
- other immunomodulators (i.e. TLR agonists).

Immune checkpoint inhibitors

Note: Drugs that block/inhibit are target are antagonists; drugs that activate/enhance a target are agonists.

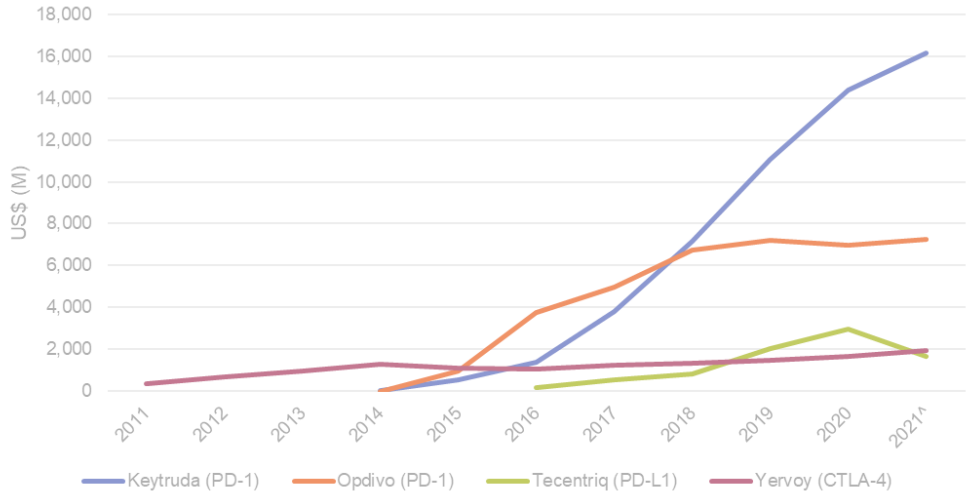
The immune checkpoint inhibitor (ICI) landscape is a busy and rapidly evolving one, with all of the major pharma players investing heavily to ensure they are receiving a part of the increasingly lucrative pie. ICI's are a relatively new drug class with the first FDA approval in 2011 of ipilimumab (BMS, anti-CTLA4) for the treatment of melanoma, and have since become standard of care in many cancer indications. Since 2011 there have been an additional 6 new ICIs approved by the FDA, targeting additional checkpoint targets, namely PD-1 and PD-L1[4].

MSD's Keytruda the dominant player. The two greatest disruptors to the oncology sector that have appeared in the last 7 years are pembrolizumab (Keytruda; MSD) and nivolumab (Opdivo, BMS), both ICIs targeting PD-1 (programmed cell death 1) alongside cemiplimab (Libtayo, Regeneron/Sanofi). Alternative checkpoint inhibitor targets include CTLA-4 targeted by ipilimumab (Yervoy, BMS) and the ligand of PD-1, PD-L1, which is targeted by atezolizumab (Tecentriq, Roche), avelumab (Bavencio, Merck/Pfizer), durvalumab (Imfinzi, AstraZeneca) and dorstarlimab (Jemperli, GSK). Pembrolizumab has thus far been approved across the greatest number of indications and continues to lead the ICI market by revenue and market share. See **Figure A1**.

Bristol Myers Squibb ahead in LAG-3 inhibitor race. Keytruda (pembrolizumab) continues to be the dominant PD-1 inhibitor in the market with latest sales figures double that of its competitor Opdivo (FY20: >US$14B vs US$7B). Keeping in mind that Opdivo is part of the newest IO-IO combination trialled by BMS in first line metastatic and unresectable melanoma with their LAG-3 antibody antagonist, relatlimab. BMS' BLA submission for relatlimab has been accepted for Priority Review by the FDA with a decision (PDUFA) date of 19th March 2022, making BMS the first potential entrant to the LAG-3 ICI market, fortifying its strong position in IO (3 potential blockbuster products).

[4] Twomey & Zhang. 2021. Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics. *AAPS Journal*. 23: 39.

Figure A1. Global sales of key approved immune checkpoint inhibitors (ICIs) since launch



^2021 figures based on annualised 1H21 reported sales.

Source: Wilsons, Roche, BMS, MSD.

Oncology players keen to keep up in LAG-3 race. Assumptions that LAG-3 is the new PD-1 and the heightened level of excitement within the oncologist community around LAG-3 as a new checkpoint target means the pipeline of LAG-3 products in development is sizable and competitive (**Table A2**). The need for MSD to compete with BMS in the IO space is a likely driver of Immutep collaborations. This rings true for other pharma also (GSK, Pfizer and Novartis), as collaborators of Immutep, wanting access to LAG-3 directed assets.

Extension of the TACTI-003 program in partnership with MSD (Keytruda + Efti) signals well for future relations with the existing market IO leader and potential for future acquisition optionality. MSD has its own anti-LAG-3 antibody in development also, favezelimab (MK-4280), which, in combination with pembrolizumab, is currently in four Phase II studies including one in 1st line NSCLC, highlighting their sizeable investment in the target.

TIGIT, the newest checkpoint inhibitor with a frenzy of deals. Alongside LAG-3 and a host of others, TIGIT stands as a potential new ICI market entrant in the near future with elevated development activity and pharma acquisitions in this space. In July we saw GSK join the TIGIT race via their collaboration with iTeos Therapeutics for their anti-TIGIT antibody asset EOS-448 [5]. The deal included a US$625M upfront payment and up to US$1.5B in milestone payments, with the asset currently in Phase I/II development. Furthermore, mid last year (May 2020) Gilead entered a 10 year collaboration agreement and took a US$200M equity stake in Arcus Biosciences (NYSE:RCUS), an IO focused biotech with three pipeline candidates including TIGIT and PD-1 assets with Phase II data in 1st line NSCLC. This deal included a $US175M upfront payment and up to US$1.2B in opt-in and milestone payments for Arcus based on advancement of these three clinical assets. We understand Gilead are keen to acquire access to a TIGIT asset to keep up with internal MSD and Roche anti-TIGIT programs.

Bi-specifics enter the IO scene. Bi-specifics are able to redirect immune cells to target tumour cells by recognizing two specific sites (one on T cells and one on cancer cells) bringing these cell types together. As such they have greater cytotoxic potential than monoclonal antibodies and can work when lower levels of antigen are present. There are currently three FDA-approved bispecific antibody drugs (two targeting oncology), the first in 2014 for Amgen's blinatumomab in B-cell leukemia and the second this year (2021) to Janssen's amivantamab in mNSCLC. There are a significant number of bispecific antibodies under development that are targeting both PD-1 and LAG-3 addressing both targets in a single drug (see **section A1.2** for more detail on these programs).

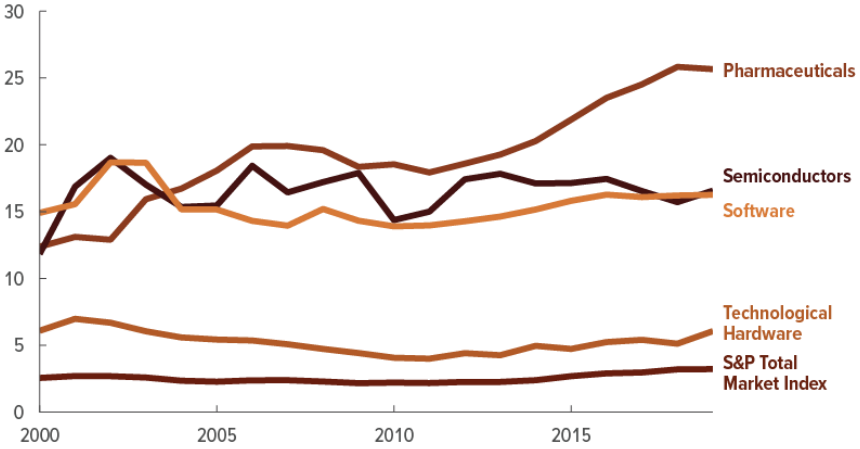
See more on bi-specifics in **section A1.2.**

[5] Mullard, A. 8 July 2021. News in Brief: Immuno-oncology target TIGIT attracts new contender. *Nature Reviews Drug Discovery*. 20: 576.

Potential bi-specific manufacturing advantages balanced with cannibalism of other blockbusters. There are advantages in manufacturing and costs of bi-specifics which may be attractive to industry however they do pose a risk of cannibalising existing single target ICIs within a drug portfolio (i.e. if a bi-specific is used instead of a drug in combination with pembrolizumab) and therefore inclusion of bi-specifics in different pharma portfolios is likely being managed to avoid this event. For instance, we note a lack of bispecific investment in MSD and BMS' portfolios, which instead are focused on further ICI monoclonal antibodies that can be used in combination with their existing PD-1 blockbusters (likely as to not cannibalise their existing portfolios). Roche on the other hand, with their lacklustre ICI Tecentriq (relative to peers), has a LAG-3/PD-1 bispecific underdevelopment.

Supported by a booming oncology industry backdrop. The level of investment in cancer therapies is at an all-time high with increased investment in a range of rarer cancer indications, compared to the classical big five (breast, lung, colorectal, prostate, gastric) that have dominated cancer R&D investment in past years. The market is supported by an increased prevalence of cancer globally, as well as a more favourable regulatory landscape (in the case of rarer cancers) where less clinical validation is required given the size and severity of the cancer population being treated. In 2020, FDA approved 53 drugs, >30% of them for cancer indications, a record level of approvals. R&D spend in pharmaceuticals in general has risen to all-time highs, with cancer, and in particularly IO responsible for this elevation which has surpassed technology and software investment levels on average (**Figure A2**).

Figure A2. Average R&D investment for publicly-traded companies (as at Jan 2020).



Source: US Congressional Budget Office as accessed at: https://www.cbo.gov/publication/57126

R&D investment in Pharmaceuticals by listed companies has averaged 19% over past 20 years, with peaks observed in 2020 of 25% on average. Cancer IO investment is a significant driver of this R&D elevation.

CAR T cell therapy

CAR T therapies struggle on the manufacturing front. There are now five FDA-approved CAR T therapies with a very busy development pipeline in the works. Thus far they are used to treat refractory, relapsed and/or high-grade myelomas and lymphomas (blood cancers) of various types with some success. Simply, CAR T therapies uses the patient's own T cells, which after modification, are reinfused to fight their own cancer as a personalised immunotherapy. The major challenge that faces CAR T is the manufacturing process and safety.

It is difficult for CAR T therapies to compete in a broader IO landscape sense perhaps given the bevy of manufacturing issues they face, which requires extraction and genetic modification of patients' white blood cells on a patient-by-patient basis. Not only is there a 2-3 week delay in preparing and multiplying the cells, there have also been notable safety issues arise in this process. There is a ~3-10% manufacturing failure rate within the industry for most CAR T therapies, meaning up to 1 in 10 patients undergo white cell collection that is lost in a production failure. These failure rates are extremely high when scored against typical pharmaceutical or medical device standards.

These manufacturing challenges are evident in Novartis' Kymriah, an approved CAR T therapy for acute lymphobastic leukemia and diffuse large B-cell lymphoma. Commercial sales of Kymriah are hampered by the fact that they are not able to charge for the therapy in many cases as it doesn't meet the required FDA-approved specifications (i.e. cell viability too low), which was shown to be 30% in some cases. Until these challenges are overcome the commercial competitiveness of CAR T within the IO landscape is limited to late lines of therapy and does not currently represent a competitive threat in first line (or even 2nd

line) settings. However, despite these challenges, CAR T-cell therapies are expected to play an important role in the IO landscape in years to come as personalised cancer medicines become an intensified R&D focus and technology improvements may support improved manufacturing capabilities/outcomes.

Cancer vaccines

Cancer vaccines, a notable competitor in adjunct IO space, albeit with limited wins thus far. The development of cancer vaccines, akin to Prima Biomed's prior lead asset, CVac, are another area of intense interest in oncology. These vaccines are being developed as adjuncts to existing SOC regimens (chemotherapy, PD-1 inhibition) just like ICIs. ASX-listed Imugene's (ASX:IMU) HER-Vaxx is an example that has shown some early promise in Phase II trials of gastric cancer patients, targeting HER-2/neu, the same target as Roche's blockbuster mAb Herceptin (trastuzumab) (US$6B sales in 2019) currently used for targeted therapy of HER2+ breast and gastric cancers.

Despite continued investment in this area however, there continues to be very few approved cancer vaccine therapies (only two). The first, Sipuleucel-T (Provenge, Dendreon) was approved by FDA in 2010 for patients with hormone resistant prostate cancer. The second approval is for a vaccine being used for treatment of invasive bladder cancer, Bacillus Calmette-Guerin (BCG), historically a tuberculosis vaccine from early 1900's, which has efficacy in a subset of high-risk bladder cancer patients. A significant supply shortage has developed however, with a bladder cancer patient requiring ~4000x the amount of vaccine as needed for tuberculosis prophylaxis. Market exits by Sanofi and smaller players along with manufacturing issues has left BCG supply shortages worldwide and subsequently its use in oncology has been limited (with undertreatment/under dosing of patients occurring and changes to SOC practice).

Oncolytic viruses

Oncolytic virus therapy; a single horse race thus far. The first and only approved oncolytic virus therapy was given the FDA nod back in 2015 for melanoma; T-VEC (Imlygic, Amgen). T-VEC is based on a modified herpes simplex virus (HSV) that enters tumour cells to destroy cells and induce anti-tumour responses. There are a multitude (30+) of other oncolytic virus platforms under clinical investigation including adenoviruses, vaccinia virus and reovirus to name a few[6]. The majority of virus candidates are now in Phase I and II trials (typically in combination with ICIs) with Phase III studies thus far focused on T-VEC. Notable pipeline candidates include Viralytic's (ASX:VLA) Cavatak, acquired by MSD mid 2020 (US$394M) being evaluated in a range of cancer types including NSCLC, melanoma, prostate and bladder.

Many shared challenges with other IO approaches; some unique. Oncolytic viruses face many of the same challenges as other IO approaches however have some unique ones also. As with other IO approaches OV's struggle to gain effective penetration of the tumour mass; face challenges with accurate tumour cell targeting but have the added problem of pre-existing immune responses (neutralizing antibodies) due to prior immunization/infection of relevant virus type[7]. Further to this there are a lack of available biomarkers to assist in patient selection for OV therapy (which is less relevant for some ICIs where target expression on the tumour (i.e. PD-1) can be used to better gauge likely response rates.

Challenges facing IO drugs, in particular Immune Checkpoint Inhibitors (ICIs)

Resistance is the case for the majority, not the few. Whilst the clinical impact of ICIs can be extreme and durable for some patients the overall proportion who experience these benefits is limited to the minority. Using PD-1 antagonists as an example (the largest of the ICI groups), responses to single agent therapy in unselected patient groups (i.e. not screened/selected based on PD-1 expression) ranges from ~40-70% across a range of cancers (e.g. melanoma). The reason for such low response rates is typically due to two things; a) primary resistance of some patients (i.e. patients lacking expression of the target checkpoint, or having an immunogenically silent tumour type) or b) via acquired resistance over time, due to a host of reasons including loss of expressed immune target and production of anti-drug antibodies (including other compensatory evasion mechanisms.

Strategies to manage primary resistance have included combination therapy (i.e. with chemo or other SOC) to enhance response as well as use of several adjunctive agents that tackle multiple immune targets

[6] Cook M & Chuahan A. 2020. Clinical Application of Oncolytic Viruses: A Systematic Review. *Int J Mol Sci.* 21 (20): 7505.
[7] Goradel et al. 2020. Oncolytic virotherapy: Challenges and solutions. Current Problems in Cancer. https://doi.org/10.1016/j.currproblcancer.2020.100639

(i.e. IO-IO combos), in addition to identification of biomarkers that can be used to better predict patient ICI response (including expression of ICI targets such as LAG-3, levels of tumour infiltrating lymphocytes (TIL) but also different genomic immune signatures such as T-Effector)[8,9].

Acquired resistance to IO key impediment to durable response. The mechanisms underlying acquired resistance are still relatively unknown, and therefore more challenging to manage than primary resistance. Some recent study data suggest that secondary/acquired resistance of ICIs is >70% in some trials/indications over a 1-5 year period[8], including where an ICI-ICI combo is used. Acquired resistance rates in some indications of interest with approved ICIs are summarised in **Table A1**.

Table A1. Acquired resistance rates for immune checkpoint inhibitors in indications of interest

Indication	ICI	Trial	Acquired resistance rate	Timeframe (median)
HNSCC	Pembrolizumab	Keynote 040	35%	8 months
		Keynote 048	54%	24 months
	Durvalumab	HAWK	44%	6 months
NSCLC	Pembrolizumab	Keynote 001	41-57%	61 months
		Keynote 042	52%	24 months
	Nivolumab	CheckMate 017, 057, 063, 003	64%	48 months
	Atezolizumab	OAK	55%	28 months

NSCLC: Non-small cell lung cancer. HNSCC: head and neck squamous cell carcinoma.
Source: Adapted from Schoenfeld & Hellmann. 2020.

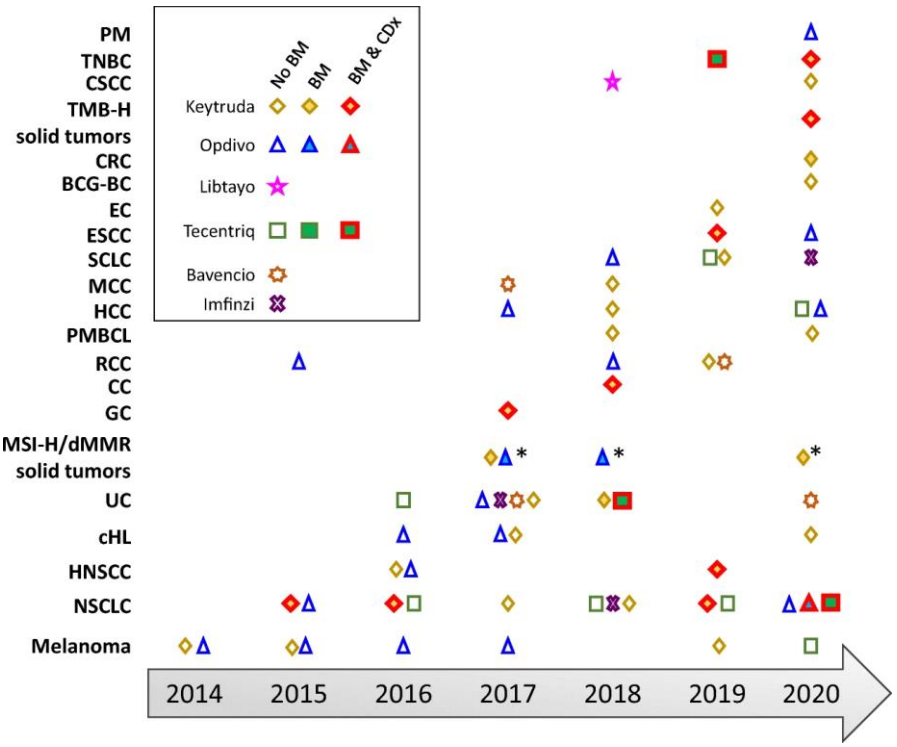
Expansion of checkpoint targets may help balance resistance. LAG-3 provides a new checkpoint target that may be effective in patients that have acquired resistance to PD-1. Theoretically, having a broader array of checkpoints that can be targeted with ICIs should assist in balancing resistance development, should patients be targeted with multiple ICIs or transition to a differently targeted ICI if they have primary and/or acquired resistance. This approach may be seen as attempting to win the battle on multiple fronts as opposed to hitting the same target endlessly and driving further resistance development. Given that ICIs are still a relatively new drug class, there is still much work to do to evaluate how to use them together and/or in a sequential paradigm to optimise long term treatment outcomes across a multitude of indications.

Alternate immune checkpoint upregulation accompanies acquired resistance. Patients with acquired resistance to PD-1 targets have shown upregulation of other immune checkpoints (including TIM3, LAG-3 and VISTA) potentially highlighting the opportunity to target these checkpoints in patients that have failed PD-1 aimed ICIs[8].

Does plethora of choice make blockbusters a thing of past? There are now eight approved ICIs which are FDA-approved for use in over 19 cancer indications, with six of the seven targeting the PD-1/PD-L1 pathway[10] (**Figure A3** overleaf). Further, the number of these ICIs being investigated in combination for a range of cancer indications expands the list further. Pembrolizumab (Keytruda) continues to dominate this space with the largest number of approved indications with nivolumab (Opdivo) a distant second. Despite the broad approvals received for these ICIs there continues to be positions for other ICIs as well as new co-targeting approaches (i.e. bi-specifics) given the nature of acquired PD-1 resistance that is known to develop over time. This provides an opportunity for new ICIs with novel targets (i.e. LAG-3), however one must expect this space to potentially become as crowded as the PD-1 ICI field with a few of the early entrants dominating the market. Safety and tolerability profiles as well as effectiveness when combined with other treatments will dictate the winners as ICI monotherapy seems reserved for only a minimal number of patients/conditions.

[8] Schoenfeld & Hellmann. 2020. Acquired Resistance to Immune Checkpoint Inhibitors. *Cancer Cell*. 37(4): 443-455.
[9] Simonaggio et al. 2021. Tumour Microenvironment Features as Predictive Biomarkers of Response to Immune Checkpoint Inhibitors (ICI) in Metastatic Clear Cell Renal Cell Carcinoma (mccRCC). *Cancers*. 13(2): 231.
[10] Twomey J & Zhang B. 2021. Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics. *The AAPS Journal*. 23: 39.

Figure A3. FDA-approved PD-1/PD-L1 targeted ICIs (as of Dec 2020).



** approval for MSI-H/dMMR colorectal cancer. PM, pleural mesothelioma; TNBC, triple-negative breast cancer; CSCC, cutaneous squamous cell carcinoma; TMB-H, tumor mutation burden high; CRC, colorectal cancer; BCG-BC, Bacillus Calmette-Guérin bladder cancer; EC, endometrial carcinoma; ESCC, esophageal squamous cell carcinoma; SCLC, small cell lung cancer; RCC, renal cell carcinoma; MCC, Merkel cell carcinoma; HCC, hepatocellular carcinoma; PMBCL, primary mediastinal large B cell lymphoma; CC, cervical cancer; GC, gastric cancer; MSI-H, microsatellite instability high; dMMR, mismatch repair-deficient; UC, urothelial carcinoma; cHL, classical Hodgkin's lymphoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer.*

Figure A3 shows the approvals for each cancer indication (left side) for each of the six approved PD-1/PD-L1 immune checkpoint inhibitors (within box inset), including whether the approval requires an accompanying biomarker (BM) or not (no BM) for patient selection, or companion diagnostic measurement (CDx), and/or both (BM & CDx).

Source: Taken from Twomey & Zhang (2021) AAPS Journal.

A1.2 LAG-3 competitive landscape

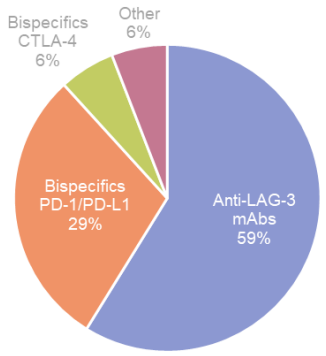
Notable players in the LAG-3 space include Bristol Myers Squibb (BMS) with their anti-LAG-3 antibody relatlimab (BLA filing expected CY21) and MSD with their anti-LAG-3 favezelimab. We note that there are 14 other assets in clinical development (Phase I-II/b stage) also focused on LAG-3 as a target (summarised in **Table A3 overleaf**).

For the most part, the LAG-3 field is focused on blocking LAG'3 role as an immune checkpoint using antagonist mAbs or bi-specifics also targeting alternative checkpoint PD-1 (**Figure A4**). When assessing the current LAG-3 pipeline all new assets are in clinical studies in combination with a PD-1/PD-L1 targeted adjunct highlighting the mounting popularity of the LAG-3/PD-1 combination strategy (in line with Immutep's TACTI program). There are 6 instances where anti-LAG-3 agents are being evaluated as a monotherapy also within the study or in combination with CTLA-4 inhibition (**Table A3**).

Bi-specifics: a new entrant. Bi-specifics, also known as poly-specific monoclonal antibodies, are antibody drugs that have two targets which they can bind simultaneously, as opposed to a singular target monospecific monoclonal antibody (i.e. pembrolizumab to PD-1 receptor). They can be used to hone T cells and cancer cells more specifically given their dual targets.

A number of anti-PD-1/LAG-3 bi-specifics are currently in clinical development which look to target both targets simultaneously (**Table A3**). These have the potential to usher in another drug class which could replace the combination use of population PD-1 ICIs such as pembrolizumab or nivolumab in a range of indications. The advantages of a combined bispecific as opposed to dual therapy with separate ICIs has not been evaluated head to head, however there are theoretical advantages and potential disadvantages of each approach. The pros and cons of bi-specifics vs single target (monospecific) mAbs is summarised in **Table A2** [11]. Developmentally, bi-specifics are sitting 12-24+ months behind monospecifics in terms of near-term Phase II trial data readouts. Given that we have seen limited evidence thus far for LAG-3 targeted monotherapy efficacy (i.e. mostly with PD-1 in HNSCC and NSCLC) it is not surprising a combination approach has caught on.

Figure A4. LAG-3 targeted assets in development by type.



Source: Wilsons, Clinicaltrials.gov.

Table A2. Pros and Cons of Bi-specific antibody drugs over monospecific antibody combination approaches

Advantages of bi-specifics over combo monospecifics	Disadvantages of bi-specifics vs combo monospecifics
Increased binding specificity given interacting with two antigen targets on the cell surface vs a single target. This may in turn reduce toxicity associated with non-specific binding.	'Fixed dose' dual target approach prevents dosing flexibility/tailoring of regimen to individual patients based on their respective immune checkpoint expression levels; or combination with a different target.
Ability to hone T cells or natural killer (NK) cells to the tumour site more specifically given dual targets.	Potential to cannibalise other ICIs in pipeline (if within same pharma portfolio).
Potential to reduce compounded toxicity/improved tolerability profile by using a single drug to modulate two targets (as opposed to the toxicity incurred by an IO-IO combo approach which is likely greater. This is yet to be shown head to head).	More challenging manufacturing requirements to produce bi-specific antibodies with typically lower yields vs monospecific antibody production.
Cost advantages to payer (single drug vs payment for two expensive ICIs). This could also favour reimbursement over IO-IO combinations when the benefit vs cost equation is considered.	Bi-specifics are typically larger molecules which can affect their accumulation/aggregation in the body. Additionally, larger molecules can have less intra-tumoural penetration.
Manufacturing and development cost advantages when compared to a combination ICI-ICI therapy.	

Source: Wilsons, Runcie et al. 2018.

[11] Runcie et al. 2018. Bi-specific and Tri-specific antibodies- the next big thing in solid tumour therapeutics. *Molecular Medicine*. 24:50.

Table A3. Other LAG-3 assets in development for oncology indications (sponsored studies)

Asset	Company	MOA	Cancer indication/s	Development stage	PD-1 combo	Trial identifier
Anti-LAG-3 antibodies						
Relatlimab (BMS-986016)	BMS	Anti-LAG-3 mAb antagonist	**Metastatic melanoma (1L)**	**BLA accepted by FDA. PDUFA date 19 Mar 2022.**	**Yes**	**NCT03470922**
			NSCLC (1L) Including metastatic	Phase IIs ongoing (2023 & 2024 ends)	Yes/No	NCT04623775 NCT04205552
			HNSCC (1L)	**Phase II ongoing (2022 top-line)**	**Yes**	**NCT04080804**
Favezelimab	MSD	Humanised anti-LAG-3 mAb antagonist	Advanced solid tumours	Phase I ongoing (Dec 2023 end)	Yes/No	NCT02720068
			Renal cell carcinoma (1L and 2L)	Phase I/II ongoing	Yes	NCT04626479 NCT04626518
			Lymphoma (1/2L)	Phase I/II ongoing (2025 top-line)	Yes	NCT03598608
			NSCLC (1L, 2L)	Phase Ib/II and II ongoing (2025 end)	Yes	NCT03516981 NCT04938817
Leramilimab (LAG525)	Novartis	Humanised anti-LAG-3 mAb antagonist	Advanced solid tumours & hematologic malignancies	Phase I/II completed Phase II completed	Yes/No	NCT02460224, NCT03365791
			Triple negative breast cancer (1L, 2L)	**Phase Ib ongoing (Early 2022 end)**	**Yes**	**NCT03742349**
				Phase II completed	Yes	NCT03499899
			Metastatic melanoma (2-4L)	**Phase II ongoing (Dec 2021 end)**	**Yes**	**NCT03484923**
Miptenalimab (BI754111)	Boehringer Ingelheim	Humanised anti-LAG-3 mAb antagonist	Solid tumours	Phase I ongoing (2022 top-line)	Yes	NCT03964233
			NSCLC, Head and Neck Neoplasms	Phase I completed	Yes	NCT03780725
			NSCLC, Neoplasms (2L, 3L)	Phase I ongoing (2022 end)	Yes	NCT03156114
Fianlimab (REGN3767)	Regeneron	Humanised anti-LAG-3 mAb antagonist	Advanced malignancies incl. lymphomas (3L)	Phase I ongoing (2024 end)	Yes	NCT03005782
		PET tracer (89Zr-DFO-REGN3767)	NA	Two Phase I/II trials ongoing investigating LAG-3 PET imaging	NA	NCT04566978, NCT04706715
INCAGN02385	Incyte	Anti-LAG-3 mAb antagonist	Advanced malignancies (2L)	Phase I/II ongoing (2023 end)	Yes	NCT04370704
TSR-033	Tesaro	Humanised anti-LAG-3 antibody antagonist	MSS^ colorectal cancer (2L)	Phase I (Dec 2021 end)	Yes/No	NCT03250832
SYM022	Symphogen	Humanised anti-LAG-3 antibody antagonist	Solid tumour malignancies and lymphomas	Phase I (Nov 2021 top line)	Yes/No	NCT03311412
			Endometrial cancer, SCLC, Urothelial cancer, Cholangiocarcinoma	Phase I recruitment paused excepting cholangiocarcinoma (2024 end)	Yes	NCT04641871
IBI110	Innovent Biologics	Humanised anti-LAG-3 mAb antagonist	Advanced malignant tumours (3+L)	Phase I ongoing (mid 2021 top-line)	Yes	NCT04085185
HLX26	Henlius	Humanised anti-LAG-3 mAb	Solid tumours and lymphomas	IND approved in China Apr 2021	Unknown	NA

Bolded studies *are those with readouts within 12-18months.*

Table A3 continued. Other LAG-3 assets in development for oncology indications (sponsored studies)

Asset	Company	MOA	Cancer indication/s	Development stage	PD-1 combo	Trial identifier
Bispecific antibodies targeting LAG-3						
RO7247669	Roche	Bispecific antibody (PD-1/ LAG-3)	Hepatocellular carcinoma (1L)	Phase Ib/II ongoing (2024 end)	No	NCT04524871
			SCC of Oesophagus	Phase II ongoing (2024 end)	No	NCT04785820
			Solid tumours, NSCLC, melanoma	Phase I ongoing (2022 end)	No	NCT04140500
Tebotelimab	MacroGenics	Bispecific antibody (PD-1/ LAG-3)	Head and Neck cancer (neoplasms + HNSCC) (2L)	Phase II ongoing (2024 end)	No	NCT04634825
			Unresectable or metastatic neoplasms (broad)	Phase I ongoing (2022 end)	No	NCT03219268
FS-118	F-star Therapeutics	Bispecific antibody (PD-L1/ LAG-3)	HNSCC (2-3L)	Phase I/II ongoing (2022 end)	No	NCT03440437
IBI323	Innovent Biologics	Bispecific antibody (PD-1/ LAG-3)	Advanced malignant tumours (3+L)	Phase I started (mid 2022 top-line)	No	NCT04916119
XmAb22841	Xencor	Bispecific antibody (CTLA-4/ LAG-3)	Advanced solid tumours (3+L)	Phase I ongoing (2024 top-line)	Yes/ No	NCT03849469
CB213	Crescendo Biologics	Bispecific antibody (PD-1/ LAG-3)	unknown	IND phase	No	NA
Other						
SNA03	MICROBIO group	Anti- LAG-3 multi-aptamer	Advanced tumours	Pre-IND phase	Yes	NA

*SCC: Squamous cell carcinoma. ^ Metastatic microsatellite stable colorectal cancer. mAb: monoclonal antibody.

Source: Company data, Clinicaltrials.gov, Wilsons.

Companion LAG-3 diagnostic imaging approach to anti-LAG-3 therapy is smart. We understand the development of LAG-3 PET tracers to aid in selection of patients appropriate for LAG-3 directed therapies is underway. Regeneron is a front runner with their 89-Zirconium labelled anti-LAG-3 mAb REGN3767 PET tracer that is being evaluated in Phase I/II studies, in parallel to their mAb therapeutic development program with REGN3767. We should see first outcomes of Regeneron's LAG-3 PET efforts in September 2022 with dosing, PK, scan timing and biodistribution of the tracer being evaluated currently in both solid tumour types and lymphomas.

Some FDA approvals require companion Dx. We keep in mind that a number of ICIs currently approved by FDA require a companion diagnostic in that indication to dictate patient selection (**Figure A3**) and therefore the theranostic strategy is a sensible one, and likely to intensify patient response when patient selection is honed to those known to express a baseline level of the target, LAG-3. Immutep has an agreement with LabCorp focused on providing their internal LAG-3 expertise to aid in the development of LAG-3 focused PET tracers and other diagnostics, however note this is less relevant for Efti given it is not an inhibitor and rather an endogenous agonist of MHC Class II signalling.

Appendix II: Eftilagimod Alpha

Eftilagimod Alpha (Efti) is Immutep's lead asset which they are progressing in three key programs in addition to out-licensing for other exploratory adjunct oncology combinations with pharma partners and supporting investigator led studies.

A2.1 LAG-3 as an important immune modulator

Lymphocyte activation gene 3 (LAG-3). LAG-3 is an important immune checkpoint within the body. Modulation of LAG-3 in various ways may have beneficial outcomes in not only cancer but also autoimmune conditions and infectious disease management. In comparison to the other well studied immune checkpoints, PD-1/PD-L1 and CTLA-4, there are still a significant number of unknowns in regards to LAG-3 and its mechanism of action despite first being discovered > 30 years ago. Its biology is much more complex in comparison to PD-1 which may explain why it is yet to be established as an approved immune checkpoint target with opportunities to better understand how best to exploit its molecular biology therapeutically[12].

LAG-3 has two distinct known mechanisms of action which may be exploited in cancer and autoimmune indications;

1. As a negative regulator of T cells
2. As an antigen presenting cell (APC) activator

1. LAG-3 can be modulated like other immune checkpoints on T-cells.

As an immune checkpoint, LAG-3 prevents activation of its host T cell, suppressing the immune response. Inhibition of LAG-3 that is expressed on T cells, i.e. via an anti-LAG-3 antagonist mAb such as relatlimab, prevents the inhibitor actions of LAG-3 on said T cell (such as reducing cytokine production) and allows T cell activation to occur which allows the body to mount an immune response to help fight cancer (akin to pembrolizumab's actions on PD-1).

Immutep's out-licensed IMP701 asset (LAG525 in partnership with Novartis) inhibits LAG-3 in this manner, on T cells, to block its ability to suppress T cell activation and subsequent immune response.

Immutep's assets, IMP731 and IMP761 both act at T cells also, however to agonise (stimulate) in the case of IMP761, or deplete the entire LAG-3 expressing T cell in the case of IMP731, which causes immunosuppression (see **Figure A5**).

2. LAG-3 activates immune response via APCs.

Major histocompatibility complex (MHC) class II molecules are found on antigen presenting cells (APCs). MHCII are the major binding partners of LAG-3. Binding of LAG-3 to MHCII molecules on APCs is able to trigger an adaptive immune response, which in a cancer indication may be beneficial in boosting the immune system to fight back against tumour cells.

Immutep's lead asset Efti acts directly on APCs to promote adaptive intra-tumoural immune responses. This approach is being investigated in various cancer indications as well as viral infections such as SAR-CoV-2 (see **Figure A5**).

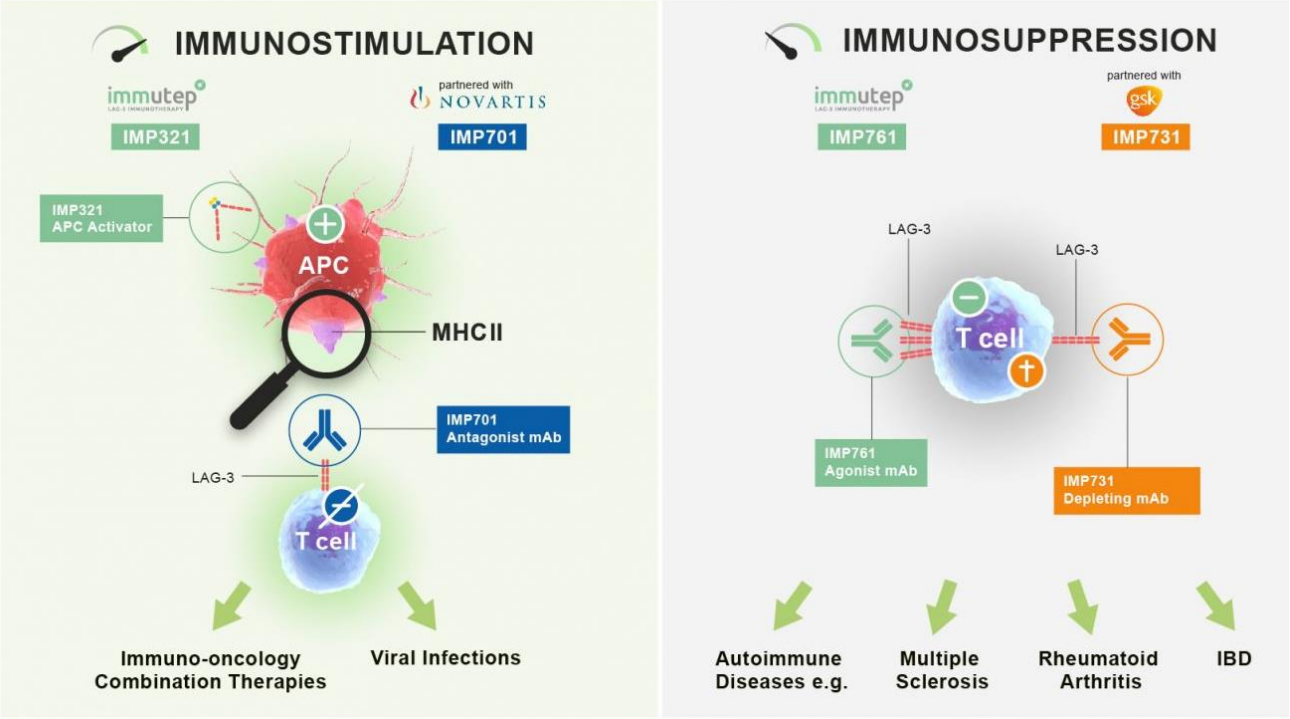
LAG-3 as a disease biomarker. LAG-3 expression and soluble LAG-3 (sLAG-3) levels are also being explored as biomarkers of disease status across a range of indications, including cancer. Soluble LAG-3 levels have been shown to be a prognostic biomarker in gastric cancer[13], as well as LAG-3 methylation potentially acting as a predictive marker for response to anti-LAG3 inhibition in melanoma[14] as examples. Furthermore, Immutep have previously shown the positive relationship between sLAG-3 expression and

[12] Graydon C, Mohideen S & Fowke K. LAG3's Enigmatic Mechanism of Action. *Front. Immunol.* 11: 615317.
[13] Li *et al.* 2018. Soluble LAG-3 acts as a potential prognostic marker of gastric cancer and its positive correlation with CD8+T cell frequency and secretion of IL-12 and INF-γ in peripheral blood. *Cancer Biomark.* 23(3): 341-351.
[14] Frohlich *et al.* 2020. Molecular, clinicopathological, and immune correlates of LAG3 promoter DNA methylation in melanoma. *EBioMedicine*. 59: 102962.

breast cancer prognosis and survival outcomes[15], highlighting that patients with high sLAG-3 levels have superior survival outcomes compared to those with low/undetectable LAG-3 expression. This further expands the relevance and visibility of LAG-3 within the oncology realm.

LAG-3 approach recently clinically validated by BMS' relatlimab. The use of a LAG-3 targeted drug to improve survival over and above PD-1 targeted IO regimes, and/or SOC, has been recently validated by the results of the BMS RELATIVITY-047 Phase II/III trial of their LAG-3 antagonist, relatlimab. Relatlimab in combination with nivolumab (anti-PD-1) showed significant synergistic benefits on PFS vs nivolumab alone (SOC) in patients with 1st line metastatic or unresectable melanoma[16]. This trial data, presented at ASCO 2021, is being used to support the first LAG-3 marketing authorisation/s currently under review by both the FDA and EMA (FDA PDUFA date 19 March 2022). Should relatlimab be successful, it would represent the first approval of drug targeting the LAG-3 checkpoint; a potential CY22 event.

Figure A5. Mechanistic action of Efti (IMP321) vs other Immutep assets (IMP761, IMP731, IMP701) in modulating LAG-3 signalling pathways



**IMP321 is another reference to Efti. IMP701 program referred to as LAG525. IMP731 program referred to as GSK2831781.*
Source: Immutep.

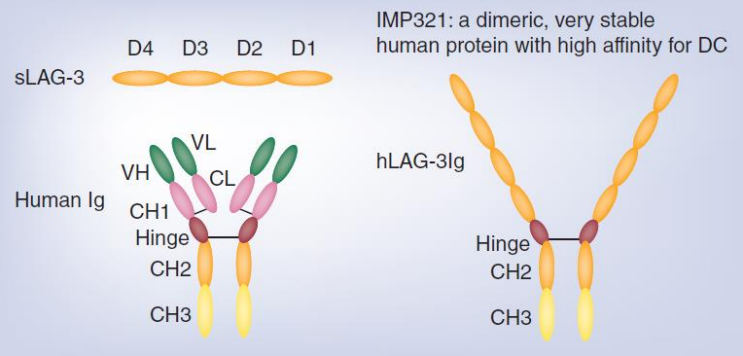
[15] Triebel F, Hacene K & Pichon M. 2006. A soluble lymphocyte activation gene-3 (sLAG-3) protein as a prognostic factor in human breast cancer expressing estrogen or progesterone receptors. *Cancer Letters*. 235(1): 147-153.
[16] Lispon *et al.* 2021. Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: Primary Phase III results from RELATIVITY-047 (CA224-047). J Clin Oncology. 39 (15). doi/abs/10.1200/JCO.2021.39.15_suppl.9503

A2.2 Efti mechanistic background: APC agonism and LAG-3 modulation

Eftilagimod alpha (Efti). Efti, also known as IMP321, is a soluble recombinant form of the LAG-3 protein, 200kDa (dimer) in size that is administered via subcutaneous injection (**Figure A6**).

Efti selectively binds a subset of immune molecules to give the immune system a 'prod', letting it do the heavy lifting. Soluble LAG-3 (Efti) has naturally high binding affinity for MHC Class II^{+} antigen presenting cells (APCs). Binding of Efti to these cells leads to an induction of the body's natural immune response (which includes stimulating T cell responses that can be beneficial in tumour rejection). Importantly, Efti has been shown to induce functional maturation of dendritic cells, a key APC type, that play a crucial role in presentation of antigens to the immune system, promoting their ability to co-stimulate T-cells.

Figure A6. Eftilagimod alpha molecule (IMP321) and its components



Source: Dirix & Triebel (2019)[17]

Low dose is best. Importantly, the response to Efti *in vivo* is optimal at low doses, and anti-tumour effects can be lost at high dose levels of the drug (due to overt inflammation or toxicity)[18]. The same dose-related response has been seen with other immune modulatory proteins acting via an MHC Class II mechanism (i.e. IL-12). In this sense, Efti can be considered as 'priming' or 'prodding' the immune system to activate and target/kill tumour cells as opposed to directly binding to an anti-tumour target to kill the cancer cell itself. This low dose requirement is beneficial from a safety and tolerability perspective but also from a financial perspective in that only small amounts of absolute protein are required (lowered COGS per dose).

Vaccine adjuvants the starting point; ICIs presented perfect partner. Cancer vaccine adjuvants are used to help vaccines work more effectively. Simply, these adjuvants are added to a vaccine to help induce and fortify an immune response to the presented vaccine antigen. Efti has been explored as a potential cancer vaccine adjuvant given its actions on immune stimulation (in Phase I/II melanoma studies[19,20]). It has also been trialled as an adjuvant to an influenza vaccine and Hepatitis B antigen in healthy volunteers displaying immune stimulatory effects[21,22]. The idea of a cancer vaccine adjuvant was the starting point for Efti (and continues to be an avenue of development) however the arrival of immunotherapies, notably checkpoint inhibitors (in 2011), presented a unique opportunity for Efti in the oncology space that was previously not available. Importantly, due to Efti's mechanism it is able to be explored in combination with a range of treatments (chemotherapy, checkpoint inhibitors, cancer vaccines) making its potential utility and applicability across indications far greater than a targeted antibody inhibitor may be.

Development and IP. Efti was developed by Immutep's CSO/CMO Dr Frederic Triebel and his team at Institut Gustave Roussy in collaboration with Merck Serono, which led the formation and spin-out out Immutep S.A. in 2001. This was following Prof Triebel's discovery of LAG-3 in 1990. Initial composition of matter patents for Efti have since lapsed (expired 2015) however Immutep holds the exclusive rights to Efti via a know-how sub-license from Merck Serono with associated undisclosed financial obligations (undisclosed by IMM).

Turning 'cold' tumours 'hot'. The ability to transform a 'cold' tumour, i.e. one that has very low immune activation or immune marker expression, into a 'hot' tumour that can be recognised by the immune system and destroyed, is a key goal of Efti. Its ability to activate APCs and reignite adaptive immune responses against the tumour antigens is evidenced by its ability to increase the numbers of cytotoxic CD8+ T cells

[17] Dirix L & Triebel F. 2019. AIPAC: a Phase IIb study of Eftilagimod alpha (IMP321 or LAG-3Ig) added weekly to paclitaxel in patients with metastatic breast cancer. *Future Oncology*. 15(17): 1963-1973.
[18] Prigent P et *al.* 1999. Lymphocyte activation gene-3 induces tumor regression and antitumor immune responses. *Eur. J Immunol.* 29: 3867-3876.
[19] Legat A et *al.* 2016. "Vaccination with LAG-3Ig (IMP321) and peptides induces specific CD4 and CD8 T-cell responses in metastatic melanoma patients—report of a phase I/IIa clinical trial." *Clinical Cancer Research.* 22(6): 1330-1340.
[20] Romano E et *al.* 2014. "MART-1 peptide vaccination plus IMP321 (LAG-3Ig fusion protein) in patients receiving autologous PBMCs after lymphodepletion: results of a Phase I trial." *Journal of translational medicine.* 12(1): 1-12.
[21] Brignone C et *al.* 2007. "IMP321 (sLAG-3) safety and T cell response potentiation using an influenza vaccine as a model antigen: a single-blind phase I study." *Vaccine.* 25 (24): 4641-4650.
[22] Brignone C et *al.* 2007. "IMP321 (sLAG-3), an immunopotentiator for T cell responses against a HBsAg antigen in healthy adults: a single blind randomised controlled phase I study." *Journal of immune based therapies and vaccines* 5(1): 1-15.

(those that attack and kill cancer cells). This was shown recently from data in the Phase IIb AIPAC study of metastatic breast cancer (see **section A2.3**).

Alternative MOA vs other IO approaches. Thus far successful checkpoint modulators have been antagonists causing direct inhibition of their immune checkpoint target (i.e. pembrolizumab, ipilimumab etc)**.** Efti represents the first antigen presenting cell (APC) activator to be explored as a potential IO candidate targeting LAG-3. As summarised previously in **section A1.2**, all other approaches to LAG-3 modulation are inhibitory in nature and targeting LAG-3 receptor expression on tumour cells. Efti does not target LAG-3 receptor expression (unlike BMS' relatlimab & others). Efti targets a complementary but distinct pathway that acts to exert immune-stimulation.

Efti avoids CRS complication; just the right level of immune stimulation. Overstimulation of the immune system in a healthy person can drive serious adverse outcomes including cytokine release syndrome (CRS) which is a serious and potentially fatal complication, which has been identified as a common toxicity associated with CAR T therapies[23]. The key to avoiding immune over-activation and the associated adverse events is the level of activation elicited. Efti only promotes low level MHC II activation given the low dose delivered which is below the threshold required to simulate an unwanted immunogenic reaction (i.e. CRS). As noted previously, high doses of Efti lost their anti-tumour effects[24]. A low dose approach is optimised to activate the immune response without having it overpower the system causing deleterious effects (i.e. inflammation etc).

In the prior trials of Efti the safety and tolerability has been favourable. In an early safety-run in phase of the AIPAC Phase IIb study, one patient was identified as having two instances of Grade 1 CRS as a serious adverse event (SAE)[25]. Subsequent to this interim analysis following further clinical evaluation, this SAE was re-defined as being a hypersensitivity reaction unrelated to Efti and not CRS. No instances of CRS have occurred in any trials with Efti treatment supporting its safety profile.

Favourable tolerability and toxicity profile. The safety and tolerability of Efti to date has been positive with local injection site reactions the most common adverse event. When compared to other ICIs (i.e. pembrolizumab, ipilimumab) we note a safety and tolerability profile that is equivalent, if not superior, that importantly does not appear to be compounded when Efti is added to pembrolizumab in an IO-IO combination (see **Tables A11 & A15**; Efti + pembro vs pembro monotherapy examples) which is a key consideration to the risk : benefit profile of a combination treatment. The low dose of Efti used is likely a contributor to this safety and tolerability profile.

[23] Santomasso *et al*. 2019. The Other side of CAR T-Cell Therapy: Cytokine Release Syndrome, Neurologic Toxicity and Financial Burden. *American Society of Clinical Oncology Educational Book*. 39: 433-444.
[24] Prigent P et *al.* 1999. Lymphocyte activation gene-3 induces tumor regression and antitumor immune responses. *Eur. J Immunol*. 29: 3867-3876.
[25] Duhoux *et al.* 2017. Combination of paclitaxel and LAG3-Ig (IMP321), a novel MHC class II agonist, as a first-line chemoimmunotherapy in patients with metastatic breast carcinoma (MBC): Interim results from the run-in phase of a placebo controlled randomised Phase II. *Journal of Clinical oncology*. 35 (15): 1062.

Table A4. Summary of clinical trials in which Efti is/has been evaluated

Trial	Phase	Asset	Adjuncts	Partner	Indication	Line of therapy	Status
AIPAC	IIb	Efti	Paclitaxel	NA	HR+HER2- metastatic breast cancer	2L, 3L	Ending CY21.
AIPAC-003	III	Efti	Paclitaxel	NA	HR+HER2- metastatic breast cancer	2L, 3L	In preparation. 1HCY22e launch
Trial name unknown	II	Efti (EOC202)	Paclitaxel	EOC Pharma (China)	HR+ metastatic breast cancer	2L	Phase II trial recruitment started 1Q21.
Trial name unknown	II	Efti (EOC202)	Anti-PD-1	EOC Pharma (China)	Advanced cancers	Undisclosed	In preparation, commence 1HCY22e.
TACTI-002 (Keynote-798)	II	Efti	Pembrolizumab (anti-PD-1)	MSD	HNSCC	2L	Ending CY23
					NSCLC	1L, 2L	Ending CY23
TACTI-003	IIb	Efti	Pembrolizumab (anti-PD-1)	MSD	HNSCC	1L	Started 2Q21
TACTI-mel	I/IIa	Efti	Pembrolizumab (anti-PD-1)	NA	Melanoma	3L +	Completed 2019
INSIGHT-001/002	I	Efti	Monotherapy (nil adjuncts)	IKF	Solid tumours amendable to direct injection	2/3L	Completed 2019
INSIGHT-003	I/IIa	Efti	Anti-PD-1 plus chemotherapy	IKF	Solid Tumours	2-3L	Started recruitment Aug 2021. First results CY22.
INSIGHT-004	I/IIa	Efti	Avelumab (anti-PD-L1)	Merck KGaA, Pfizer, IKF	Advanced solid tumours (GI primarily)	2-4L	Completed. Final results 2021.
INSIGHT-005	I/IIa	Efti	M7824 bifunctional fusion protein against PD-1 & TGF-β	Merck KGaA, GSK, IKF	Advanced solid tumours	2-4L	Announced mid CY21. First results CY22.
YNP01, YCP02, CRESCENT 1	I	Efti	CYT001 vaccine	CYTLIMIC	Advanced metastatic solid tumours	2L	Two Phase I's completed.
EAT COVID	II	Efti	Monotherapy (nil adjuncts)	Investigator initiated	COVID-19	1L	Ongoing.

Source: Immutep, Wilsons, clinicaltrials.gov.

LAG-3 provides a new avenue to fight IO resistance. Development of resistance to existing IO agents (i.e. anti-PD1s) continues to diminish the potential of these drugs to be additive to patient outcomes over the longer term. Recent IO trials have shown that >40% of patients develop resistance within 6 months of treatment in some cases (refer **Table A1**), making these drugs less useful for later stage cancers, and/or chronic treatment. The unearthing of LAG-3 as a new checkpoint target reinvigorates the IO landscape and potentially aids in treating some of these otherwise IO resistant patients that have developed anti-drug antibodies against current PD-1 targeted ICIs.

*See **section A1.2** for further notes on IO resistance.*

No anti-IMP321 (Efti) antibody development in existing studies. Antidrug antibodies can reduce drug efficacy, neutralise target binding, affect drug pharmacokinetics and in some cases induce adverse immunogenic reactions (i.e. anaphylaxis). Positively, in past studies of Efti, there has been no evidence of neutralizing antibody development[26,27]. This included the initial Phase I AIPAC study (NCT00349934) in which patients (n=30) with HR+/HER2- mBC were treated with Efti for 24 weeks with three dose ranges (0.25-6.25mg). Two patients receiving the mid (1.25mg) dose of Efti showed a 15% increase from baseline in anti-IMP321 antibodies after 6 months, however when this result was interrogated on a more sensitive assay (via MSD collaboration) levels were below detectable limits (rendering them non-relevant physiologically). No anti-IMP321 antibodies were induced via repeated Efti administration over 6 months

[26] Brignone et *al.* 2009. A Phase I Pharmocokinetic and Biological Correlative Study of IMP321, a Novel MHC Class II agonist, in patients with Advanced Renal Cell Carcinoma. *Clin Cancer Res.* 15 (19).
[27] Brignone et *al.* 2010. First-line chemoimmunotherapy in metastatic breast carcinoma: combination of paclitaxel and IMP321 (LAG-3Ig) enhances immune responses and anti-tumour activity. *Journal of Translational Medicine.* 8:71.

at the highest dose (6.25mg) in this study [17].

In a Phase I trial of metastatic renal cell carcinoma (NCT00351949) similar results were observed [16]. Of the 18 patients evaluated, there was no evidence to support induction of anti-IMP321(Efti) antibodies over a 12-week treatment period. This study included five dosing arms up to a 30mg Efti dose (n=3), which is relevant to the current AIPAC and TACTI programs underway.

The caveat to these studies being that they were ≤6 months in length and Efti exposure was limited to this relatively short timeframe. Resistance is known to develop over a longer timeframe/is progressive and is more likely with higher drug concentrations (i.e. only RCC trial went up to 30mg in a small sample set).

Samples have been taken to evaluate anti-IMP321 antibody development in both the TACTI-002 and AIPAC Phase IIb trials with longer Efti exposure periods. The results are yet to be made public however we would not anticipate any material changes given this has not be highlighted by the company. Lack of anti-drug antibody development supports the safety and potentially durable efficacy of Efti in oncology indications.

Clinical evidence to support efficacy of Efti as an adjunct IO drug

There are currently three major trial programs in which Efti is being evaluated across four oncology indications;

- Metastatic breast cancer – Chemo-Efti combo **(AIPAC)**
- Head and neck squamous cell carcinoma – IO-Efti combo **(TACTI-002, TACTI-003)**
- Non-small cell lung cancer – IO-Efti combo **(TACTI-002)**
- Non-resectable solid tumours – various combinations (IO-Efti, IO-Chemo-Efti) **(INSIGHT)**

In this section we summarise the relative indication opportunity, the existing clinical evidence to support Efti progression in each setting and the next steps in each development pathway, including timelines to potential market approvals.

A2.3 HR$^+$/HER2$^-$ metastatic breast cancer (2nd /3rd line)

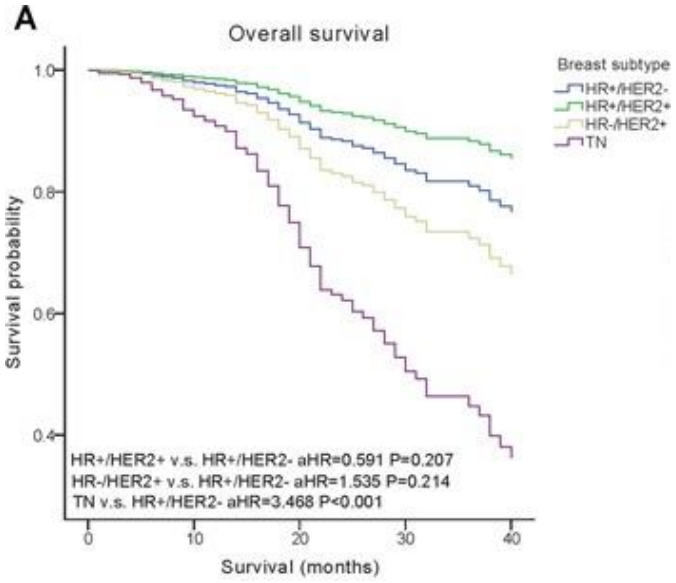
A2.3.1 HR$^+$/HER2$^-$ mBC opportunity

Breast cancer defined by HR and HER2 status to aid in elucidating best course of treatment. Hormone receptor (HR) positive, human epithelial growth factor receptor 2 (HER2) negative (HR$^+$/HER2$^-$) breast cancer is the most common subtype accounting for ~70% of all breast cancers. Each mBC subtype is associated with varied survival rates with triple negative breast cancer (TNBC) being associated with the highest mortality and HR$^+$/HER2$^+$ & HR$^+$/HER2$^-$ the lowest (**Figure A7; Table A5**).

HR$^+$/HER2$^-$ market size. The global breast cancer therapy market is ~US$20B with HR$^+$/HER2$^-$ BC accounting for >30%[28]. The US accounts for ~80% of this market. The incidence of HR$^+$/HER2$^-$ breast cancer is estimated at 66 per 100,000 in US[29] and ~84 per 100,000 in EU5 [30,31].

Development of metastatic disease. Metastatic disease is when the initial cancer cells (i.e. in a breast tumour) have spread to secondary organs or systems within the body. Most commonly these include the lungs, bones, liver and brain. Once patients progress to metastatic disease their 5-year survival rate decreases significantly (i.e. no cure) and their treatment options narrow, and typically involve more toxic widespread therapies (i.e. some chemotherapies reserved for metastatic disease). Between 5-10% of patients have metastatic disease at the time of diagnosis, with approximately 30% being initially diagnosed with Stage I-III disease that eventually progresses to metastatic (Stage IV) breast cancer over time.

Figure A7. Survival differences between breast cancer subtypes.



Source: Goldberg et al. 2021[32]

Table A5. Breast cancer subtype summary

Subtype	Estrogen receptor expression	Progesterone receptor expression	HER2 receptor expression	5-year survival rate	Age-adjusted rate of new cases per 100,000 women^
HR+/HER2+	Yes#	Yes/No	Yes	90.5%	13.4
HR+/HER2-	Yes#	Yes/No	No	94.3%	88.1
HR-/HER2+	No	No	Yes	84.0%	5.5
HR-/HER2- (Triple negative)	No	No	No	76.9%	13.1

^ Based on SEER 21 data collated from 2014-2018 as a representation of the relative incidence of each subtype.
 # There are rare cases (1-4%) where patients can be ER- and PR+ however this is not the norm (ER+/PR+, ER+/PR-).
Source: Wilsons, NIH SEER program[33].

[28] Research and Markets; 2020. HR+/HER2- breast cancer- market insights, epidemiology and forecast to 2030.
[29] NIH National Cancer Institute; Surveillance, Epidemiology, and End Results program. Interactive DataExplorer. Accessed Aug 2021.
[30] Dafni et al. 2019. Breast cancer statistics in the European Union: Incidence and Survival across European Countries. *Breast Care (Basel)*. 14(6): 344-353.
[31] Gao et al. 2012. Tumor hormone/HER2 receptor status and pharmacologic treatment of metastatic breast cancer in Western Europe. *Curr Med Res Opin*. 28(7): 1111-1118.
[32] Goldberg et al. 2021. The Immunology of Hormone Receptor Positive Breast Cancer. *Front. Immunol*. 12: 674192.

Existing SOC for HR+/HER2- metastatic breast cancer. This breast cancer subtype is known to be quite responsive to hormone (endocrine) therapy. Hormone therapy + CDK4/6 inhibitors is a typical 1st line SOC[34]. Approved therapies for HR+/HER2- mBC are summarised in **Table A6**.

1st line: Hormonal (endocrine) therapy is a typical first line response in mBC with tamoxifen and toremifene as commonly used approved choices. The anti-estrogen drug fulvestrant is also approved for postmenopausal women in this setting as a first line treatment. Aromatase inhibitors are also approved 1st line options (anastrozole, letrozole) for postmenopausal patients or for those that have failed tamoxifen.

1st line adjuncts: Targeted therapies including CDK4/6 inhibitors (palpociclib, ribociclib, abemacicilib) in combination with hormonal therapies/aromatase inhibitors are now considered the first line standard of care. mBC patients with specific mutations (i.e.BRCA or PI3KCA) are often treated with PARP inhibitors (olaparib, talazoparib) or PI3K-blockers (alpelisib) respectively.

Hormonal therapies are typically prefaced given the reduced side effects associated with them over standard chemotherapy approaches. Despite some patients receiving good progression free responses on combination hormone/CDK4/6 therapy for 2-5 years they eventually progress requiring chemotherapy.

Neoadjuvant treatment with hormonal therapy prior to surgery. Efficacy of aromatase inhibitors as a neoadjuvant in postmenopausal women prior to surgery has shown promise, however premenopausal efficacy is yet to be confirmed.

2nd line: Failure of these approaches typically leads to use of chemotherapy in ~30% of cases with paclitaxel being a common choice, which can also be coupled with antibody-drug conjugates (i.e. Trodelvy) which can help facilitate chemotherapy targeting and efficacy. Targeted mTOR therapy (everolimus) is also used in postmenopausal patients after failure of endocrine therapies (i.e. tamoxifen).

3rd line: Failure of hormonal therapies, CDK4/6 inhibitors and chemotherapy/ies leaves patients few options. Eribulin (another chemotherapy) is approved in this heavily pre-treated setting with some efficacy for these last-line patients. Immunotherapy is a target for this patient subset along with higher therapy lines (i.e. 2nd line, adjunctive 1st line)[35].

Existing standard of care falls by the wayside after patients fail chemotherapy. Despite the available approved treatments, and the success of CDK4/6 inhibitors in HR+/HER2- patients, there is no established standard of care once patients fail endocrine therapies and chemotherapy, hence the need for other options such as IO. This is where the highest clinical unmet need resides in HR+/HER2- mBC.

Table A6. Approved treatments in HR+/HER2- metastatic breast cancer

Drug	Type	Combination	Status	mBC subtype	Line of therapy	PFS Δ
Palpociclib (Pfizer)	CDK4/6 inhibitor	Aromatase inhibitor	Approved First in 2015	HR+HER2-	1st line (postmenopausal)	+10.3 months (HR=0.57, p<0.0001)
Ribociclib (Novartis)	CDK4/6 inhibitor	Fulvestrant	Approved 2017	HR+HER2-	1st line (postmenopausal women)	+7.7 months (HR 0.59, p<0.0001)
Ribociclib (Novartis)	CDK4/6 inhibitor	Aromatase inhibitor	Approved 2018	HR+HER2-	1st line (pre & perimenopausal women)	+13.7 months (HR 0.57, p<0.0001)
Abemaciclib (Eli Lilly)	CDK4/6 inhibitor	Aromatase inhibitor	Approved 2018	HR+HER2-	1st line (postmenopausal women)	+13.4 months (HR 0.54, p<0.0001)
Talozoparib (Pfizer)	PARP inhibitor	Chemotherapy	Approved 2018	BRCA-mutated HR+HER2-	2nd line +	+3 months (HR 0.54, p<0.0001)
Alpelisib (Novartis)	PI3K inhibitor	Fulvestrant	Approved 2019	HR+HER2- PIK3CA mutated	2nd line +	+5.3 months (HR 0.65, P=0.001)
Olaparib (AstraZeneca)	PARP inhibitor	Chemotherapy	Approved 2018	BRCA-mutated HR+HER2-	2nd line	+2.8months (HR 0.58, p=0.0009)

Source: FDA, Wilsons.

[33] NIH National Cancer Institute; Surveillance, Epidemiology, and End Results program. Accessed 22 Sept 2021 at: https://seer.cancer.gov/statfacts/html/breast-subtypes.html

[34] Hui et *al.* 2021. CDK4/6 inhibitor plus endocrine therapy for hormone receptor-positive, HER2-negative metastatic breast cancer: the new standard of care. *Asia Pac J Clin Oncol.* 17 (1): 3-14.

[35] Schreiber et *al.* 2021. Clinical Outcomes for patients with metastatic Breast Cancer Treated with Immunotherapy Agents in Phase I Clinical Trials. *Front. Oncol.* 11: 800.

IO monotherapy has failed to show adequate efficacy thus far & toxicity. At present, there are no approved IO, including PD-1/PD-L1 directed, therapies for the HR+/HER2- mBC population.

PD-1/PD-L1 monotherapy has failed. The response rate to PD-1/PD-L1 monotherapy has been low in past trials in this patient subset, and also restricted to those with adequate PD-L1 expression (in the case of MSD's KEYNOTE-028 Phase Ib trial of pembrolizumab[36] and Merck Serono's JAVELIN Phase Ib trial of avelumab[37]). Response rates in these populations (5-23%), regardless of PD-L1 expression, have been in the range of 5-23%[38].

Chemo-IO combinations thus far underwhelming. Similar outcomes have been seen in combinations of PD-1/PD-L1 ICIs with chemotherapy in heavily pre-treated patients. Several small Phase II trials have investigated pembrolizumab in combination with different chemotherapy regimens, with limited benefit. The combination of pembrolizumab + capecitabine chemotherapy in HR+HER2- mBC patients that had failed endocrine therapy, did not improve progression free survival (PFS) in a small (n=14) open label Phase II study when compared to historical controls[39]. Furthermore, pembrolizumab in combination with eribulin chemotherapy in 2nd and 3rd line HR+HER2- mBC patients (n=44) showed some benefits when compared to other trials of the two monotherapies alone, however the lack of control prevented statistical comparisons. A larger, recent RCT of this same pembrolizumab + eribulin combination (n=88 patients) however showed a lack of benefit (with no PFS or ORR differences).

Endocrine + CDK4/6 + anti-PD-1 triple combo halted due to toxicity. A triple combination Phase II study of nivolumab (anti-PD-1) with endocrine therapy and CDK4/6 inhibitor abemaciclib in HR+HER2- metastatic patients was recently stopped (Dec 2020) due to safety concerns with the combination's high toxicity profile.

Thus far IO drug approvals restricted to TNBC subtype with limited efficacy. There have now been two IO approvals in mBC. The anti-PD-L1 drug Tecentriq (atezolizumab) was approved in 2019 for triple negative mBC (TNBC) patients that are PD-L1 positive in combination with chemotherapy (nab-paclitaxel). This has very recently (27 Aug 2021) been withdrawn by Genentech in the US market due to it failing to meet its primary trial endpoint of Overall Survival (OS) vs taxol chemotherapy in the Impassion131 study, after being approved by the FDA last year on a surrogate PFS endpoint[40].

Last year (2020) we saw the second IO approval of pembrolizumab in the same patient setting (PD-L1 positive, TNBC) also in combination with chemotherapy, albeit a broader range (paclitaxel, nab-paclitaxel, gemcitabine + carboplatin), despite this combo showing no substantive benefit in HR+/HER2- subtype.

Chemotherapy choices within SOC relevant to AIPAC design. The AIPAC trial is premised around the combination of Efti with paclitaxel chemotherapy. At present ~13% of mBC patients are receiving paclitaxel as the first-line chemotherapy of choice in US, with it being used more commonly in Europe as a first line chemotherapy option (first line taxane)[41] alongside anthracycline-based options (i.e. doxorubicin). Capecitabine is another popular choice in the US (and EU to some extent) as first line chemotherapy after patients have failed endocrine therapy options. Within clinical trials, we have seen capecitabine, eribulin and nab-paclitaxel chemotherapy combinations all employed with IO adjuncts in this patient population. One key difference between the use of paclitaxel chemotherapy between the two major markets (EU vs US) is the dosing regimen. In Europe (and as per AIPAC design) patients are treated with paclitaxel for 6months (six 4-weekly infusions), as opposed to the US where it is typical to continue paclitaxel treatment until tumour progression (which could be > 6months).

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[36] Rugo *et al*. 2018. Safety and antitumour activity of pembrolizumab in patients with estrogen receptor-positive/Human epithelial growth factor receptor 2-negative advanced breast cancer. *Clin Cancer Res*. 24(12): 2804-2811.
[37] Dirix *et al*. 2018. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a Phase Ib JAVELIN Solid Tumour study. *Breast Cancer Res Treat*. 167(3): 671-686.
[38] Schreiber *et al*. 2021. Clinical Outcomes for patients with Metastatic Breast cancer treated with Immunotherapy Agents in Phase I Clinical trials. *Frontiers in Oncology*. 11: 640690.
[39] Shah *et al*. 2020. Phase II study of pembrolizumab and capecitabine for triple negative and hormone receptor-positive, HER2-negative endocrine-refractory metastatic breast cancer. *J Immunother Cancer*. 8(1): e000173.
[40] https://www.breastcancer.org/research-news/genentech-withdraws-breast-cancer-indication-from-tecentriq#:~:text=On%20Aug.,other%20approved%20indications%20for%20Tecentriq.
[41] Cardoso *et al*. 2020. 5th ESO-ESMO international consensus guidelines for advanced breast cancer. *Ann Oncol*. 31(12): 1623-1649.

Notable pipeline competitors in HR+HER2- mBC indication.

ADC conjugates making waves. Antibody-drug conjugates (ADCs) are as they sound; comprised of a targeted surface antigen monoclonal antibody linked chemically to a small drug molecule which is able to target and deliver the drug (aka toxic payload) to the tumour site. ADCs aim to reduce drug-induced toxicity to healthy cells and target only cancer cells with the cytotoxic drug payload. ADCs are the hottest new pipeline candidates in mHR+/HER2- breast cancer, with one particularly notable program in Phase II.

Gilead's Trodelvy (sacituzumab govitecan). Trodelvy is an ADC that targets Trop-2 receptors, a receptor expressed frequently in epithelial tumours. High Trop-2 expression has been associated with higher mortality and relapse. The Saci-IO Phase II trial (NCT04448886) is being sponsored Dana-Farber Cancer Institute in partnership with Gilead and MSD evaluating a) Gilead's Trodelvy in combination with pembrolizumab; and b) as a monotherapy in HR+/HER2- mBC. The trial is restricted to only PD-L1 positive (≥1% CPS) patients. Trodelvy has recently gained FDA approval (April 2021) as a 3rd line monotherapy treatment in mTNBC showing impressive gains in PFS and OS vs SOC chemotherapy based on the results of the recently completed Phase III ASCENT study[42].

Other notable approaches targeting old pathways better with mixed results.

New CDK4/6 inhibitor, SHR6390, due to report late CY21. The Phase Ib/II trial of SHR6390 is underway, expected to report data later this year evaluating the new CDK4/6 inhibitor in combination with SOC approaches. Of course, there are notable successes with CDK4/6 inhibitors already (including Novartis' Kisqali). The increasing success of CDK4/6 inhibitors may potentially delay or reduce the available market for IO therapies over a longer time frame, noting that 10-20% of patients [43,44] have primary resistance to current CDK4/6 therapies.

Novel endocrine therapy Elacestrant. Endocrine therapy is the current first line SOC in HR+/HER2- mBC patients. Elacestrant has showed efficacy in multiple breast cancer estrogen receptor (ER)-positive subtypes and importantly seems to show benefit in patients that are resistant to CDK4/6 inhibitors. The Phase III EMERALD trial (NCT03778931) is focused on evaluating Elacestrant monotherapy vs SOC endocrine therapy in those that have failed CDK4/6 inhibitors or for those with ER mutations making existing therapies less effective. The primary analysis is expected to be underway (2H CY21).

Oral taxane chemotherapy stumbles with FDA. The development of an oral taxane chemotherapy agent, tesetaxel, by Odonate therapeutics in mBC has been discontinued (as of March 2021) due to FDA feedback suggesting an inadequate clinical data package.

MSD's version of AIPAC limited to PD-L1 positive patients only. Merck have recently started (June 2021) their KEYNOTE-B49 trial (NCT04895358); a Phase III RCT of pembrolizumab (anti-PD-1) in combination with chemotherapy (including paclitaxel) in the same patient subset at Immutep are targeting with their AIPAC program (2nd/3rd line metastatic, chemotherapy-naïve, HR+/HER2- breast cancer). MSD, akin to IMM in AIPAC, are evaluating the synergistic benefits of an IO-Chemo combination versus SOC chemotherapy; the hypothesis being that PFS and OS will be superior with pembrolizumab added to chemotherapy in patients with PD-L1 positive tumours. Previous approaches of adding pembrolizumab to chemotherapy regimens in mBC have not fared well (see comments earlier in this section), however this would be the first program to evaluate it in combination with taxane chemotherapy (including paclitaxel).

Study inclusion is limited to patients with PD-L1 positive tumours (CPS ≥1) which is not the case in AIPAC (PD-L1 all comers). MSD have also prioritised the high PD-L1 expressing subset (CPS ≥10) PFS as the primary endpoint for the trial. This of course leaves opportunity for PD-L1 negative patients (CPS <1) which are not included in this study.

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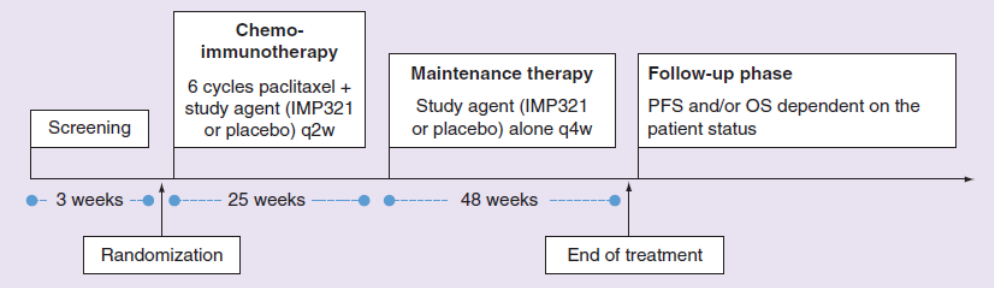
[42] Bardia et *al*. 2021. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *NEJM*. 384: 1529-1541.
[43] Hui *et al*. 2021. CDK4/6 inhibitor plus endocrine therapy for hormone receptor-positive, HER2-negative metastatic breast cancer: The new standard of care. *Asia-Pacific Journal of Clinical Oncology*. 17(S1): 3-14.
[44] Nakayama T & Fujisawa F. 2020. Therapy options after CDK4/6 inhibitors for HR+ HER2- postmenopausal metastatic/recurrent breast cancer in Japan: a role for mammalian target of rapamycin inhibitors? *Future Oncology*. 16 (24).

A2.3.2 Summary of clinical evidence: AIPAC Phase IIb trial of adjunct Efti in 2nd/3rd line HR+/HER2- mBC

AIPAC trial summary. The Active Immunotherapy PAClitaxel (AIPAC) study recruited 226 patients with metastatic HR+/HER2- breast cancer who had already failed endocrine therapy and/or other adjunctive therapy including CDK4/6 inhibitors (2L and 3L). Patients were randomised 1:1 to paclitaxel chemotherapy in combination with either Efti or placebo and were treated as summarised in **Figure A8** below. The trial is currently in the follow up phase with final overall survival (OS) data to readout in 4Q'21.

Progression free survival (PFS) was the primary endpoint with OS, safety and tolerability, duration of response and objective response rate (ORR; per RECIST 1.1) included as secondary endpoints, among others[45]. AIPAC was conducted at >30 sites across 7 European countries. The SOC arm (paclitaxel) reflects the standard EU approach in mBC cases; six 4-weekly chemotherapy cycles before being ceased.

Figure A8. AIPAC Phase IIb trial design.



Source: Dirix & Triebel (2019).

Phase IIb AIPAC data supports efficacy of Efti over SOC chemotherapy combination; however, restricted to subgroup populations. AIPAC failed to achieve its primary study endpoint; PFS (HR= 0.93, p=0.34). The Phase IIb data from AIPAC (**Table A7**) highlights that the opportunity for Efti lies in specific patient subgroups, where differences in OS and PFS were observed that were absent in the total analysis cohort. The challenge lies in understanding how important and clinically relevant these three patient subsets are and how they will be interrogated in the follow on AIPAC-II Phase III trial that is currently in preparation (estimated 1H CY22 start).

We still await complete/final OS data from AIPAC expected by end CY21 (~75% events reporting).

Study powered to show PFS endpoint however missed. The AIPAC Phase IIb study was 80% powered for the primary endpoint, progression free survival (PFS) to show a hazard ratio (HR) of at least 0.667 in favour of Efti based on a 226 patient sample size. AIPAC missed this primary endpoint with a PFS HR of 0.93 for the overall cohort with a non-significant difference versus the paclitaxel arm (p=0.34) at the time of the first interim analysis in April 2020. Subsequent data analysis of overall survival (OS) in Dec 2020 has supported its continued development, noting that the second and final OS data readout is 4Q'21.

Three subsets of AIPAC cohort identified as relevant targets for Efti adjunct where efficacy was observed in subgroup analysis:

*Refer to **Table A7** for subgroup data.*

1. Patients younger than 65 years;
2. Patients with luminal B type tumours; and
3. Patients with low monocyte levels (<25x10^9 cells/L) at treatment outset.

ORR in AIPAC control group potentially higher than historical expectations. As seen in **Figure A9,** the addition of Efti to a paclitaxel regimen increased the objective response rate (ORR) by ~10% to 48.3%. The placebo + paclitaxel ORR of 38.4% is perhaps higher than expected based on comparative historical cohort data[46] suggesting closer to 25% is the expected paclitaxel response[47]. We note however that recent trials incorporating placebo/paclitaxel arms have seen ORR thresholds in the 40-50% range.

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[45] Dirix L & Triebel F. 2019. AIPAC: a Phase IIb study of Eftilagimod alpha (IMP321 or LAG-3Ig) added weekly to paclitaxel in patients with metastatic breast cancer. *Future Oncology*. 15(17): 1963-1973.

[46] Miller et *al.* 2007. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 357(26):2666-2676.

[47] Brignone et *al.* 2010. First-line chemoimmunotherapy in metastatic breast carcinoma: combination of paclitaxel and IMP321 (LAG-3Ig) enhances immune responses and antitumor activity. *J Transl Med*. 8: 71.

Younger patients (<65) more receptive to Efti. The AIPAC sub-analysis has clearly identified that younger patients (<65 years) benefit to a greater extent that those >65 years. We observe a significant OS benefit (+7.1 months, HR 0.62, p=0.012) vs SOC chemotherapy with Efti treatment (**Table A7**), however are yet to see ORR broken out for this patient subset. The effects observed here could be explained to some degree by a host of factors associated with the aging process including: a) biological changes associated with aging in relation to DNA repair affecting malignancy potential; b) changes in how the body processes drugs from a pharmacokinetic and pharmacodynamic perspective related to liver and renal function as well as multi-drug resistance gene prevalence; and c) potential for more comorbidities[48].

~30% of mBC patients are diagnosed at >70 years of age.

Performance status (i.e. ECOG) and menopausal status we would expect to potentially have an effect on treatment outcomes, noting that a 67-year-old may have superior performance status (ECOG 0) compared to a 55-year-old (ECOG 1) which may potentially impact treatment outcomes to a greater degree than their age difference. We expect further data on these factors and sub-analyses in time from Immutep. Based on the AIPAC data at hand, we understand why this subgroup is the most commercial (and de-risked) to target in a registration Phase III trial.

Luminal subtype defined by Ki-67 immunohistochemistry. Gene expression profiling is a comprehensive way in which to identify the intrinsic subtype of a tumour. Typically, surrogate markers such as Ki67 (a nuclear marker expressed when a cell is actively replicating) alongside hormone receptors are used to classify tumours as luminal A or B via staining of the tumour biopsy (per **Figure A9**). This is a way to classify tumours by their level and pattern of proliferation. AIPAC defined luminal B status by 'high' Ki67 staining (% Ki67 level undisclosed).

It is known that Luminal B cancers are more aggressive by nature, have less favourable clinical outcomes (vs Luminal A) and are often thought to respond better to chemotherapy approaches, however this hypothesis is being tested with the advent of immunotherapies more recently. Ultimately, this cohort reflects a more challenging to treat subset and therefore superior benefit with Efti suggests a robust anti-tumoural response. Given these patients are all metastatic and many are chemotherapy experienced the additive information that luminal subtypes provide is lessened in terms of it being factored into clinical decision making (i.e. compared to a 1L Stage III patient).

Figure A9. Luminal B classification

Table 1. Proposed Surrogate IHC Markers for Classification of Luminal B Breast Cancer

Study	ER Status	PgR Status (%)	HER2 Status	Ki67 Level (%)
Blows et al[10]*	Positive	Positive	Positive	
Cheang et al[11]*	Positive	Positive	Negative	≥ 13.25
Prat et al[6]	Positive	> 20	Negative	≥ 14
Goldhirsch et al[12]*	Positive	Positive	Negative	≥ 14
Harbeck et al[13]*	Positive	Positive	Negative	≥ 20 to 25

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor.
*ER positive and/or PgR positive.

Source: Ades et al (2014)

Low monocyte levels challenging to interpret. Patients with 'low' monocyte count as defined by <25x10^{9}cells/L at baseline were the subset within AIPAC that have shown the greatest benefit of adjunct Efti. This was the only subset in which a significant PFS benefit was found (+2.3 months, HR 0.44, p=0.012; **Table A7**). Further these patients have also gained the largest OS benefit (+9.4months, HR 0.47, p=0.02). The degree of this OS benefit is substantial. The question remains, what does this subset represent in terms of an addressable clinical cohort, and why do these patients have a superior response to Efti vs those with higher monocyte counts. On a simplistic level, one could suggest that these patients had a dampened or 'weak' immune system at baseline which has benefitted more from Efti immune-stimulation versus others (i.e. ceiling effect) however this does not get to the root of the query; how does Efti via activating MHC II APCs differentially affect tumours when patients have reduced circulating monocytes?

We are yet to see a confirmed mechanistic answer to this complex question at a signalling level, however understand that Immutep are working to develop a hypothesis to explain this phenomenon. Unlocking this mystery is likely a crucial step to understanding a vulnerability of this tumour type which may be able to be exploited more effectively.

[48] Tesarova P. 2013. Breast cancer in the elderly – Should it be treated differently? *Rep Pract Oncol Radiother*. 18(1): 26-33.

Table A7. AIPAC Phase IIb trial results: Comparison of adjunct Efti vs paclitaxel chemotherapy SOC in HR+/HER2- mBC

	Efti + Paclitaxel	Placebo + Paclitaxel	Δ (Benefit)	Comments
Therapy Line	2nd			
N (ITT population)	114	112		Baseline characteristics balanced for both study treatment arms.
Median age	58y	61y		
<65 years	66.7%	63.4%		
CDK4/6 pre-treated	43.9%	42.9%		
Baseline monocyte count <0.25x10⁹/L	21.9%	19.8%		
Luminal A subtype (HR+/HER2- low Ki-67)	34.1%	36.7%		
Luminal B subtype (HR+/HER2- high Ki-67)	48.8%	49.4%		
Median PFS (BICR)	7.29 months	7.29 months	nil	Nil improvement over SOC overall.
Low monocyte subgroup	**7.5 months**	**5.2 months**	**2.3 months (+44%)**	**Significant, clinically meaningful improvement.**
Luminal B subtype	7.29 months	5.45 months	1.84 months (+34%)	Clinically meaningful improvement but not significant.
<65 years	7.2 months	5.5 months	1.7 months (+31%)	Clinically meaningful improvement but not significant.
PFS Hazard Ratio	0.93 (p=0.341)	-	7% lower risk	Non-significant benefit Missed HR target despite being powered to do so (80% powered to detect HR=0.667 with 226pts)
Low monocyte subgroup	0.44 (p=0.012)	-	39% lower risk	**Significant benefit.**
Luminal B subtype	0.65 (p=0.058)	-	35% lower risk	Non-significant benefit
<65 years	0.77 (p=0.077)	-	23% lower risk	Non-significant benefit
% progression free at 6 months	63%	54%	9% (+17%)	Non-significant benefit
DCR	85.1%	75.9%	9% (+12%)	Not significant.
Median OS	**20.2 months**	**17.5 months**	**2.7 months (+15%)**	95% CI overlap observed, awaiting updated data.
Low monocyte subgroup	**22.4 months**	**12.9 months**	**9.4 months (+73%)**	Significant benefit. Awaiting updated data.
Luminal B subtype	Not yet reported			To be reported with full data, end CY21e.
<65 years	**21.9 months**	**14.8 months**	**+7.1 months (48%)**	Significant benefit. Awaiting updated data.
OS Hazard Ratio	0.83 (p=0.14)	-	17% lower risk	Non-significant benefit.
Low monocyte subgroup	**0.47 (p=0.02)**	**-**	**53% lower risk**	**Significant improvement in OS with Efti**
Luminal B subtype	Not yet reported			
<65 years	**0.62 (p=0.012)**	**-**	**38% lower risk**	**Significant improvement in OS with Efti**
ORR	48.3%	38.4%	10% (+26%)	Non-significant increase (p=0.118).
Treatment-Emergent Adverse Events (TEAEs)				
TEAEs leading to discontinuation	5.3%	6.3%	1% (-16%)	Difference between groups immaterial.
TEAEs leading to death	1.8%	2.7%	0.9% (-33%)	Too small a sample size to note benefit.
≥1 Grade ≥3 TRAE	68.4%	65.2%	+5% in Efti group	Difference between groups immaterial.
Key TEAEs linked to Efti administration				
Injection site reaction	34.2%	3.6%	>10x increase due to Efti	Key TRAE present in Efti group absent in placebo. Mild-moderate AE.
Injection site erythema	30.7%	1.8%		
Frequent (≥10%) Grade 3 AEs				
Gamma-glutamyl transferase increase	19.3%	29.5%	30% less occurrence	
Aspartate aminotransferase increase	8.8%	10.7%	negligible	
Neutropenia	15.8%	14.3%	negligible	

Source: Wilsons, Immutep.

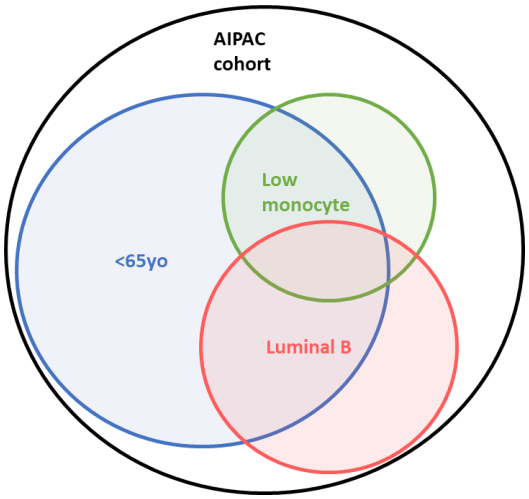
Safety profiles consistent with chemotherapy backbone. The AIPAC Phase IIb data highlights the lack of toxicity posed by the addition of Efti to paclitaxel. It is widely understood that IO therapies have a superior tolerability profile (reduced AEs) in comparison to chemotherapies (in general) and therefore the contribution of Efti to the total AE profile on a backbone of paclitaxel chemotherapy is hypothesized to be minimal; which is the case. The major AE that was frequently observed related to Efti-treatment was injection site reactions (ISRs). These occurred at a 10-fold higher rate (~30%) in patients receiving Efti vs placebo and included local site swelling, redness and pain. These events were mild to moderate in nature. The rates of treatment-related deaths and study discontinuations were largely consistent between the two groups (**Table A7**), as was the level of occurrence of more severe Grade 3 AEs.

No sign of development of Efti drug resistance. Prior studies of Efti have shown that the development of anti-Efti antibodies has been low/absent as summarised in **Section A2.2**. We note that samples were collected in the AIPAC study for this purpose however we have yet to see data published on this endpoint.

Unsure the extent to which efficacy subgroups overlap. Efficacy of Efti was seen in three subgroup HR+HER2- populations; a) those with low monocyte counts (~21% of AIPAC cohort); b) those with Luminal B type disease (~49% of AIPAC cohort) and c) those under 65 years of age (~65% of AIPAC cohort). The extent to which patients fall into one or more of these categories is currently unknown, however we understand there is overlap between these subgroups. We have attempted to visualise this overlap based on available data and interpretations thus far in **Figure A10**.

Based on this, should the Phase III trial design base inclusion criteria on an age cut-off of < 65 years there is likely a portion of low monocyte and luminal B patients that fall outside of this (% unknown) – however we understand that the 'majority' would be captured. Priority being placed on the < 65 years subset, if an all-comers approach is out of question, is both practical (from a recruitment perspective) and commercial (as it is the largest subset by patient number).

Figure A10. Our semi-quantitative interpretation of the relevant efficacy subgroups and potential overlap within the AIPAC Phase IIb cohort



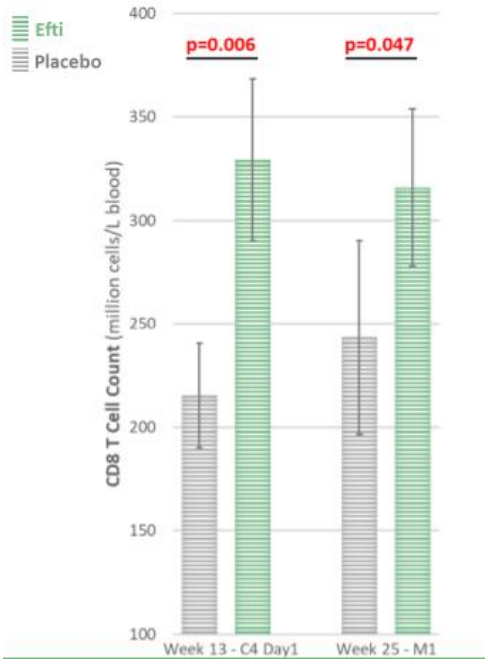
Source: Wilsons

Molecular proof of principle shown in Phase IIb AIPAC subset. A significant increase in Cytotoxic CD8+ T cells were measured in patients receiving Efti treatment vs placebo at Week 13 that was sustained out to Week 25 of Efti treatment ($p<0.05$; **Figure A11.A**). These results were obtained from a pre-defined subset of AIPAC patients from select study sites that participated in this trial sub-analysis (n=70 of the total 226 patient cohort). Additionally, Immutep have shown that this outcome was significantly positively correlated to Overall Survival (OS) in this subset population with Efti treatment ($p=0.020$). (Note: **Figure A11. B** shows n=17 for placebo and n=14 for Efti, given the OS data available for correlation at the time of analysis).

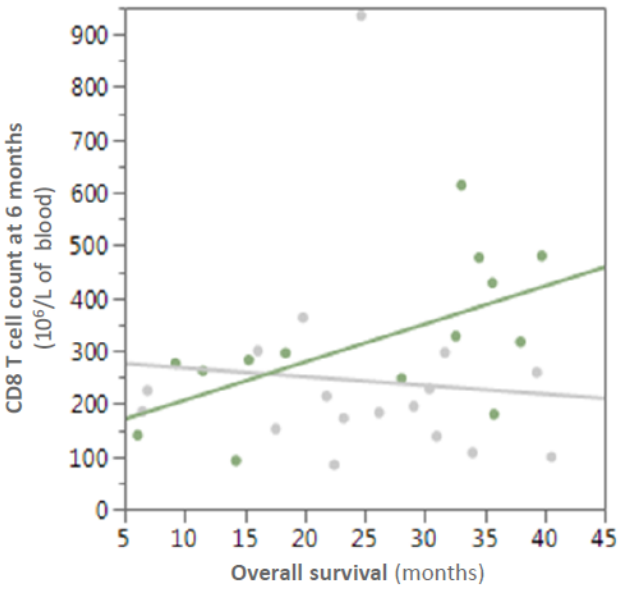
These findings highlight that Efti treatment is working in the manner intended, by activating MHC II antigen presenting cells (APCs) it is inducing immunogenicity (elevated CD8+ cytotoxic T cells) thus restoring the body's ability to fight the tumour response. This proof of principle is an important finding given that Efti is the only LAG-3 asset in oncology development thus far taking an activator approach to LAG-3 modulation (as opposed to antagonistic). This data is not expected to be collected as part of the Phase III trial, likely due to additional cost and operational considerations, however could provide valuable for further Efti development (if collected).

Figure A11. Data to support the mechanism of action of Efti from the AIPAC immune monitoring patient subset.

A. Cytotoxic CD8⁺ T cell count increases with Efti treatment



B. Correlation between OS and cytotoxic CD8⁺ T cell count (Efti; p=0.020)



Source: Immutep.

Clinical benchmarking of AIPAC results. Direct benchmarking of AIPAC Phase IIb data is challenging given the dearth of relevant comparable studies in HER⁺/HER2⁻ mBC patients at this point in time. We note MSD's Keynote-B49 Phase III of pembrolizumab + chemotherapy (including paclitaxel) and Gilead's ADC Trodelvy in Phase II have both only just started and therefore readouts will be some time yet.

We look to recent IO data in other breast cancer subtypes for indicative benchmarks (Table A8).

Table A8. Summary of select IO clinical trials in mBC

	Efti + paclitaxel	Pembrolizumab + nab-paclitaxel	Pembrolizumab + eribulin	nivolumab + paclitaxel + bevacizumab	atezolizumab + nab-paclitaxel	margetuximab + chemo	alpelisib + fulvestrant
	IO - chemo	IO - chemo	IO - chemo	IO-chemo-VEGF	IO-chemo	HER2 - chemo	PI3KA - hormone
Study	AIPAC	NCT02752685	KELLY	NEWBEAT	Impassion130	SOPHIA	SOLAR-1
Phase	IIb	II	II	II	III	III	III
Therapy Line	2/3L	2/3L	2/3L	1L	1L	2L	2L
Subtype	HR+/HER2-	HR+/HER2-	HR+/HER2-	HR+/HER2-	TNBC	HER2+	HR+/HER2-
n	114	20	44	39	451	266	115
Median age	58	56	53	49	55	55	62
Prior CDK4/6	44%	60%	48%	23%	NA	NA	6%
Median PFS	7.3 months	5.6 months	6.0 months	19.1 months	7.5 months	5.8 months	7.4 months
Median OS	20.2 months	15.7 months	not reached	not reached	21.0 months	21.6 months	39.3 months
DoR median	NR	3.9 months	4.6 months	NR	NR	6.9 months	NR
ORR	38%	25%	41%	72%	56%	25%	36%
Response criteria	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1
Adverse Events (AEs)							
Discontinuation AEs	5%	NR	14%	9%	16%	3%	25%
Grade ≥3 AEs	68%	70%	73%	58%	50%	50%	76%
AE related death	2%	0%	3%	0%	1%	1%	3%

NR = not reported.

SOLAR-1 data shown are for the HR+HER2- cohort without PIK3CA mutations; with measurable disease at baseline.

Source: Wilsons, published clinical trial manuscripts.

A2.3.3 Next steps for Efti in HR+/HER2- mBC

Final OS data reported at SITC 10-14 November. We expect an updated look at AIPAC OS data in early November hoping for a maintained and/or improved effect vs paclitaxel alone at the whole cohort level but also within relevant subgroups (notably the <65 years group). These data are key to designing the follow-on Phase III AIPAC study and to give investors' confidence in the choice of <65 years as the dominant subset for the Phase III trial inclusion criteria along with the OS endpoint. We also expect to see an update on safety and tolerability out to a longer follow-up timepoint.

Patient overlap used to guide Phase III trial design. The use of this subgroup analysis and data overlap to craft the AIPAC Phase III trial design will be extremely important to ensure study inclusion criteria and statistical planning is adequate to target patients with the greatest chance of efficacy. As a caveat to this, Immutep may choose to keep broader study inclusion criteria in the hopes of expanding the addressable population/potential label indication. In this case we would hope to see prespecified subgroups for randomisation, powered in their own right to detect effects. Recent discussions with the company suggest that they will refine the inclusion criteria by age (<65 yo) in order to optimise power with ~500 patient sample size but ensure they balance cohorts for pre-specified subgroup analysis (i.e. luminal B, low monocyte) to further evaluate efficacy differences in these populations.

AIPAC-003 Phase III registration study; age exclusion considerations. Based on the learnings from AIPAC Phase IIb Immutep are now planning a Phase III registration directed trial targeting a 1H CY22 start. This study, unlike the prior Phase IIb will include US sites and be used to support both major market submissions (EMA, FDA). We understand meetings with the respective regulators are underway (4Q'21) after an extensive clinical trial design consultation process. The challenges Immutep face will be getting agreement from the regulator concerning exclusion of patients 65 years and older (if they do in fact choose to limit inclusion to <65 years).

We keep in mind the recent (2020) FDA guidance released urging inclusion of patients ≥65 years in cancer trials given they represent a growing segment of the US cancer population and are underrepresented in clinical studies[49]. The evidence from the Phase IIb AIPAC study we expect should justify this age-based exclusion however it is unclear what initial regulator reactions have been. It appears the FDA is most focused on those over 75 years of age and has provided suggestions of discrete age subgroups for clinical studies (i.e. <65 years, 65-74 years & >75 years) given the differences in response that can be associated with age. We question whether IMM could adopt an all age design to satisfy regulator preferences with the <65 years cohort as the pre-specified primary analysis cohort. Noting this would likely increase the total sample size requirements.

Trial design is yet to be confirmed; best summary thus far We understand AIPAC-II will be targeting use of adjunctive Efti in 2nd and 3rd line clinical settings in combination with paclitaxel chemotherapy in ~460 HR+/HER2- mBC patients with the primary endpoint being OS. Patients are expected to be randomised 2:1 to Efti and placebo arms. Slight changes to the paclitaxel backbone therapy treatment duration are expected to bring it more in line with current SOC in USA (vs EU), with patients being treated with paclitaxel until disease progression, as opposed to chemotherapy stopping after 6 months (which is EU SOC). The study will incorporate EU, AUS and US trial sites (many of which were involved in AIPAC Phase IIb study). Approximately 35 sites globally are expected.

Is the trial size too small; hampered by capital availability? A proposed Phase III trial of ~460 patients is small relative to other IO agents. If we assume ~300 of these patients were to be in the Efti treatment arm, this is on the small end of what has been seen in acceptable Phase III mBC studies in the past. If we look to predicate studies; MSD's KEYNOTE-B49 Phase III of pembrolizumab + chemotherapy also in 2L/3L HR+/HER2- metastatic patients (NCT04895358) is recruiting 800 patients (1:1) with 400 patients to receive the IO-chemo combination. We will receive further detail regarding the AIPAC Phase III trial design in the coming months, however we understand Immutep's interactions with the relevant regulatory bodies are thus far supporting a ~500pt trial. We note the study is adequately statistically powered and therefore moderate our concerns regarding the sample size. We note the use of funds at the most recent June capital raise allocated $44M to fund clinical trial programs. We anticipate the majority of this to be earmarked for AIPAC Phase III.

[49] Food and Drug Administration. March 2020. Guidance Document: Inclusion of Older Adults in Cancer Clinical Trials: Draft Guidance for Industry. FDA-2019-D-5572.

Surrogate endpoints to support accelerated approval. We assess ORR as a likely choice for a surrogate approval endpoint given that PFS has thus far been a less reliable measure of OS benefit with Efti in this indication (based on AIPAC Phase IIb observations, and recent atezolizumab observations in TNBC – see below). We note the use of an ORR endpoint in several peer studies. Additionally, ORR will provide more near-term data than an OS primary endpoint which could support an accelerated marketing approval. This would be with the view that OS is the key follow up endpoint to support continued market approval.

Recent breast cancer IO withdrawal heightens awareness of this accelerated approach. The recent (August 2021) withdrawal of atezolizumab in TNBC due to failure to meet its final OS endpoint (after being approved on a surrogate PFS outcome) reminds us of the importance of a good surrogate endpoint choice. It would be our expectation that Immutep are discussing these options with experts and regulators which allows for optionality should they fail to meet a chosen surrogate endpoint allowing them to continue to a final OS outcome to support BLA submission. This would of course affect timelines to potential market access considerably if an OS endpoint was used initially to support approval (i.e. ~1.5-2yr additional delay from initial ORR/PFS data to OS data).

Scope of label that Immutep may look to achieve. The scope of a potential label for Efti in breast cancer we expect to be restricted to:

- for treatment of metastatic patients with confirmed HR+/HER2- subtype disease;
- 2nd or 3rd line therapy in combination with paclitaxel;
- for patients under 65 years of age;
- no restrictions on PD-L1 or LAG-3 expression status.

Do not see Luminal subtype or monocyte level as relevant for indication approval. We do not see the Luminal B and low monocyte subgroups identified in AIPAC as relevant cohorts that would be defined on a label given that these evaluations are not a routine part of the clinical-decision making process in some cases and do not factor into guideline treatment decisions. Additionally, we are not able to find any predicate approvals for oncology drugs that list either Luminal subtype nor monocyte levels on an approved label.

Luminal B status less impactful for decision making in Stage IV cancers. Whilst Luminal status can be helpful in aiding with clinical decision making in early stage breast cancer (I-III) this is lost to a degree when patients have progressed to Stage IV (metastasized). Luminal B subtypes are notably more aggressive type tumours. Once tumours are metastasized this information becomes less relevant and an aggressive treatment plan is formulated irrelevant of Luminal subtype.

Age limitations in mBC typically based on hormonal status. We are yet to find any mBC drug examples that are approved for an age subset that is not based on hormonal status (i.e. pre-, postmenopausal; see **Table A6**). We note that 65 is a typical age used for segregation of this population in surveillance datasets and therefore moderate our scepticism with regards to this age limit making its way to a label.

New Phase Ib 'AIPAC-002' study exploring dosing of Efti on the same day as paclitaxel; alternative to AIPAC dosing. We have also noted the registration of a Phase Ib (n=24) exploratory AIPAC-002 study in HR+ mBC patient (NCT04252768). The focus of this trial being the dual administration of Efti and paclitaxel on the same day, with Efti being given after paclitaxel. In the AIPAC Phase IIb study Efti was given on a day subsequent to paclitaxel dosing. This Phase Ib is evaluating the safety and tolerability of a same day approach, which we anticipate is likely to inform a Phase III dosing regimen. We note an estimated start date of June 2022 on this trial. Company updates on this study have been scarce thus far.

Timeline for potential BLA filing in mBC. Based on a 3-year timeline for the AIPAC-II study to reach its primary endpoint after initiation of recruitment (estimated 2Q 2022) we could see a potential BLA filing with FDA/EMA as early as 4Q 2024, which could see an approval in 2025 (FY26e launch potential).

Estimate: 12month recruitment + 24month treatment + >18 month follow up.

A2.4 Head and Neck Squamous Cell Carcinoma (2nd line)

A2.4.1 HNSCC opportunity (metastatic/advanced)

HNSCC 101. Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common cancer globally with a high associated mortality rate (66% 5-year survival rate)[50]. HNSCC encompasses a number of cancers including nasopharyngeal, nasal cavity/sinus, oral and oropharyngeal, salivary gland and laryngeal/hypopharyngeal cancer depending on the area of the head/neck in which the tumour/s are located. Squamous cell carcinoma describes a cancer of the skin, or epithelium. Approx. 90% of all head and neck cancers are SCCs. If SCC is caught early is relatively curable however once metastasized has a poor prognosis and rapid disease progression.

HNSCC is a heterogenous cancer type making targeted therapies more challenging than in some other cancer types. Development of HNSCC can be attributed to tobacco smoking, excessive alcohol consumption and/or Human Papilloma Virus (HPV) most commonly. Patients with HPV-positive HNSCC have better survival outcomes due to improved prognosis than their non-HPV associated counterparts. Furthermore, survival rates in HNSCC are further reduced due to high associated suicide rates (the 2nd highest of any cancer after pancreatic). This represents a population with high unmet clinical need urgent for improved treatment options.

HPV status significantly affects survival and median age onset. The incidence of HPV-related HNSCC is increasing as HPV infection rises globally. Those with HPV-positive HNSCC are typically more likely to be diagnosed earlier in life, include those without smoking history (50% of cases) and have a higher survival rate than their HPV-negative counterparts (**Table A9**). There is a higher unmet need in those with HPV-negative disease, given their poorer prognosis and treatment response rates.

HPV-associated cases more likely to express PD-L1; market growing. Analyses have suggested a positive correlation between HPV-status and PD-L1 expression status in HNSCC cohorts[51]. This is positive in the sense that HPV-positive HNSCC is progressively accounting for more HNSCC cases and therefore the proportion of immunogenic PD-L1 expressing cases is likely to rise - further growing the potential market for ICIs and immunotherapies including Efti.

Table A9. Differences between HPV-negative and HPV-positive HNSCC.

Parameter	HPV-	HPV+
Gender	2-3 fold more common in men	4-5 fold more common in men
Age at diagnosis	Median age late 60s and 70s	Median age early 50s
Race		More common in Whites
Smoking	90% smoking history	50%-65% smoking history
Sexual behaviour	Not a significant risk factor	Number or oral and vaginal sex partners is an important risk factor
Site	Oral cavity and larynx most commonly	Oropharynx HPV+ <20% at other sites
Clinical picture	Varies	Early T stage, enlarged nodes
Incidence trends	Decreasing	Increasing
Survival rates	All sites: 65% 5-year survival Oropharynx: 25% 5-year survival	60%-80% 5-year survival

HPV-, Human papillomavirus negative; HPV+, human papillomavirus positive.

Source: ESMO[52]

Incidence of HNSCC far higher in Europe than US. The estimated incidence of HNSCC in the US is ~11.2 cases per 100,000 and is steadily declining[53]. Meanwhile it is almost double that in Europe with an annual incidence of ~43 per 100,000[52] This difference is attributed to the continued and increasing use of tobacco in European countries alongside increasing HPV infection rates.

Current SOC (pre-IO) plagued with significant toxicity. The current first-line standard of care (SoC) for metastatic HNSCC (that is not able to be removed surgically or targeted with radiation) is cetuximab (an epidermal growth factor inhibitor) in combination with a platinum-based chemotherapy regimen (i.e. cisplatin-F-fluoroacil) which has been used for over a decade. Median OS of ~10 months is the expected benefit of this current SoC approach. Unfortunately, this treatment paradigm is associated with significant side effects and dose-limiting toxicities making it difficult to tolerate for patients.

[50] Johnson et al. 2020. Head and neck squamous cell carcinoma. *Nature Reviews Disease Primers*. 6: 92.
[51] Qiao et al. 2020. The Evolving Landscape of PD-1/PD-L1 Pathway in Head and Neck Cancer. *Frontiers in Immunology*. 11:1721.
[52] Economopoulou & Psyrri. 2017. ESMO Essentials for Clinicians: Head and Neck Cancers. Chapter 1; Epidemiology, risk factors and pathogenesis of squamous cell tumours. Accessed online.
[53] Fakhry et al. 2018. Head and Neck Squamous Cell Cancers in the United States are Rare and Risk is Now Higher Among Whites than Blacks for the First Time. *Cancer*. 124(10): 2125-2133.

Chemotherapy a sound partner for ICIs in HNSCC. The use of checkpoint modulators in combination with chemotherapy is hypothesized to give the greatest benefit given that the chemotherapy can disrupt tumour architecture potentially helping with IO drug access to the tumour, in addition to driving antigen shedding making the tumour more IO amendable. This is the same principle supporting the use of IO-Chemo combinations in metastatic breast cancer also.

Pembrolizumab approval ushered in new SOC; but only for those with PD-L1 positive tumours. In 2016 we saw the first PD-1 ICIs (pembrolizumab and nivolumab) approved for use in HNSCC when patients had progressed following SOC (chemotherapy). The landmark MSD Keynote-048 study has since shown that pembrolizumab is effective in a first line mHNSCC setting in combination with chemotherapy or alone to enhance overall survival (OS) and importantly the duration of response (DoR) (**see Table A11**). This study resulted in the approval of pembrolizumab + chemotherapy becoming the new first line SOC in mHNSCC in 2019 (for all patients), alongside an approval for pembrolizumab monotherapy in PD-L1 positive patients (CPS ≥1) using an approved companion diagnostic.

Major market regulators differ in HNSCC IO approvals. The European Medicines Agency (EMA) has taken a more conservative approach to the approval of pembrolizumab in first line metastatic HNSCC. They have restricted use to patients with confirmed expression of PD-L1 positive tumours (≥1% CPS) as a combination with chemotherapy and further restricted pembrolizumab monotherapy use to those with high PD-L1 expression levels only (≥50% TPS). This reflects a markedly reduced patient pool vs US approvals.

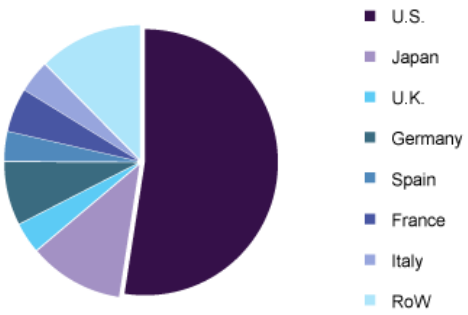
Unmet need: significant population with low PD-L1 expression or non-responders. Meta analyses have shown that ~60% of mHNSCC patients are PD-L1 negative (<1% CPS)[54]. This represents a significant proportion with limited options after they have failed SOC, with a high mortality burden. Targeting of alternative immune checkpoints (i.e. LAG-3) in these populations provides an alternative mechanism by which to reinvigorate the immune system to turn 'cold' tumours 'hot' and improve outcomes as anti-PD-1 agents have done for other mHNSCC patients.

The TACTI-003 trial will address those with no PD-L1 expression in Cohort B.

HNSCC market size is growing due to HPV infection rising. It is estimated that more than 800,000 new HNSCC cases are diagnosed each year globally[55]. The HNSCC market is expected to reach US$2.6B by 2026 [56] with rising HPV-associated HNSCC and ICI approvals as the driving growth factors of market size/value. The global HNSCC market was estimated at ~US$900M in 2017 dominated by sales of Opdivo and Keytruda (~60% total) which has only increased with ICI adoption in this indication in major markets.

Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 continue to comprise greater market share versus EGFR inhibitors (cetuximab) which is expected to continue with further ICIs in the pipeline heading toward potential approvals (including anti-PD-L1 avelumab, and anti-CTLA4 ipilimumab). The US and 5 major European markets make up just over 75% of the total current market (**Figure A12**) with growth opportunities in emerging markets including Brazil, China and India. Japan is another large drug market for HNSCC (~10% global market share).

Figure A12. Global Head & Neck Cancer drugs market share, by region (2016).



Source: GrandView Research.

TACTI-002 data shone a light on HNSCC. Despite the star of the TACTI-002 trial initially being the NSCLC indication, the data that was gathered as part of the TACTI-002 study in 2nd line HNSCC (Part C) with Efti in partnership with pembrolizumab was impressive (data summarised in **Table A11**). These have prompted further investigations of HNSCC in the new TACTI-003 trial program (see **section A2.4.3**).

HNSCC an interesting and attainable indication for Immutep to tackle. Despite HNSCC being a smaller market when compared to NSCLC (<50% size) there are clear advantages to advancing Efti in this indication for Immutep; including a) the limited treatment options and very clear significant unmet need; b) the lessened competitive noise in this indication; c) the relative size of Phase IIb/III registration trials being manageable without partnering from a cost perspective; and d) the relatively fast timeline of HNSCC treatment and clinical trials (given the shortened survival rates in this indication vs mBC for example).

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[54] Yang et al. 2018. The prognostic role of PD-L1 expression for survival in head and neck squamous cell carcinoma: A systematic review and meta-analysis. *Oral Oncology*. 86: 81-90.
[55] Bray et al. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 68: 394-424.
[56] IndustryArc. 2021: Global Head and Neck Cancer Drugs market report.

Resistance development in HNSCC to IOs is high. As highlighted in **section A1.1** earlier, development of acquired resistance to ICIs is particularly high in HNSCC. Rates of 35-54% acquired resistance were found in the Phase II and III pembrolizumab Keynote trials within 8-24 months of starting treatment (**Table A1**).

Competitive landscape relatively quiet; numerous failures.

The competitive landscape in HNSCC continues to be dominated with the same approved targets (EGFR, PD-1/PD-L1) with several studies investigating new anti-CTLA-4 combination approaches (BMS' ipilimumab and AstraZeneca's tremelimumab).

New EGFR inhibitors failed in Phase III; cetuximab the mainstay. Cetuximab (the existing first line approach in most cases) is an EGFR inhibitor. Amgen's panitumumab is a human anti-EGFR mAb that is used in treatment of metastatic colorectal cancer. A Phase III RCT (SPECTRUM) in mHNSCC assessed panitumumab combined with cisplatin + 5-FU versus SOC chemotherapy alone (cisplatin + 5-FU) and showed a failure to significantly increase median OS as a first-line therapy approach (11.1months vs 9 months, p=0.14). Improvement in PFS was seen with panitumumab vs SOC however (5.8 months vs 4.6 months, p=0.0036)[57]. Analysis of the trial showed that HPV-negative HNSCC patients had significantly better OS outcomes (p=0.0115) perhaps suggesting a beneficial subgroup of patients for this therapy. We of course note that cetuximab remains the first line EGFR agent in HNSCC SOC.

Notable recent Phase III failures of anti-CTLA-4 + anti-PD-1 combo.

BMS' Phase III Checkmate-651 IO-IO combination study in 1st line metastatic/recurrent HNSCC with nivolumab (anti-PD1) and ipilimumab (anti-CTLA4) failed to meet its primary OS endpoint when compared to a SOC regimen (cetuximab + 5-FU + platinum-based chemotherapy)[58]. The failure to show superior OS benefit (despite their being a positive trend) was put down to a better than expected response in the comparator SOC arm versus historical expectations. The failure of the Opdivo + Yervoy combination in mHNSCC, which has shown survival benefits in five other cancer types (incl. NSCLC, metastatic melanoma, advanced renal cell carcinoma) perhaps highlights the challenge associated with mHNSCC treatment, its resistance to IO approaches and its high mortality rate.

AstraZeneca's Phase III EAGLE trial also failed to show an overall survival (OS) benefit vs SOC using a different PD-1/CTLA-4 drug combination in 1st line mHNSCC[59]. Duravelumab (anti-PD-1) and tremelimumab (anti-CTLA-4) in combination (HR=1.04, p=.76) or duravelumab alone (HR=0.88, p=0.2) did not produce statistically significant improvements in OS however the single anti-PD-1 arm did show higher response rates and higher survival rates at 12 and 24 months suggesting some clinical utility (akin to the other approved anti-PD-1 agents in this indication).

These late stage failures together show that thus far the additional targeting of CTLA-4 is hindering clinical benefit as opposed to being synergistic with anti-PD-1 drugs in mHNSCC.

A potential CTLA-4/PD-1 combo win in oesophageal SCC for BMS; a similar case. Oesophageal SCC (ESCC) shares many similarities to HNSCC, in terms of body location but also risk factors (tobacco, alcohol), shared molecular pathway dysregulation and in up to 12.5% of cases patients develop synchronous HNSCC and ESCC[60]. HPV would be the clear difference between the two as HPV-infection is not associated with ESCC, in which case HPV-negative HNSCC and ESCC are most aligned.

The Phase III Checkmate-648 trial evaluated a combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) and nivolumab in combination with cisplatin chemotherapy +5-FU as 1st line treatments in metastatic, recurrent or unresectable advanced oesophageal SCC (ESCC) patients (versus chemotherapy alone). The trial showed a significant benefit to OS for both treatment combinations (irrelevant of PD-L1 status - however a greater effect in PD-L1 positive tumours). The nivolumab + chemotherapy arm also showed significant increases in median PFS vs chemotherapy alone in those with PD-L1 expressing tumours.

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[57] Vermorken et *al.* 2013. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. *Lancet Oncol.* 14(8): 697-710.

[58] BMS market announcement: 16 July 2021. Accessed online: https://news.bms.com/news/corporate-financial/2021/Bristol-Myers-Squibb-Provides-Update-on-CheckMate--651-Trial-Evaluating-Opdivo-nivolumab-Plus-Yervoy-ipilimumab-Versus-EXTREME-Regimen-as-First-Line-Treatment-for-Squamous-Cell-Carcinoma-of-the-Head-and-Neck/default.aspx

[59] Ferris et *al.* 2020. Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomised, open-label Phase III study. *Ann Oncol.* 31(7): 942-950.

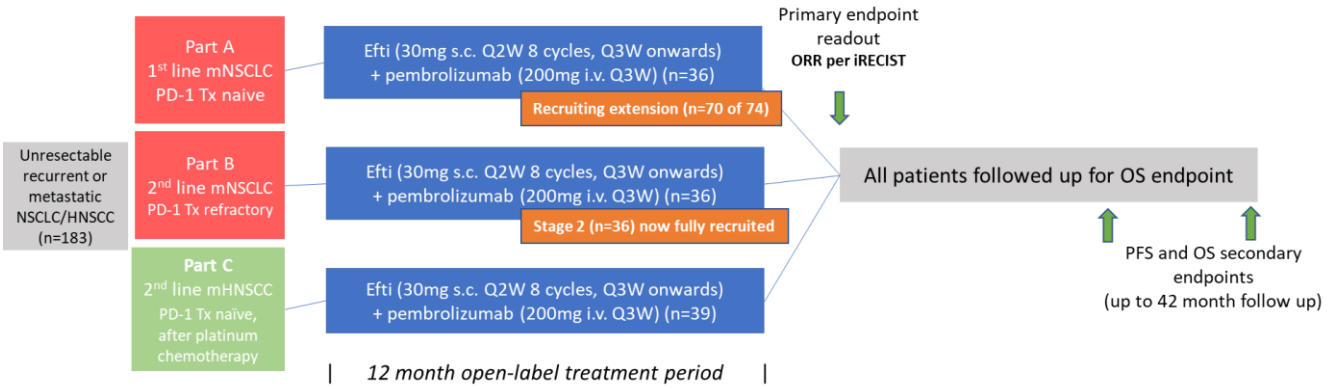
[60] Businello et *al.* 2020. The pathologic and molecular landscape of esophageal squamous cell carcinogenesis. *Cancers (Basel).* 12(8): 2160.

FDA has now accepted BMS' supplementary BLA for a nivolumab + ipilimumab combination and a nivolumab + chemotherapy combination for consideration as new 1st line treatments in ESCC. The PDUFA date is set for May 28th, 2022. Approval of the nivolumab + ipilimumab combination would represent the first multi ICI (multi immune target) approach in cancer of the head or neck.

A2.4.2 Summary of clinical evidence: TACTI-002 Phase II trial of adjunct Efti in 2nd line HNSCC

TACTI-002 trial design. Part C of the TACTI-002 trial (NCT03625323) focused on treatment of 2nd line metastatic HNSCC after patients had failed platinum-based therapy and/or were ineligible for EGFR inhibitors and were naïve to any PD-1/PD-L1 targeted therapies (**Figure A13**). This trial was sponsored by Immutep in collaboration with MSD. Part C enrolled 39 patients with mHNSCC who were treated for 12 months with an Efti + pembrolizumab combination. Patients were not selected based on PD-L1 status (all-comer trial). ORR was the primary endpoint for the study based on iRECIST criteria (See **Table A10**) with PFS, OS, safety and pharmacokinetics all secondary endpoints.

Figure A13. TACTI-002 trial design. Part C is focused on HNSCC.



Source: Wilsons, Immutep, Clinicaltrials.gov.

iRECIST used to define ORR criteria in immunotherapy studies. As outlined in **Table A10 overleaf,** there are differences between criteria to calculate objective response rate (ORR) in oncology clinical trials. iRECIST was developed specifically for immunotherapy studies and is the accepted method for ORR evaluation in IO clinical trials[61]. iRECIST criteria were used to determine patient responses in the TACTI-002 trial (CR, PR, SD or PD) and subsequently used to calculate ORR and disease control rate (DCR) as follows;

The TACTI-003 primary ORR endpoint will be per RECSIST 1.1 criteria.

ORR = % of patients with complete response (CR) + % of patients with partial response (PR)

DCR = % of patients with CR + % of patients with PR + % of patients with stable disease (SD)

Comparisons to foundational trials that supported existing IO approvals in HNSCC. Relevant comparable trials are summarised in **Table A11**. With the caveats of cross trial comparisons aside, we can see that the initial OS data from the TACTI-002 Part C trial with Efti in combination with pembrolizumab is on par with the outcomes of the Phase III Keynote-048 trial (1st line) as well as the Phase III Keynote-040 study (2nd line). Without the relevant control and comparison groups within the TACTI-002 trial the degree of superiority cannot be evaluated in a reliable manner.

Efti beats pembrolizumab monotherapy in past studies with superior safety profile. For illustrative purposes we note that the Efti + Pembrolizumab combination in TACTI-002 produced superior OS (+1 to +4.2 months) and ORR (+12.8% to +16.4%) measures when compared to pembrolizumab monotherapy arms in the Keynote-040 (2L) and -048 studies (1L). This preliminary comparison gives us confidence in the potential synergy of the Efti combination in the controlled TACTI-003 trial and superior efficacy (see **Section A2.4.3** below). Furthermore, this was achieved with a lower rate of Grade ≥3 AEs (8%) vs anti-PD-1 monotherapies (nivolumab, 13%; pembrolizumab, 13-17%).

[61] Borcoman et al. 2018. Patterns of Response and Progression to Immunotherapy. *Am Soc Clin Oncol Educ Book*. 38: 169-178.

Table A10. Objective response rate (ORR) assessment in solid tumours via different methods; summary of criteria.

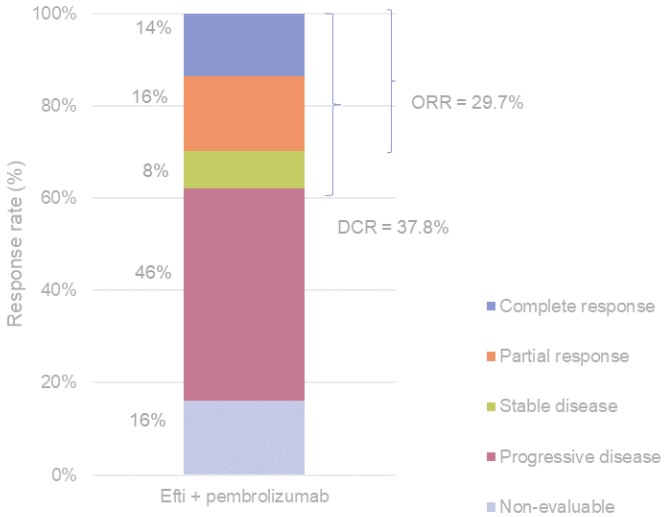
	WHO	RECIST v1.0	RECIST v1.1	iRECIST
Method	Sum of products of two longest diameters in perpendicular dimension (bidimensional; surface area)	Sume of longest diameters of target lesions (unidimensional)	Sum of longest diameters of non-nodal target lesions and short axis of nodal target lesions (unidimensional)	as per RECIST v1.1
No. of measured lesion	All lesions	Target lesions: max 5 per organ, 10 in total	Target lesions: max 2 per organ, 5 in total	Target lesions; min 2 lesions per organ, 5 in total
Response				
Complete response (CR)	Dissappearance of all known disease confirmed at 4wk	Dissappearance of all known disease confirmed at 4wk	Dissappearance of all known disease confirmed at 4wk; lymph nodes must be <10mm short axis	Dissappearance of all lesions
Partial response (PR)	≥50% decrease from baseline, confirmed at 4wk	≥30% decrease from baseline, confirmed at 4wk	≥30% decrease from baseline, confirmed at 4wk	as per RECIST v1.1
Stable disease (SD)	Neither PR nor PD criteria met			
Progressive disease (PD)	≥25% increase, no CR,PR or SD, new lesion(s), ≥25% increase in 1 lesion.	≥20% increase in nadir, no CR,PR or SD, new lesion(s).	≥20% increase in nadir, no CR,PR or SD, new lesion(s). The sum must also demonstrate an absolute increase of ≥5mm.	as per RECIST v1.1

Source: Wilsons, adapted from Aykan et al. 2020.[62]

Efti combination on par with 1st line pembrolizumab + chemotherapy with improved toxicity. The OS and ORR outcomes shown in TACTI-003 Part C are broadly in line with the data from the Keynote-048 Phase III study IO-chemo combo (**Table A11**). This combination therapy is currently FDA approved for all patients regardless of PD-L1 expression status and could be thought of as the most broadly encompassing 1st line SOC regimen in mHNSCC at present. The notable comparison is the consistent efficacy (OS/ORR) with a significant reduction in toxicity (72% Grade ≥3 AEs with pembro +chemo vs 8% Efti + pembro) which greatly skews the risk benefit ratio in Efti's favour.

Even greater efficacy seen in PD-L1 positive patients. The superior efficacy of the Efti + pembrolizumab combination (vs pembrolizumab monotherapy) is further intensified when comparing in PD-L1 positive (≥1% CPS) cohorts only. See **Figure A15** below where we compare to pembrolizumab monotherapy in both a 1st line and 2nd line setting.

Figure A14. Objective response rate per iRECIST for TACTI-002 (HNSCC)



Source: Immutep, Wilsons.

Figure A15. Efti shows indicative superiority to pembrolizumab monotherapy in both 1st and 2nd line mHNSCC including in PD-L1 ≥1% CPS

Cross trial comparison

PD-L1 subgroup	Median PFS			ORR			Median OS		
	Efti + pembro (2L)	pembro (2L)	pembro (1L)	Efti + pembro (2L)	pembro (2L)	pembro (1L)	Efti + pembro (2L)	pembro (2L)	pembro (1L)
All (unselected)	2.1 months	2.1 months	2.3 months	**30%**	15%	17%	**12.6 months**	8.4 months	11.6 months
≥1% CPS	**4.1 months**	2.1 months	3.2 months	**46%**	NR	19%	**12.6 months**	8.7 months	12.3 months
≥20% CPS	NR	NR	3.4 months	NR	NR	23%	NR	NR	14.9 months

NR: Not reported

Source: Wilsons, Immutep, Cohen (2019)[63]*, Burtness (2019)*[64]*.*

[62] Aykan NF & Ozatli T. 2020. Objective response rate assessment in oncology: Current situation and future expectations. *World J Clin Oncol.* 11(2): 53-73.
[63] Cohen et al. 201. KEYNOTE-040. https://doi.org/10.1016/S0140-6736(18)31999-8
[64] Burtness et al. 2019. KEYNOTE-048. https://doi.org/10.1016/S0140-6736(19)32591-7

Table A11. Comparison of Efti vs other checkpoint inhibitors and SOC in 1st and 2nd line metastatic HNSCC

	Efti + pembrolizumab	Pembrolizumab	Nivolumab	Platinum-based chemo		Pembrolizumab	Pembro+ chemo	Cetuximab + chemo
	IO - IO	IO monotherapy	IO monotherapy	SOC		IO monotherapy	IO - Chemo	SOC
Checkpoint target	PD-1 + LAG-3	PD-1	PD-1	NA	NA	PD-1	PD-1	NA
Study	TACTI-002 Part C	Keynote-040	Checkmate-141	Keynote-040	Checkmate-141	Keynote-048	Keynote-048	Keynote-048
Phase	II	III	III	III	III	III	III	III
Therapy Line	2nd	2nd	2nd	2nd	2nd	1st	1st	1st
n	39	247	240	248	121	301	281	300
Demographics (% male)	90%	84%	82%	83%	85%	83%	80%	87%
Median age	62	60	59	60	61	62	61	61
PD-L1 TPS <1%	33%	42%	30%	38%	31%	78%	77%	78%
TPS 1-49%	62%	32%	37%*	35%	50%*			
TPS ≥50%		26%		26%		22%	23%	22%
Median PFS	2.1 months	2.1months	2.0 months	2.3 months	2.3 months	2.3 months	4.9 months	5.2 months
HR (for progression)	-	0.96 (p=0.32)	0.89 (p=0.32)	-	-	p>0.05	0.84 (p>0.05)	-
PF at 6 months (%)	>30%	25%	20%	22%	10%	25%	45%	45%
Median OS	12.6 months	8.4 months	7.5 months	6.9 months	5.1months	11.6 months	13.0 months	10.7 months
HR (for death)	-	0.80 (p=0.016)	0.70 (p=0.01)	-	-	0.83 (p=0.02)	0.77 (p=0.034)	-
Median Duration of response	>6 months	18.4 months	NR^	5.0 months	NR^	22.6 months	6.7 months	4.5 months
ORR	29.7%	14.6%	13.3%	10.1%	5.8%	16.9%	36.0%	36.0%
Response criteria	iRECIST	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.2
Treatment-related Adverse Events (AEs)								
Discontinuation AEs	3%	6%	NR	5%	NR	0%	8%	9%
Grade ≥3 AEs	8%	13%	13%	36%	35%	17%	72%	69%
AEs leading to death	0%	2%	1%	4%	1%	1%	4%	3%

^NR - not reported quantitatively. Qualitatively noted DoR greater in nivo group vs SOC

*PD-L1 ≥1%. Remainder of group of were not quantifiable in their PD-L1 expression levels.

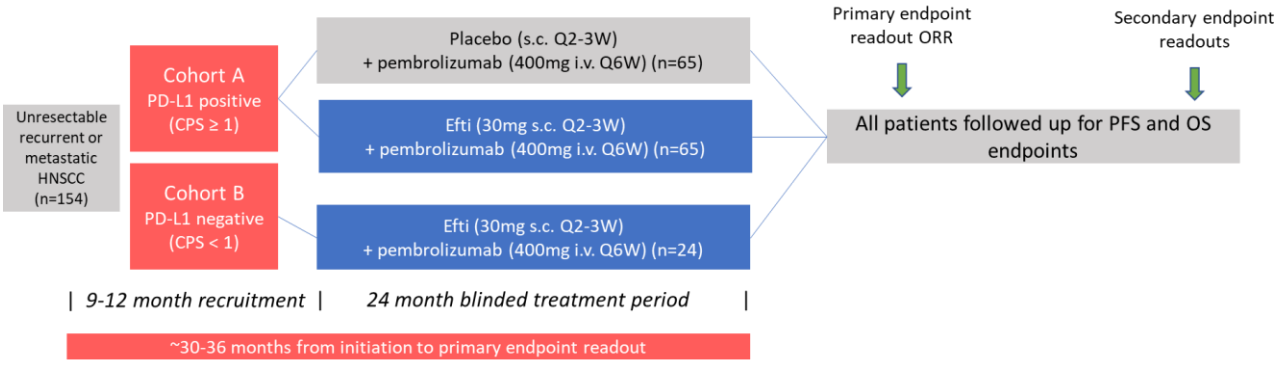
Source: Wilsons, Ferris et al. (2016)[65], Burtness et al. (2019)[66], Cohen et al. (2018)[67]

[65] Ferris et al. 2016. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 375 (19): 1856-1867.
[66] Burtness et al. 2019. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet*. doi.org/10.1016/S0140-6736(19)32591-7
[67] Cohen et al. 2018. Pembrolizumab versus methotrexate, docetaxel or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet*. doi.org/10.1016/S0140-6736(18)31999-8

A2.4.3 Next steps for Efti in mHNSCC

TACTI-003 Phase IIb trial design. Immutep are now progressing the Efti + pembrolizumab combination moving into 1st line metastatic HNSCC in the TACTI-003 Phase IIb trial (NCT04811027); trial design summarised in **Figure A16**). Briefly, the trial will comprise of two cohorts based on PD-L1 expression status with a focus on those with PD-L1 positive tumours based on the TACTI-002 results in this subgroup. Objective response rate (ORR) per RECIST v1.1 criterion is the primary endpoint with PFS and OS key secondary endpoints. The trial is randomised to evaluate pembrolizumab monotherapy versus the Efti + pembrolizumab combination (used in TACTI-002). The trial is expected to recruit from ~35 sites across Australia, Europe and USA.

Figure A16. TACTI-003 trial design summary



Source: Wilsons, Immutep.

Primary endpoint (ORR) in Phase IIb consistent with Phase II study; OS the key endpoint to support marketing authorisation. The maintenance of the ORR primary endpoint in the TACTI-003 is supported by the solid ORR response seen in the TACTI-002 trial with Efti. We note that in other ICI trials in HNSCC we have seen mixed/absent improvements in PFS measures in comparison to OS and ORR improvements which have been of a greater magnitude and significance (**Table A11**). We would anticipate ORR to be used as a surrogate endpoint to potential support accelerated approvals following future pivotal trials with OS still be the confirmatory efficacy endpoint to support marketing approval. We note that the FDA approval of pembrolizumab in 1st line mHNSCC was based upon the KEYNOTE-048 trial with OS being the primary efficacy measure supporting approval[68].

Pembrolizumab dosing changed. We note in TACTI-003 Immutep are moving to a Q6W dosing of pembrolizumab (400mg) in comparison to the Q3W 200mg regimen used in TACTI-002 with Efti dosing remaining at the same Q2-3W frequency as prior. This halves the number of pembrolizumab infusions for patients with the total dose delivered remaining consistent. We understand this change is to reflect the changes in the field where clinicians are preferencing more infrequent, higher dose regimens.

Current trial status. The TACTI-003 trial received IND approval from the FDA on July 6th allowing US sites to proceed. We understand US patient recruitment is now underway with Australian and European sites to follow once regulatory approvals (TGA and EMA respectively) are received which are expected across the balance of CY21. The TACTI-003 trial is being conducted in collaboration with MSD under a new collaboration agreement signed in March 2021.

Fast track designation received for Efti in HNSCC. Immutep received Fast Track Designation (FTD) status for Efti in 1st line HNSCC from the FDA in April of this year based on the TACTI-002 Part C data in HNSCC patients[69]. This provides them with increased access to the FDA in the form of meetings and written communications regarding their trial plans and progress as well as eligibility for Accelerated Approval and/or Priority Review should they meet relevant criteria. FTD status is awarded to drug programs that show promise where there is significant clinical unmet need and aims to aid in the development of these drugs in addition to expediting the review process. This is a positive sign highlighting the FDA sees

[68] FDA alerts; 10 June 2019. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-first-line-treatment-head-and-neck-squamous-cell-carcinoma
[69] ASX announcement; Immutep 8 April 2021. https://www.asx.com.au/asx/statistics/displayAnnouncement.do?display=pdf&idsId=02361380

significant potential benefit of the Efti + Pembrolizumab combination in the HNSCC indication.

Keynote-048 trial represents the best efficacy comparator for TACTI-003. The Phase III trial of pembrolizumab in 1st line mHNSCC (KEYNOTE-048) is the best predicate to evaluate what the pembrolizumab monotherapy response may be in the TACTI-003 Cohort A pembrolizumab only arm (**Table A11**). As noted, thus far Efti appears to have effects superior to pembrolizumab monotherapy.

PD-L1 positive patients initial target; PD-L1 negative have greatest unmet need. We view the opportunity for Efti in 1st line mHNSCC as likely restricted to PD-L1 expressing tumours at this point in time (akin to pembrolizumab approvals in this setting). The design of TACTI-003 suggests this is the initial clinical population of interest as opposed to PD-L1 negative patients where some, albeit lesser, benefit was seen. Given the lack of control in Part B of the trial design (PD-L1 negative), we would anticipate further studies would be required to support a potential all-comers PD-L1 label. As such, we limit our current modelling assumptions in HNSCC to PD-L1 positive cohorts (~42% of HNSCC in total based on a recent meta-analysis)[70]. The opportunity for Efti to benefit PD-L1 negative cohorts is meaningful given they are the currently the patients with the highest unmet need, given the availability of pembrolizumab-based regimens for PD-L1 positive mHNSCC patients.

Marketing authorisation potentially requires support of a larger Phase III trial. It is unclear the extent to which the Phase IIb TACTI-003 trial can be used to solely support a BLA submission. Our conservative assumption, based on predicate approvals of pembrolizumab in the 1st line mHNSCC setting, is that a follow-on Phase III trial would be required given the limited sample size of TACTI-003 (n=65 per arm in randomised Part A). For reference, the KEYNOTE studies supporting pembrolizumab approval included a 250-300 patients per arm. Based on this assumption we model a potential market approval/entry in FY27-FY28e (see **section A5.2** for HNSCC market model).

Stellar TACTI-003 data could support accelerated scenario and upside. We do note the possibility that should TACTI-003 produce very strong results Immutep could pursue an approval based on this Phase IIb data alone which the FDA may be amenable given they have granted this program Fast Track Designation and have a good understanding of the efficacy of the comparative backbone therapy from prior trials. We model this scenario in our valuation sensitivities (**pp17**) which could see a 3 year pull forward in first market approvals and entry for Efti.

Summary opportunity for Efti in 1st line mHNSCC:

- opportunity to expand the current addressable market for pembrolizumab monotherapy in Europe (i.e. include patients with 1-49% TPS) based on positive PD-L1 all-comers data (which will also be specifically interrogated in Cohort B of TACTI-003 trial);
- opportunity to increase the level of treatment responders within the current approved pembrolizumab monotherapy cohorts (i.e. PD-L1 ≥1% CPS and ≥50% TPS) given the increased ORR observed with adjunct Efti, in US and EU markets, respectively;
- opportunity remove the PD-L1 restriction on use of pembrolizumab monotherapy in 1st line HNSCC to include PD-L1 negative patients.

[70] Yang et *al*. 2018. The prognostic role of PD-L1 expression for survival in head and neck squamous cell carcinoma: a systematic review and meta-analysis. *Oral Oncol*. 86: 81-90.

A2.5 Non-Small Cell Lung Cancer (NSCLC) (1st & 2nd line)

A2.5.1 NSCLC opportunity (metastatic/advanced)

NSCLC 101. Lung cancer is the second most common cancer worldwide with non-small cell lung carcinoma (NSCLC) accounting for ~84% of all lung cancer diagnoses[71]. The incidence of NSCLC is approximately 45 per 100,000 population in US[72] and 44 per 100,000 in Western Europe[73], with a decline in incidence of ~2% per year being witnessed in the past 10-15 years. Tobacco smoking is the primary risk factor for development of NSCLC followed by asbestos exposure. Typically, it is a cancer associated with advanced age with an average age of diagnosis of ~70 years. Metastatic NSCLC is associated with an incredibly high mortality with 5-year survival rates of only 7%, however these survival statistics continue to improve in this field and have greatly benefitted from the introduction of immunotherapies, mostly notably anti-PD-1 ICIs.

NSCLC is a very busy IO space; Immunotherapy is SOC for mNSCLC. Metastatic or locally advanced NSCLC is an example of a cancer where immunotherapy has revolutionised patient care in recent years and there are numerous immune checkpoint inhibitors (ICIs) approved as first line therapies, either in combination with chemotherapy or as monotherapy (**Table A12**). mNSCLC continues to be a very busy IO space in terms of pipeline clinical programs, with many new programs focused on IO-IO combos removing the need for chemotherapy use in the 1st line metastatic setting (we highlight four programs focused on LAG-3/PD-1 in **Table A13** overleaf).

Pembrolizumab dominates this indication, however the first adjuvant IO approval could see atezolizumab take share. Despite there being more than four ICIs approved for mNSCLC in the 1st line setting, pembrolizumab continues to dominate the clinical landscape as the established physician preference in mNSCLC patients with the caveat of it only being used in PD-L1 positive tumours (PD-L1 TPS ≥ 1%). Atezolizumab was first approved as a monotherapy in 1st line mNSCLC in mid-2020 however just last month (Oct 2021) Roche secured the first adjuvant approval for an ICI in the NSCLC setting. Those with PD-L1 positive (TPS ≥ 1%) early stage tumours (Stage I-III) are eligible for atezolizumab monotherapy post-surgery. We could see this impact the dominance of pembrolizumab in this indication over time.

Table A12. Approved IO treatments in NSCLC (FDA and/or EMA approvals)

Drug	Target	Combination	Approval date	PD-L1 expression	Line of therapy
Pembrolizumab (MSD)	Anti-PD-1	Monotherapy	April 2019	≥ 1% TPS	1L (using companion PD-L1 diagnostic)
		Chemotherapy	Oct 2015	≥ 1% TPS	2L after chemo
				≥50% TPS	1L (only for those with no EGFR or ALK aberrations)
Atezolizumab (Roche)	Anti-PD-L1	Monotherapy	May 2020	≥50% TPS	1L
		Adjuvant	Oct 2021	≥ 1% TPS	Adjuvant in Stage I-III cancers
		Chemotherapy	Dec 2019	All	1L (only for those with no EGFR or ALK aberrations)
Nivolumab + ipilimumab (BMS)	Anti-PD-1 + anti-CTLA-4	IO-IO combo	May 2020	≥1% only	1L (using companion PD-L1 diagnostic)
		Chemotherapy	May 2020	All	1L (only for those with no EGFR or ALK aberrations)
Nivolumab (BMS)	Anti-PD-1	Monotherapy	Mar 2015	All	2L metastatic after chemo failure
Cemiplimab (Sanofi/Regeneron)	Anti-PD-1	Monotherapy	June 2021	≥50% TPS	1L (only for those with no EGFR, ALK or ROS1 aberrations)
Durvalumab (AstraZeneca)	Anti-PD-1	Monotherapy	Feb 2018	All	2L after chemo, Stage III

**TPS; tumour proportion score which represents the percentage of viable tumour cells expressing PD-L1.*

Source: FDA, EMA, Wilsons.

[71] ASCO.org; Cancer.Net. January 2021. Lung Cancer – Non-small Cell: Statistics. https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics
[72] National Cancer Institute: SEER program. SEER Database Explorer. Accessed at seer.cancer.gov.
[73] Planchard et al on behalf of ESMO Guidelines Committee. 2018. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 29(4): 192-237.

Recent IO approvals and failures in mNSCLC. In 2020 the FDA approved two new IO regimens in 1st line metastatic NSCLC (see **Table A12**); a) Roche's atezolizumab (anti-PD-L1) as a monotherapy; and b) the first IO-IO combo targeting two different immune checkpoints – BMS' nivolumab (anti-PD-1) + ipilimumab (anti-CTLA-4). It is relevant to note that MSD halted their Phase III Keynote-598 trial in late 2020 also evaluating an anti-PD-1 (pembrolizumab) + ipilimumab combo in mNSCLC which failed to show clinical benefit over pembrolizumab monotherapy and resulted in increased toxicity vs monotherapy[74].

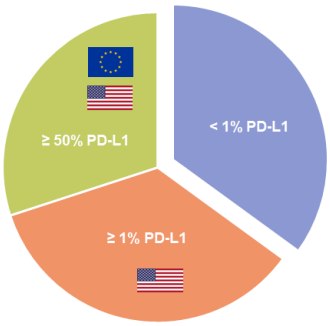
PD-1 resistance in mNSCLC; a clear gap Efti is looking to address. Primary or acquired resistance to anti-PD-1/PD-L1 directed therapies is common in NSCLC as described previously (refer to **Table A1**). Efti has a unique mechanism of action which may allow it to boost the efficacy of anti-PD-1 directed therapies in both 1st line (PD-X naïve) and 2nd line (PD-X refractory) patient cohorts. Given the high acquired resistance rates of anti-PD-1 therapies over a relatively short space of time (<2 years) we see a growing market for therapies that can synergistically boost anti-PD-1 strategies or restimulate affinity for these drugs via immune stimulation in patients that have tried and failed due to lack of efficacy (not tolerability/safety). The continued interest and collaboration with MSD highlight their reliance on novel strategies like Efti to solve the inevitable challenge of PD-1 resistance.

Potential for Efti to address all PD-L1 expression cohorts; greater than current pembrolizumab opportunity. Tumour positive score (TPS) is used to define the level of PD-L1 expression of tumours, which are typically categorised into three 'buckets' representing absent/low/high levels of expression (<1%, ≥ 1%, ≥ 50% respectively). In metastatic NSCLC, TPS score defines the applicable populations for pembrolizumab monotherapy based on their current EMA and FDA approved labels (**Table A12**).

At present, FDA approvals for pembrolizumab monotherapy include patients with ≥ 1% PD-L1 expression (~65% total), whilst in Europe EMA approvals for pembrolizumab monotherapy only support use in cohorts with high (≥ 50% TPS) PD-L1 expression only (~30% total). In both major markets, patients negative for PD-L1 (< 1%) are not eligible for pembrolizumab monotherapy (~35% total mNSCLC) (**Figure A16**).

We assess opportunities for Efti in all PD-L1 expression categories, where it has the opportunity to boost pembrolizumab efficacy (in ≤65% of addressable market) in addition to potentially making 'cold' or <1% PD-L1 tumours responsive to pembrolizumab therapy gives its use as an immune stimulating adjunct (remaining ≥35% of market).

Figure A16. Pembrolizumab monotherapy approvals in mNSCLC (1L & 2L) based on PD-L1 expression status.



Source: Wilsons.

Four notable LAG-3 + PD-1 targeted combinations in Phase II/III studies of NSCLC. We note there are four other LAG-3/PD-1 directed programs in clinical development in the NSCLC indication (refer **Table A13**). The most progressed are the two relatlimab Phase II programs; a) as a triple-combination with nivolumab + chemotherapy (NCT04623775) in 1st line mNSCLC patients; b) as a combination with nivolumab in a neoadjuvant setting in stage I-III NSCLC (NCT04205552). Readouts for both trials >CY23.

Table A13. LAG-3 targeted assets in development for NSCLC in combination with anti-PD-1

Asset	Company	MOA	Cancer indication/s	Development stage	PD-1 combo	Trial identifier
Relatlimab (BMS-986016)	BMS	Anti-LAG-3 mAb antagonist	NSCLC (1L) Including metastatic	Phase IIs ongoing (2023 & 2024 ends)	Yes/No	NCT04623775 NCT04205552
Favezelimab	MSD	Anti-LAG-3 mAb antagonist	NSCLC (1L, 2L)	Phase Ib/II and II ongoing (2025 end)	Yes	NCT03516981 NCT04938817
Leramilimab (LAG525)	Novartis	Anti-LAG-3 mAb antagonist	Advanced malignancies including NSCLC (subgroup 1)	Phase I/II completed	Yes	NCT02460224
Miptenalimab (BI754111)	Boehringer Ingelheim	Anti-LAG-3 mAb antagonist	NSCLC (2L, 3L)	Phase I ongoing (2022 end)	Yes	NCT03156114

Source: Clinicaltrials.gov, Wilsons. Adapted from **Table A3**.

[74] Merck & Co (MSD) Press Release; November 09, 2020; here.

Recent Amgen approval of sotorasib in NSCLC limited in applicability; could see more targeted therapies in future reduce the applicable pool for 1st line IO. The landscape of NSCLC is slowly reducing with the approval of targeted therapies such as sotorasib. It was recently (May 2021) FDA approved as a 2nd line therapy in mNSCLC patients with the KRAS G12C-mutation[75]. This mutation represents ~13% of NSCLC patients and represented a cohort that were extremely resistance to therapy (including immunotherapy and chemotherapy). This approval is conditional on positive biomarker testing for the mutation. Sotorasib represents the first KRAS-targeted therapy to be approved in NSCLC. Approximately half of NSCLC patients carry a targetable driver mutation however to date the ability to target these mutations effectively to enhance treatment outcomes has been limited. We might expect further advancements in targeted mutation therapies that over time may reduce the applicable patient pool for immunotherapy (noting that this approval is still for those failing 1st line approaches).

MSD have their own TACTI-002 program of sorts. The KEYNOTE-495 Phase II trial (NCT03516981) is evaluating pembrolizumab in combination with a range of other novel checkpoint inhibitors including favezelimab (MSD's own anti-LAG-3 mAb) and quavolimab (anti-CTLA-4) in a 1st line metastatic NSCLC setting (akin to TACTI-002 Part A). Initial data from a Phase I of favezelimab + pembrolizumab in colorectal cancer showed good synergistic efficacy and tolerability of the combination[76]. We don't expect results from this trial for some time (~CY24). ORR is the primary endpoint.

Innovent's anti-LAG-3, IBI110 shows positive initial efficacy to support further expansion into NSCLC. Innovent Biologics have recently presented data from their Phase Ia/Ib trial of their anti-LAG-3, IBI110, at ASCO 2021. It has displayed good safety and tolerability with an ORR in patients with solid tumours of 16.7% when combined with an anti-PD-1 (sintilimab). It too has shown synergistic effects with the anti-PD-1 supporting the "*further exploration of this molecule in a variety of tumour types, including non-small cell lung cancer…*"[77]. This program will run in parallel to Innovent's IBI323 program of their PD-1/LAG-3 directed bispecific antibody.

[75] Amgen press release: 2021. Accessed: https://www.amgen.com/newsroom/press-releases/2021/05/fda-approves-lumakras-sotorasib-the-first-and-only-targeted-treatment-for-patients-with-kras-g12cmutated-locally-advanced-or-metastatic-nonsmall-cell-lung-cancer

[76] Garralda et *al*. 2021. A phase I first-in-human study of the anti-LAG3 antibody MK4280 (favezelimab) plus pembrolizumab in previously treated, advanced microsatellite stable colorectal cancer. *J Clin Oncol*. 35(15): 3584-3584.

[77] Innovent Biologics press release; Jun 7 2021. Accessed: https://www.biospace.com/article/releases/innovent-releases-the-phase-ia-ib-dose-escalation-trial-results-of-ibi110-anti-lag-3-in-patients-with-advanced-solid-tumors-at-asco-annual-meeting-2021/

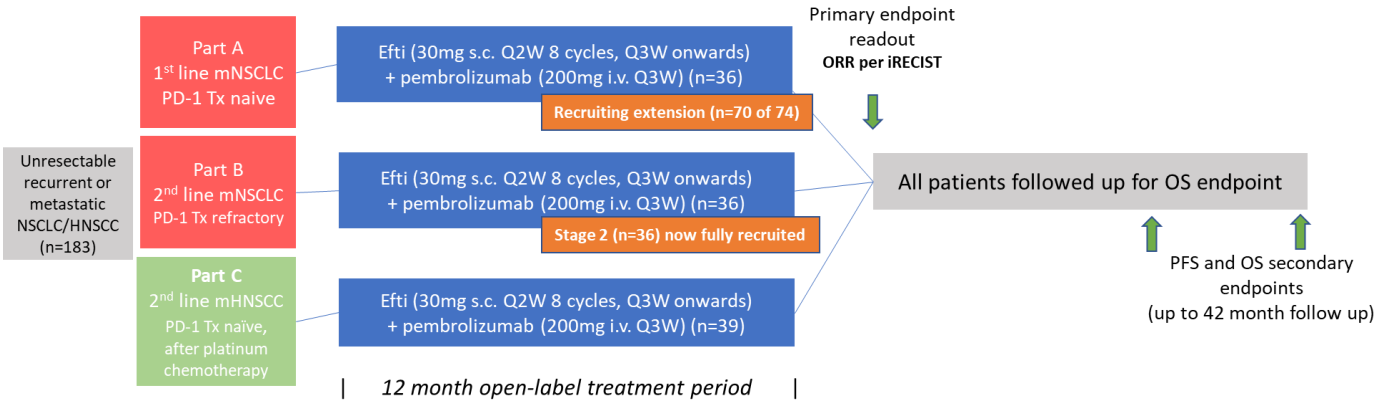
A2.5.2 Summary of clinical evidence: TACTI-002 Phase II trial of adjunct Efti in 1st and 2nd line NSCLC

TACTI-002 trial design. Refer to **Figure A13** for a summary of TACTI-002 trial design. Part A and B of the trial were focused on NSCLC patients.

Part A included metastatic NSCLC patients that were naïve to PD-1/PD-L1 targeted treatments and were undergoing 1st line therapy for their metastatic disease. A total of 36 patients were enrolled in the initial Part A (summarised in **Table A15**) with an extension cohort (n=74) currently recruiting now. This will bring the total evaluable 1L cohort to 110 patients. It is understood that completion of this extension recruitment will be in CY21.

Part B of the TACTI-002 study focused on 2nd line therapy in metastatic NSCLC patients that had previously failed PD-1/PD-L1 directed therapies (i.e. pembrolizumab, nivolumab, avelumab, durvalumab, atezolizumab alone or in combination with chemotherapy) as 1st line metastatic treatment. Part B aimed to evaluate the most prominent gap in the current NSCLC market which is busy with anti-PD-1 directed therapies and tested the hypothesis that adjunct Efti is able to boost pembrolizumab efficacy, which may previously have failed in these patients. Adequate (i.e. ≥1% TPS) PD-L1 expression levels were not a pre-requisite of trial entry.

Figure A13 restated. TACTI-002 trial design and status. Part A & B focused on mNSCLC.



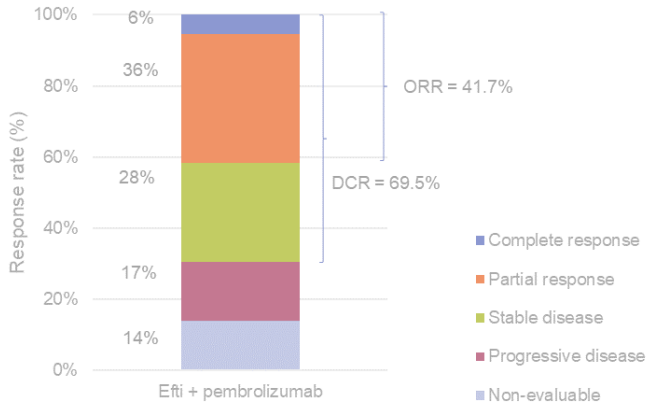
Source: Wilsons, Immutep, clinicaltrials.gov.

PD-L1 all comers approach is smart. Unlike other IO trial programs, TACTI-002 did not select for patients based on PD-L1 expression and was recruited on a PD-L1 all comers basis (Part A & B). Overall efficacy in both PD-L1 positive and PD-L1 negative patients (**Table A14 & 15**) highlights the key opportunity for Efti in this indication. Current anti-PD-1 therapies are hampered by PD-L1 expression levels. The ability for Efti to adequately boost tumour immunogenicity to a level that even low or PD-L1 absent tumours respond markedly expands the anti-PD-1 (pembrolizumab) addressable market, and by virtue that of Efti in mNSCLC.

Cross trial comparison to Keynote-042 the most relevant comparator dataset for TACTI-002 Part A. TACTI-002 does not include a pembrolizumab monotherapy 'control' arm for comparison, and therefore we look to key studies to benchmark the effects of Efti + pembrolizumab vs pembrolizumab alone. MSD's Phase III Keynote-042 trial in 1st line mNSCLC with confirmed positive PD-L1 tumours (TPS ≥1%) formed the basis of their 2019 monotherapy FDA approval in which pembrolizumab was compared to SOC chemotherapy (see **Table A15 overleaf**). Neither PFS nor ORR was improved in pembrolizumab arm vs SOC however there was a significant increase of 4.6 months in median OS and duration of response (DoR; 20.2 months vs 8.4 months respectively). We note (on all comers PD-L1 basis) that median PFS of Efti + pembro is improved +2.8 months vs Keynote-042 data and to an even greater extent in high PD-L1 (≥50%) patients (11.8 months vs 7.1 months respectively)[78].

[78] Pacheco JM. 2019. KEYNOTE-042: is lowering the PD-L1 threshold for first-line pembrolizumab monotherapy a good idea? Editorial Commentary; *Transl Lung Cancer Res.* 8(5): 723:727.

Figure A17. TACTI-002 Part A Objective Response per iRECIST criteria as determined by BICR.



BICR: Blinded Independent Central Review.
Source: Immutep, Wilsons, Clay et al. (2021)[79].

Note the difference in ORR criteria (Table A10). RECIST v1.1 for other IO studies vs iRECIST for TACTI. See section A2.4 for further detail on criteria.

Superior efficacy in those with high PD-L1 expression (≥50% TPS). As expected, there was superior efficacy (by ORR and PFS measures) in the high PD-L1 expressing cohort (~31% of total) versus the low (1-49% TPS) or PD-L1 negative (<1 % TPS) cohorts (see **Table A14**). When benchmarked again pembrolizumab monotherapy (Keynote-042 ≥50% TPS cohort)[79] we see superior indicative efficacy with respect to ORR (39% pembro vs 53.8% Efti) and PFS measures (7.1 months pembro vs 11.8 months Efti) with the Efti combination.

More notable is the high ORR in patients with < 50% TPS. As at the April 2021 interim analysis ORR for patients with low/absent PD-L1 expression (<50% TPS) was 31.6% (**Table A14**). This compares to an ORR of 27% with pembro alone in a total PD-L1 expression cohort (≥1% TPS) given <50% distinction was not reported[80]. This low PD-L1 expression cohort (1-49% TPS) represents the subset that have been the most debated[81] with regards to their relative benefit of pembrolizumab monotherapy versus a chemo + pembrolizumab combination (i.e. Keynote-407) given there was no OS benefit for the 1-49% cohort with pembrolizumab monotherapy vs SOC in Keynote-042. This presents a cohort where Efti could highlight superior efficacy to both pembrolizumab and chemo+ pembrolizumab combinations with an improved tolerability profile making it a clear first choice in 1st line treatment of these patients.

Table A14. Efficacy responses by PD-L1 subgroup (TACTI-002 Part A)

PD-L1 subgroup	Proportion of cohort	ORR (IR)	Median PFS
All (unselected)	100%	36%	8.2 months
<1% TPS	23%	27%	4.1months
≥1% TPS	77%	44%	NR
<50% TPS	69%	32%	NR
≥50% TPS	31%	54%	11.8 months

ORR per Investigator read (not BICR)
NR: Not reported
Source: Immutep, Wilsons.

High correlation between ORR and OS benefit in NSCLC IO trials supports conviction in TACTI-002 OS data readout. In trials of immune checkpoint inhibitors in NSCLC there is suggested to be a strong correlation between ORR benefit and OS benefit (as assessed by meta-analysis)[82]. We note this is positive when reflecting on the available TACTI-002 Part A data where we are yet to see OS data readouts. Taking this on board we expect that to see beneficial OS improvements with the Efti + pembrolizumab combination based on the high ORR to date.

[79] Clay et al. 2021. Results from a phase II study of Eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with PD-L1 unselected metastatic non-small cell lung carcinoma. [Abstract] *J Clin Oncol*. 39 (S15): 9046.

[80] Mok et al. 2019. Pembrolizumab versus chemotherapy for previously untreated, PD-L1 expressing, locally advanced or metastatic non-small-cell-lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 393: 1819-1830.

[81] Pacheco JM. 2019. KEYNOTE-042: is lowering the PD-L1 threshold for first-line pembrolizumab monotherapy a good idea? *Transl Lung Cancer Res*. 8(5): 723-727.

[82] XiangJi et al. 2020. Relationship between progression-free survival, objective response rate, and overall survival in clinical trials of PD-1/PD-L1 Immune checkpoint blockade: a meta analysis. *Clinical Pharmacology & Therapeutics*. 108 (6).

Table A15. Comparison of Efti vs other checkpoint inhibitors and IO combos vs SOC in 1st line metastatic NSCLC^

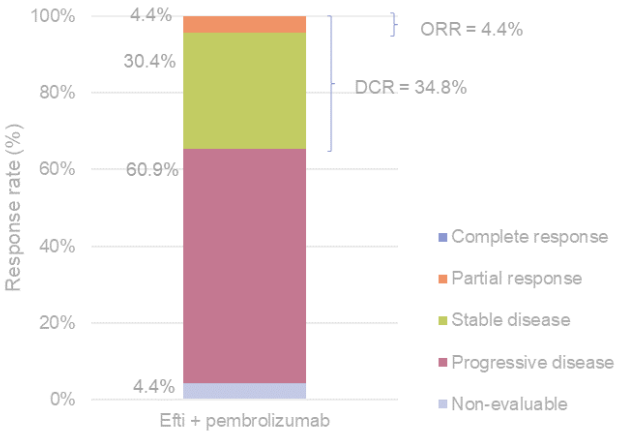
	Efti + pembrolizumab	Pembrolizumab	Atezolizumab	Pembro+ chemo	Nivolumab + ipilimumab	Atezolizumab + tiragolumab (anti-TIGIT)	Platinum-based Chemo (SOC)		
	IO - IO	IO monotherapy	IO monotherapy	IO - Chemo	IO - IO	IO - IO			
FDA approval	-	April 2019	May 2020	Oct 2018	May 2020	-			
Study	TACTI-002 Part A	Keynote-042	IMpower110	Keynote-407	Checkmate-227	CITYSCAPE	Keynote-042	Keynote-407	IMpower110
Phase	II	III	III	III	III	II	III	III	III
Therapy Line	1st	1st	1st	1st	1st	1st	1st	1st	1st
n	36	637	277	278	583	67	637	281	277
Demographics (% male)	69%	71%	71%	79%	67%	58%		84%	70%
Median age	69	63	64	65	64	66	63	65	65
% current/former smoker	94%	78%	87%	92%	85%	NR	78%	93%	87%
PD-L1 TPS <1%	23%	**nil**	**nil**	34%	32%	NR	**nil**	35%	**nil**
TPS 1-49%	46%	53%	61%	37%	33%	NR	53%	37%	65%
TPS ≥50%	31%	47%	39%	26%	35%	NR	47%	26%	35%
Median PFS	**8.2 m**	**5.4 m**	**5.7 m**	**6.4 m**	**7.2 m**	**5.6 m**	**6.6m**	**4.8 m**	**5.5 m**
HR (for progression)	-	1.07, p>0.05	0.77	0.56, p<0.001	0.79	0.58	-	-	-
Median OS (months)	**Not yet reached**	**16.7m**	**17.5 m**	**15.9 m**	**17.1 m**	**NR**	**12.1m**	**11.3 m**	**14.1 m**
HR (for death)	-	0.81, p=0.0018	0.83, p>0.05	0.64, p<0.001	0.73	-	-	-	-
DoR median	>13 m	20.2 m	not estimatable	7.7 m	19.6 m	NR	8.4m	4.8 m	5.7 m
ORR	**42%**	**27%**	**29%**	**58%**	**33%**	**37%**	**27%**	**38%**	**32%**
Response criteria	iRECIST	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1	RECIST v1.1
Adverse Events (AEs)									
Discontinuation AEs	3.5% #	8%	6%	23%	18%	8%	7%	12%	16%
Grade ≥3 AEs	50% #	18%	34%	70%	33%	15%	41%	68%	57%
Treatment related death	0%	2%	4%	4%	1%	NR	2%	2%	4%

^Note this is not an exhaustive list of all approved IO combinations and drugs ; simply a summary of interesting trial predicates and comparisons.
For trials with PD-L1 subgroups, the most inclusive dataset is shown (i.e. all PD-L1 levels) to make most comparable to TACTI-002 data. i.e. for some IO higher OS data was found in TPS>50% groups etc.
NR = not reported. # total TACTI-002 population.
*ORR is shown as the blnded independent central review values, not investigator assessed. * HR when compared to chemotherapy arm.*

Source: clinicaltrials.gov, Company data, Wilsons.

TACTI-002 Part B results showcase immunostimulatory potential of Efti in previously refractory/resistant patients. The initial results from Stage 1 (n=23) presented at SITC 2020 (8 Oct 2020 data cut-off) showed that the addition of Efti to pembrolizumab in previously anti-PD-1/PD-L1 refractory mNSCLC patients could induce a positive response (**Figure A18**). This highlights the ability of Efti to stimulate immune engagement even in those with previously unresponsive tumours. ORR was 4.4% and DCR was 34.8%. Further, 17.4% of patients (n=4) were progression-free at 6 months. The prognosis for 2nd line PD-1 refractory metastatic patients is far poorer than those in a 1st line metastatic setting, as one would expect. Primary resistance to anti-PD-1 therapies is a known driver of poor treatment response. Therefore, the potential to control disease in a third of this cohort due to the addition of Efti alone is impressive. More than 50% of patients were still alive at 12 months in this first dataset. This compares favourably to chemotherapy and anti-PD-1 monotherapy (2L nivolumab following 1st line chemo) in similar patient cohorts (42% and 24% respectively)[83] in Checkmate-017. Notably 85% of Stage 1 patients had PD-L1 expression <50% and therefore are likely to have lower responses to anti-PD-1 approaches. ~70% of patients fall within the <50% PD-L1 expression bucket and therefore they are a sizable and important cohort to focus on in order to expand the applicability of ICI therapies.

Figure A18. TACTI-002 Part B (Stage 1) responses in PD-1/PD-L1 refractory 2nd line metastatic NSCLC patients (per iRECIST).



Source: Immutep, Wilsons.

[83] Brahmer et al. 2015. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *NEJM*. 373: 123-135.

A2.5.3 Next steps for Efti in NSCLC (1st and 2nd line)

TACTI-002 Part A (1st line) extension ongoing. As of September 2021, there were 43 of 74 patients (58%) recruited in the expanded Part A cohort of TACTI-002, focused on 1st line metastatic NSCLC patients that are PD-X naïve. The recruitment of this expansion cohort is expected to be complete by end CY21. The fully recruited Part A cohort will comprise 110 patients (36 + 74 extension) which provides Immutep with a more robust sample size to evaluate differences in response with different PD-L1 expression cohorts and provides a total patient sample size closer to other historical control sets of pembrolizumab monotherapy (albeit still much smaller). At present we estimate final Part A data from the expansion cohort to have a top-line interim readout ~4Q CY22.

TACTI-002 Part B (2nd line) to report updated results in FY22 – most important cohort. We have yet to see an update on the results of TACTI-002 Part B, evaluating adjunct Efti in difficult to treat patients which have been refractory to chemo/PD-1 directed approaches, since the preliminary data presented in November 2020 at the SITC conference from Stage 1 (n=23 of 36 patients total in Part B) (**Figure A18**). Initial Stage 1 data suggested a positive effect of Efti with 17.4% progression-free at 6 months despite 100% of these patients being PD-1/PD-L1 resistant/refractory. Efficacy in this hard-to-treat patient cohort would be a significant win for Immutep, in that this patient subset (>35% total mNSCLC population) have very limited treatment options, poor prognosis and high unmet need. The ability for Efti to 'sensitise' patients to an anti-PD-1 therapy (e.g. pembrolizumab) after having previously failed treatment highlights a powerful immunogenic effect of Efti which could translate to other anti-PD-1 ICIs (which currently comprise >90% of the IO market and represent >US$30B in annual sales). Complete TACTI-002 Part B results will be the first evidence to support this potential opportunity. We understand that updated Part B data from Stage 2 (n=13) is expected in 1H 2022.

Significant opportunity presented by growing PD-1 ICI market; ability for Efti to further expand this market. The anti-PD-1 ICI market currently dominates IO with 5+ approved anti-PD-1/PD-L1 drugs. Despite this bevy of approvals in NSCLC, the majority all suffer the same fate, in that 100% of the approved combinations to date target the PD-1/PD-L1 axis and are amenable to the same acquired PD-1 resistance issues. The emergence of the first PD-1 + other checkpoint combinations (i.e. nivolumab + ipilimumab) highlights the direction the field is taking with several other ICI-ICI combinations in late stage studies with promising results (i.e. Genetech's tiragolumab + atezolizumab combination). The opportunity presented for Efti, is two-fold; a) to increase the applicability and efficacy of existing anti-PD-1 therapies for a boarder NSCLC population, in turn growing the anti-PD-1 market; and b) being used in combination with other novel checkpoint inhibitors or therapies (including chemo) to target the significant proportion of patients that fail to respond to any PD-1 directed approaches (i.e. Efti + ipilimumab).

Out-licensing opportunity for this indication. We view NSCLC as an indication that may be challenging for Immutep to clinically develop without investment from a strategic partner given the size and length of the clinical studies required to support a BLA submission (n>1000 patients). We view this indication as a key out-licensing opportunity for Efti (as opposed to mBC and HNSCC indications) where Immutep may derive the most value for shareholders through a licensing agreement with a large pharma development partner. We view potential for Immutep to use any upfront payment from this deal to support their existing clinical development programs in mBC and HNSCC.

*See **Table 3** for our estimates for a licensing deal and terms.*

MSD is the obvious licensee choice given their involvement in the TACTI-002 program to date and the use of pembrolizumab in generating the existing Phase II data. The level of interest in Efti for NSCLC from other oncology players is likely to wane the further development continues with Efti paired to pembrolizumab.

Phase II triple combination in NSCLC. We understand Immutep are currently planning a new Phase II in NSCLC evaluating a triple combination of Efti + an anti-PD-1 (i.e. pembrolizumab, nivolumab etc) + chemotherapy (n=80). This trial is separate to the INSIGHT-003 program also exploring a similar triple combination approach in 20 patients with advanced solid tumours. We expect the INSIGHT-003 data to be used as a guide prior to proceeding with this 80 patient Phase II trial.

The use of pembrolizumab in combination with chemotherapy appears to be the preferred standard of care treatment option in metastatic NSCLC patients with low PD-L1 expression (TPS 1-49%) at present (particularly in Europe where anti-PD-1 monotherapy is not indicated for those with low PD-L1 expression). This new Phase II study could demonstrate further expanded applicability of the anti-PD-1 + chemo treatment regimen (e.g. for those with low PD-L1 expression) and improve outcomes for those patients that currently have a poor response. The TACTI-002 Part B data supports this hypothesis.

Opportunity to attract a pharma collaborator (other than MSD) and expand Efti's broad anti-PD-1 appeal.
The lack of disclosure around the specific anti-PD-1 drug for this proposed Phase II triple combo trial suggests that Immutep may be looking to partner with players other than MSD (i.e. not wed themselves again to pembrolizumab in another Phase II NSCLC study). Exploring alternative anti-PD-1 partners we view as a positive for Efti's appeal to potential licensee's (other than MSD). Further, combination (synergistic) efficacy with another approved anti-PD-1 drug would highlight the broad applicability of Efti as an IO adjunct agent further expanding its label and market potential.

It is key to note that Immutep have explored this option already with their INSIGHT-004 collaboration with Pfizer & Merck KGaA evaluating their anti-PD-1 avelumab with Efti in a Phase I of advanced solid tumours with positive initial outcomes (see **section A2.7** for further detail).

A2.6 Metastatic melanoma

A2.6.1 Melanoma opportunity

Limited opportunity for Immutep in this indication; used as a foundation to enter IO scene. Melanoma is the home ground of immunotherapy, being the first indication in which an immune checkpoint inhibitor (ICI) was approved (ipilimumab in 2011). As such it has developed as a proving ground of sorts for new immunotherapy candidates in which to prove their clinical efficacy and is a highly competitive IO space which is relatively well treated compared to other cancer areas at present (given the huge advances and good responses of melanoma to IO approaches). Immutep were smart in using the TACTI-mel trial as a foray to enter the IO scene with Efti and establish relative efficacy to other IO combinations in development (a benchmarking exercise which got Efti noticed).

Data used to support future deals and valuation. The data from the TACTI-mel trial summarised below highlights the exciting efficacy of an Efti + pembrolizumab combination. This data will be, and no doubt has been used, by interested pharma partners looking to understand the clinical profile of Efti as a potential asset of interest for licensing, partnership or acquisition. As noted previously, the TACTI-mel trial represents Efti's 'right of passage' in IO clinical development and highlights its efficacy profile in refractory populations; still a key issue in IO treatment and opportunity for market expansion.

LAG-3/PD-1 combination looks to overtake CTLA-4/PD-1 combination SOC. The potential approval of relatlimab in combination with nivolumab for metastatic melanoma could be likely to replace the currently used SOC combo of nivolumab with ipilimumab. The key benefit being safety. We note that the comparative clinical efficacy of the two combinations (see **Table A16**) is similar with the ipilimumab combo only beating relatlimab incrementally on progress free survival measures, however carrying a far lower toxicity burden (Grade 3-4 TRAEs of 59% with ipilimumab vs 18.9% with relatlimab combo). This highlights the superior synergies of LAG-3 with PD-1 vs CTLA-4/PD-1 combo approach, making a good case for LAG-3 as an efficacious, but safe option. FDA's decision on relatlimab BLA is expected in early CY22 (PDUFA data of 19 Mar 2022).

A2.6.2 Summary of clinical evidence: TACTI-mel Phase I of adjunct Efti in 2nd/3rd line metastatic melanoma

TACTI-mel trial design. The TACTI-mel trial was a Phase I dose escalation trial of Efti in metastatic melanoma that evaluated three ascending doses of Efti (6, 12, 30mg) in combination with pembrolizumab backbone therapy. The trial recruited 24 patients (18 Part A + 6 Part B) that had previously failed or had an inadequate response to pembrolizumab monotherapy with late stage disease. Efti was administered subcutaneously every 2 weeks for up to 6 (Part A) or 12 months (Part B). The primary endpoint for the trial was safety and tolerability alongside defining the Phase II recommended dose. Secondary endpoints included ORR and DCR.

Final data presented at World Immunotherapy Congress in Oct 2019; showed ability of Efti to convert pembrolizumab non-responders. The Efti pembrolizumab combination achieved ORRs of 33% in Part A (6-month treatment) and 50% for Part B cohort (12-month treatment). These response rates are impressive given they were achieved in patient cohorts that were non-responders to pembrolizumab monotherapy and therefore had limited clinical treatment options. Data summarised in **Table A16** benchmarks these data against other key melanoma IO trials for reference. Further, the safety and tolerability of Efti + pembrolizumab combination holds up against other IO monotherapies and IO-IO combinations in this indication, which when compared to the high levels of efficacy, showcases a novel IO approach in melanoma that makes others take notice of Immutep.

Efti combo similar to BMS' PD-1/LAG-3 combo at first glance. The benchmarking of Efti vs relatlimab (albeit in a cross-trial comparison fashion) is a key activity that prospective partners/acquirers would be doing to evaluate Efti given that relatlimab is the first LAG-3 targeted candidate to validate (with a likely near-term approval) LAG-3 as a new checkpoint target, and its synergy with anti-PD-1 ICIs.

Keeping in mind the patient inclusion differences between the trials (TACTI-mel were PD-1 refractory 2nd/3rd line; RELATIVITY-047 are 1st line metastatic patients), (Phase I vs Phase II/III) we observe progression free survival at 6 months with Efti of 58%. Unfortunately, we are yet to see 6-month data reported for the relatlimab study. 12-month progression-free rates of 48% suggest a similar level of efficacy or greater could be achievable at 6 months. We view the Efti data as promising given the refractory population in which they are being measured which is more challenging than that of the RELATIVITY-047 study.

Efti combo also shows indicative superiority over other approved ICIs/combos. When comparing the ORR from TACTI-mel to other IO monotherapies and combinations we see it is on par with approved nivolumab + ipilimumab combination at 58% vs 56% respectively (noting the small n), and ahead of monotherapy (nivolumab, pembrolizumab) response rates which are <33% (see **Table A16**) all when comparing to first line settings (which are typically much higher than pre-treated and refractory settings as in TACTI-mel).

Table A16. Comparison of Efti vs other checkpoint inhibitors in metastatic melanoma

	Efti + pembrolizumab	Relatlimab + nivolumab	Nivolumab	Pembrolizumab		Ipilimumab	Nivolumab + ipilimumab
Checkpoint target	PD-1+LAG-3	PD-1+LAG-3	PD-1	PD-1		CTLA-4	PD-1+CTLA-4
Study	TACTI-mel	Relativity-047		Keynote-006			Checkmate-067
Phase	I	II/III		III			III
Therapy Line	2nd/3rd	1st		1st			1st
n	24*	355	359	279	277	278	314
Demographics (% male)	92%	~58%	~58%	58%	63%	58%	66%
Median age	62	63	63	61	63	62	61
Dose	30mg Efti + 2mg/kg	160mg	480mg	Q2W 10mg/kg	Q3W 10mg/kg	3mg/kg	1mg/kg nivo + 3mg/kg ipi
PD-L1 ≥ 1%	NR	41%	41%	81%	80%	81%	22%
LAG-3 ≥ 1%	NR	~75%	~75%	NR	NR	NR	NR
Median PFS	Not reached	**10.1 months**	4.6 months	5.5 months	4.1months	2.8 months	11.5 months
LAG-3 ≥ 1%	-	12.58 months	4.76 months	-	-	-	-
LAG-3 <1%	-	4.83 months	2.79 months	-	-	-	-
HR (for progression or death)	-	0.75 (p=0.0055)	-	0.58 (p<0.001)	0.58 (p<0.001)	-	0.43 (p<0.001)
PF at 6 months (%)	58.0%	47.7%^	36%^	47.3%	46.4%	26.5%	56%
Median OS	not reached	not reached	not reached	not reached	not reached	16.0months	not reached (>36months)
HR (for death)	-	-	-	0.68 (p=0.0009)	0.68 (p=0.0008)	-	0.55 (p<0.001)
ORR	**58.0%**	still blinded	still blinded	33.7%	32.9%	11.9%	58.0%
Response criteria	RECIST v1.1	RECIST v1.1		RECIST v1.1			RECIST v1.1
Treatment-related Adverse Events (AEs)							
Discontinuation AEs	4%	15%	7%	4%	7%	9%	39%
Grade ≥3 AEs	25%	19%	10%	13%	10%	20%	59%
AEs leading to death	0%	1%	0.5%	0%	0%	<1%	<1%

NR - not reported. ^There are 12 month PFS rates. 6 month rates not yet reported.

**Dual cohort analysis (18 + 6).*

Source: Wilsons, Company data, trial publications.

Efti as a vaccine adjuvant in melanoma. In addition to the TACTI-mel study Efti has been evaluated in another Phase I/IIa trial of metastatic melanoma patients, this time as a cancer vaccine adjuvant[84]. This trial was completed prior to TACTI-mel. This small trial of 16 patients highlighted that Efti did not add incremental toxicity when present as an adjuvant (consistent with its clinical profile across other cancers thus far) and that it was able to elicit T cell responses in a sustained and durable fashion. This clinical data further supports the package for Efti and its robust immunostimulatory effects in melanoma.

[84] Legat et *al.* 2016. Vaccination with LAG-3Ig (IMP321) and Peptides Induces Specific CD4 and CD8 T-Cell responses in Metastatic melanoma patients – Report of a Phase I/IIa Clinical Trial. *Clinical Cancer Research*. 22(6): 1330-40.

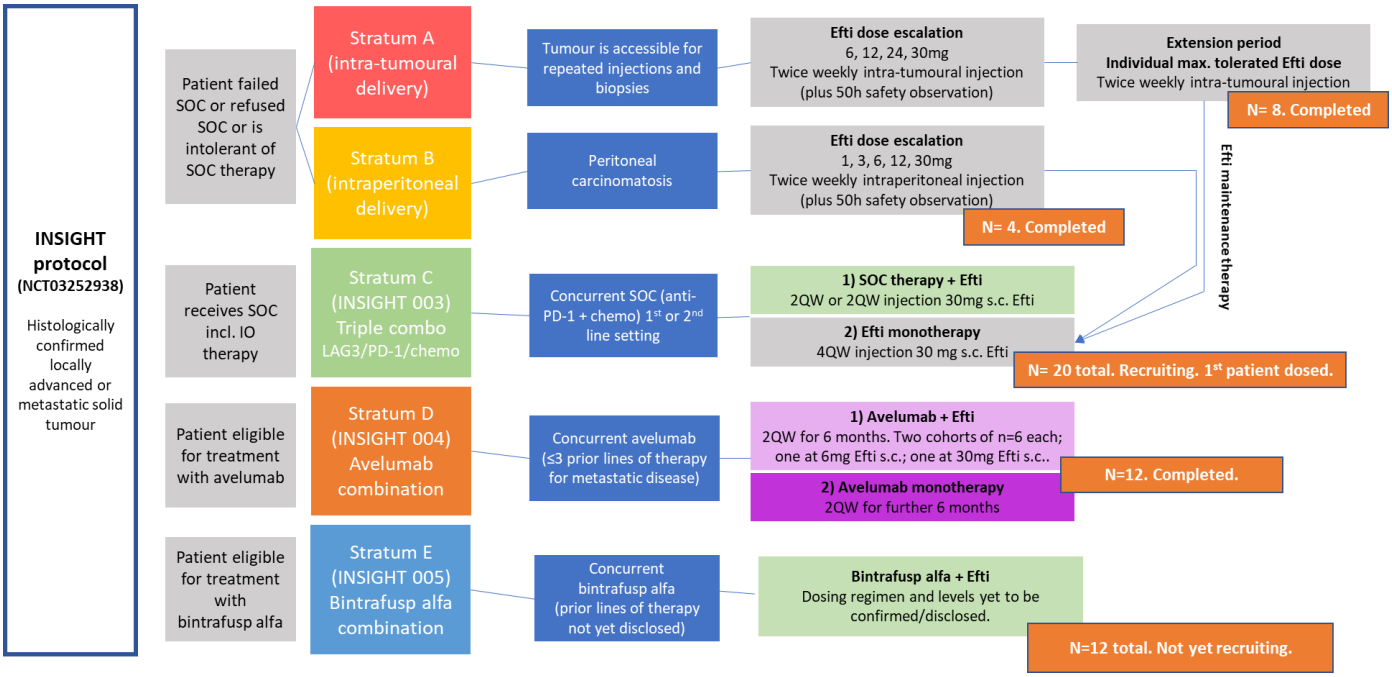
A2.7 Solid tumours (INSIGHT program)

INSIGHT paradigm

The initial INSIGHT protocol is an investigator-led, exploratory program to identify a) key indications with preliminary clinical efficacy; b) explore different administration routes of Efti (systemic vs direct); and c) explore different drug combinations with Efti (IO-IO, IO-chemo etc). This Phase I program started in mid-2017 and now consists of five different 'stratum' or trial programs within the INSIGHT protocol umbrella (NCT03252938).

Investigator led program. The INSIGHT program is conducted in collaboration with and sponsored by the Institute of Clinical Cancer Research Krankenhaus Nordwest GmbH in Frankfurt, Germany (IKF). There are a number of pharma partner collaborators across the protocol arms including Merck KGaA (Merck Germany) (INSIGHT-005 & INSIGHT-004), Pfizer (INSIGHT-004) and GSK (INSIGHT-005). The principal investigator on these studies is Prof. Salah-Eddin Al-Batran from IKF Frankfurt.

Figure A19. Trial design overview for INSIGHT program including the 5 study arms.



Source: Immutep, Wilsons.

INSIGHT Stratum A & B

INSIGHT – direct in situ immunisation. The initial focus of the first two arms of the INSIGHT protocol was to evaluate different routes of drug administration to better reach the tumour mass. Stratum A focused on direct (intra-tumoural) delivery of Efti into the solid tumour mass, as opposed to systemic administration. Stratum B focused on intraperitoneal injections for patients with tumours in this region (i.e. peritoneal carcinomatosis). The focus of these trial arms was safety of these delivery approaches.

Targeting delivery of Efti directly to tumour mass. Efti has traditionally been administered systemically via subcutaneous injection in other trial programs (i.e. AIPAC, TACTI). The INSIGHT program (arm 1 & 2) focuses on the potential benefits of targeting therapy delivery directly into the tumour mass (i.e. direct injection of Efti into tumours in vivo). The idea of direct delivery, as opposed to systemic, is being investigated for several reasons including; a) ability to delivery higher concentrations of Efti to the target cells/site; b) reducing systemic side effects of Efti delivery; c) gaining greater dose flexibility depending on the tumour location and size.

Trial design. Design for the INSIGHT stratum A and B are summarised in **Figure A19** above.

Data to date. Data was presented at ESMO 2020 on the first two arms of the INSIGHT program (n=12 patients; 8 in Stratum A, 4 in Stratum B). Patients were on their 3rd or more line of therapy with one case on their 7th line of therapy. Gastric (33%) and colon (33%) cancers were the most common. The conclusion from these arms was that administration of Efti via the intra-tumoural and intraperitoneal routes was

feasible however was technically challenging. There was one death associated with the study procedure (drug delivery) in Stratum B. The direct injection of Efti appeared to produce positive immune responses compared to baseline with incrementally positive clinical efficacy supporting the study hypothesis in these heavily pre-treated patients.

INSIGHT-003

Triplet combination focus. The focus of the 3rd arm of INSIGHT is to evaluate Efti in a triple combination approach with Efti added to both anti-PD-1 therapy (i.e. nivolumab, pembrolizumab etc) and chemotherapy. This evaluates Efti as an adjunct to the standard of care combo (anti-PD-1 + chemo) that is used in a range of advanced cancers (e.g. NSCLC, hepatocellular carcinoma, HNSCC, myeloma, melanoma). Discerning the synergies, and toxicity profile, of adding Efti to SOC regimens in these indications is key to understanding its broad potential appeal in making tumours more responsive to IO therapies (increasing the proportion of patient responders).

Provides data to inform NSCLC Phase II program. We note the mention of an 80 patient Phase II trial in NSCLC with a triple combination akin to INSIGHT-003 in Immutep's clinical development pipeline. INSIGHT-003 will provide key data to investigate the feasibility of this approach and inform Immutep's proposed triple combo Phase II in NSCLC. We note that first interim results from INSIGHT-003 are expected CY22. These data will also likely support the TACTI (002 & 003) program readouts given the overlap in indications and dual combination therapy approach (likely to include pembrolizumab backbone therapy).

Trial design is anti-PD-1 agnostic. The INSIGHT-003 program will recruit 20 patients with advanced solid tumours and will include a range of anti-PD-1 + chemo backbone therapy regimens. This program further expands the evaluation of Efti in combination with a broad range of chemotherapy and anti-PD-1 regimens. We view this data, albeit a small Phase I, as highly valuable for any pharma partner looking at Efti as a potential asset of interest. Combining it with a broadening range of SOC therapies increases its value proposition and applicable market size.

Trial design. Design for the INSIGHT stratum C arm (003) is summarised in **Figure A19** above.

Status. The INSIGHT-003 program safely enrolled and dosed the first patient in August 2021. Based on the recruitment target of n=20 we anticipate recruitment to be completed by end 1Q CY22 (currently 4 of 20 as at Sept update). The first patient has mNSCLC and is being treated with a combination of Efti + pembrolizumab + doublet chemotherapy (carboplatin + pemetrexed).

INSIGHT-004

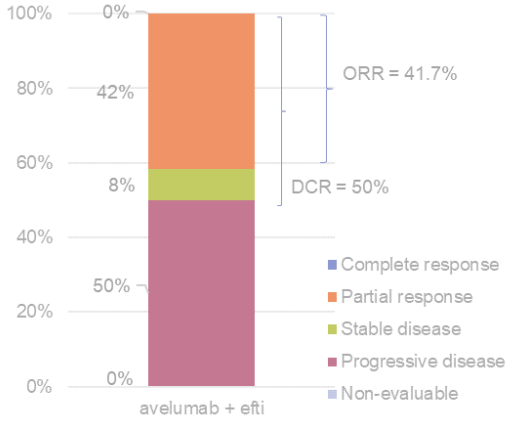
Focused on combination with another novel anti-PD-1, avelumab. The focus of the INSIGHT-004 arm is to evaluate the safety, tolerability and recommended Phase II dose of Efti in combination with avelumab, an anti-PD-1 inhibitor under development by Merck (Germany) and Pfizer. This study is key to the clinical development of Efti in that it has the potential to show the broadening applicability of Efti across different anti-PD-1 agents (and not just MSD's pembrolizumab).

In collaboration agreement with Merck Germany and Pfizer. INSIGHT-004 is conducted under a clinical trial collaboration agreement between Immutep, Merck KGaA and Pfizer, with IKF still the study sponsor.

Trial design. Design for the INSIGHT stratum D arm (004) is summarised in **Figure A19** above. Unlike other INSIGHT arms, patients progressed to avelumab maintenance monotherapy after the initial combination therapy phase.

Status. The INSIGHT-004 study is now complete with final data presented at both ASCO and ESMO conferences in 2021[85]. This data was gleaned from 12 patients, divided across two Efti doses (6mg and 30mg s.c.). The majority of patients had adenocarcinomas of the GI system (>58%). Overall, the combination of avelumab + efti was safe and tolerable with no serious AEs deemed related to treatment.

Figure A20. Clinical responses to avelumab + efti combination in INSIGHT-004.



Source: Goetze et al. (2021), Wilsons.

[85] Goetze et al. 2021. ASCO Poster #2518. Phase I INSIGHT platform trial: Advanced safety and efficacy data from stratum D evaluating feasibility and safety of Eftilagimod alpha (Soluble LAG-3 protein) combined with avelumab in advanced stage solid tumours. Accessed here.

A summary cohort ORR of 44.7% was observed with disease control in 50% of patients (**Figure A20**). Encouragingly responses were seen in some patients with low/nil PD-L1 expression levels suggesting a promising synergistic effect of Efti in this combination across a wide range of solid tumours including those that are typically unresponsive to IO approaches (i.e. cervical).

INSIGHT-005

Focused on combination with PD-L1 bispecific. INSIGHT-005 is the fifth and most recent arm of the INSIGHT protocol. This arm will evaluate Efti in an IO-IO combination with bintrafusp alfa (M7824), a bifunctional fusion protein that inhibits both PD-L1 and TFG-β, being co-developed by Merck KGaA (GSK recently announced their decision to terminate co-development of bintrafusp alfa with Merck KGaA). This further expands the range of combination therapies in which Efti will be clinically evaluated, in this triple target IO approach (three immune targets = LAG-3/PD-1/TGF-β) looking at simultaneous modulation of these three targeted signalling pathways in advanced cancers.

We do note however that Merck has had a recent failure with this drug asset (bintrafusp alfa) with its Phase III NSCLC program being discontinued (Jan 2021) following an interim data evaluation concluding it would not meet its co-primary endpoint of progression free survival (PFS).

Collaboration and supply agreement with Merck KGaA. This study is being conducted under a new (June 2021) clinical trial collaboration and supply agreement with Merck Germany (the second agreement; first agreement for INSIGHT-004). The study is funded by Immutep with Merck KGaA supporting the biomarker-related research costs of the trial. The study is sponsored and conducted by the IKF.

Trial design. Design for the INSIGHT stratum E arm (005) is summarised in **Figure A19** above. The trial design specifics for this study are yet to be disclosed with regards to drug dosing and regimen as well as specific inclusion criteria (i.e. prior lines of therapy). The *clinicaltrials.gov* registration is yet to be updated to include stratum E with this information also. Given this is a newly announced study (June 2021) we expect this data to be forthcoming in the near future.

Status. We are unconfirmed on the recruitment status of INSIGHT-005 at present but understand the study should recruit this CY at two German sites with 12 previously treated patients to be enrolled in total. Immutep have announced they expect initial interim data from this trial in CY22.

A2.8 Manufacturing

Focus and investment in manufacturing ahead differentiates from crowd. We have seldom seen other ASX biotech peers of this size and development stage engage on the manufacturing front the same extent as Immutep have. They understand the importance and challenges associated with biological agent manufacturing and the importance this aspect, which can often be deprioritised over clinical readiness, in the regulatory approval process. Immutep have invested heavily in manufacturing capabilities and building strong partnerships with expert CDMOs including Wu Xi Biologics. The discussion and focus on manufacturing at this stage of Immutep's development highlights a quality management and operations team that are forward thinking with a commercially directed mindset.

Partnership with Wu Xi instrumental. Immutep entered into a partnership with Chinese speciality CDMO Wu Xi Biologics in 2015 to help support their advancement of Efti manufacturing. Efti supply for the early AIPAC and TACTI-mel trials was undertaken by Wu Xi, with the AIPAC trial representing the first time a Chinese manufactured biologic drug was used in a European clinical trial. Wu Xi continue to be the exclusive manufacturer of Efti being used in all of Immutep's clinical trial programs. Further, we see the commercial value in this partnership which is able to deliver quality, commercial-grade biological product at a very reasonable price expanding IMM's future margin potential.

Batch scale up to commercial quantities underway. We understand that Immutep have started the scale up process to produce Efti in batch sizes that are adequate to supply large Phase III clinical trials and ultimately in batch sizes that are relevant for commercial manufacture. Immutep and Wu Xi are currently working to complete scale up from a 200L bioreactor to a 2,000L bioreactor batch size. They plan to advance their Drug Master File (DMF) with the FDA ahead of a Phase III IND submission for their AIPAC Phase III study in 2022. The composition of a BLA (biologics license application) submission involves detailed manufacturing documentation to support marketing authorisation. We note $13.5M use of funds from the recent July (2021) capital raise is earmarked for manufacturing which we understand support these activities (scale up, DMF preparation, drug manufacture for AIPAC Phase III and TACTI-003).

Ahead of peers with regards to Phase III supply readiness. Immutep are now well setup and supported from a manufacturing perspective to produce adequate quantities of Efti for their ~500 patient Phase III AIPAC study, their new Phase II triple combination study in NSCLC and also their TACTI-003 Phase IIb in HNSCC. Additionally, they have capacity to support their investigational collaborations and research efforts. Given this preparation we would not expect delays following completion of their registration trial (AIPAC Phase III) before a BLA could be submitted due to manufacturing preparedness.

Appendix III: Out-licensed assets, R&D pipeline

Out licensed assets

Alongside their in-house assets (Efti, IMP761) Immutep have two assets (also directed toward LAG-3) they have out licensed to strategic partners (GSK, Novartis). In each case Immutep receive milestone payments and have the future optionality of royalties associated with commercial revenue. Immutep do not fund any R&D expense associated with these programs, and retain the IP associated with both assets.

A3.1 LAG525 (Ieramilimab)

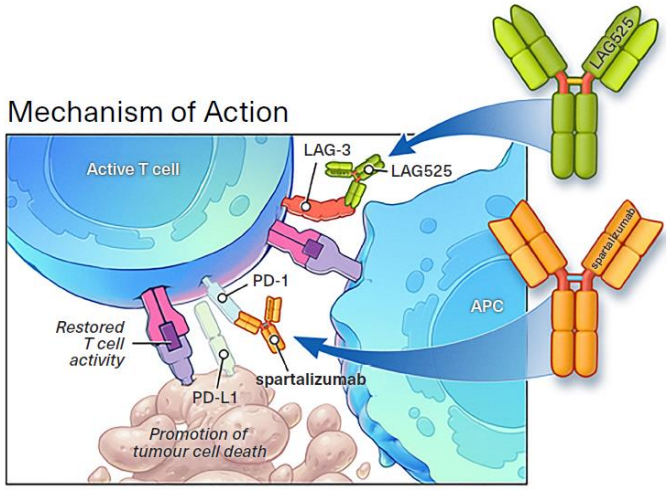
Current asset based on IMP701; IP retained by IMM. LAG525 was developed Novartis based on Immutep's licensed asset, IMP701. The initial agreement struck in 2012 for IMP701 was between Immutep SA (prior to its 2014 acquisition by Prima Biomed) and CoStim Pharmaceuticals (acquired by Novartis in early 2014). This was an exclusive licensing agreement covering the development and commercialisation of antagonist LAG-3 antibodies.

Novartis modified IMP701 creating a humanised antibody version (Ieramilimab) which they are developing. Despite modification by Novartis (CoStim), Immutep retain the fundamental IP that supports the LAG525 asset which included scope for humanisation.

A recently granted (Aug 2021) Chinese patent for LAG525 and its uses is co-owned by Novartis and Immutep and will expire in March 2035. This sits alongside granted Japanese, European, Australian and US (x2) patents covering the LAG525 asset (composition of matter) and its use in combination therapy.

LAG-3 antagonist asset. LAG525 (Ieramilimab) is a humanised anti-LAG-3 monoclonal antibody being developed by Novartis in a range of oncology indications. It is mechanistically similar to BMS' relatlimab that is currently under FDA review. It is a classical antagonist monoclonal antibody that is targeted to blocking LAG-3 on tumour infiltrating lymphocytes preventing the inhibitory signalling to effector T cells (allowing for their activation) and at the same time inhibiting regulatory T cells which sit as a "guard" of sorts preventing T cells responding to antigen presentation. This removes the 'brake' on the immune system at two points so that it is free and able to aid in fighting tumour cell growth & survival. The ability for LAG525 to act on both effector and regulatory T cell types differentiates it from other ICI assets (that just modulate effector T cell actions, only removing 1 of 2 inhibitory 'brakes'). LAG525's mechanism of action is shown in combination with an anti-PD-1 (**Figure A21**).

Figure A21. Mechanism of action for LAG525 + spartalizumab combo.



Source: Carey et al. (2021).

Programs focused in TNBC, melanoma & others. Novartis have >3 Phase II clinical programs evaluating Ieramilimab across a range of indications including triple negative breast cancer, NSCLC, melanoma and haematological cancers (See **Table A3**).

Novartis has paired LAG525 with their anti-PD-1 spartalizumab, however likely to change moving forward. We understand the anti-PD-1 drug, spartalizumab, that has been used in combo with LAG525 thus far, has since been deprioritized by Novartis (following a Phase III melanoma failure last year) in favour of a newly acquired anti-PD-1 mAb asset from Chinese biotech BeiGene, tisleziumab (US$650M upfront payment +US$1.55B in milestones paid in Jan 2021). This likely restarts several of the Phase II programs.

Data thus far underwhelming; signal in anti-PD-1 pre-treated patients more encouraging. Recent data (2020)[86] from the Phase II study in advanced cancers (including NSCLC, RCC, mesothelioma & TNBC) which evaluated LAG525 in combination with anti-PD-1 spartalizumab showed underwhelming results, including when compared to the outcomes of Efti + pembrolizumab in some of these indications (see data in **Table A17**). The trial did show some (albeit limited) efficacy in anti-PD-1 pre-treated patients; i.e. 9.1% ORR in melanoma pre-treated patients. As noted previously, Novartis now seem to be pivoting their anti-PD-1 program away from spartalizumab owing to low efficacy, which is likely a key feature of the data in in this program thus far. Encouragingly safety is good (i.e. LAG525 appears well tolerated). Earlier data from the initial Phase I/II was more positive[87] and showed that when tumours were re-biopsied after treatment and compared there was conversion from "cold" to "hot" or immune-activated tumours indicating a beneficial effect of LAG-3 targeting with LAG525.

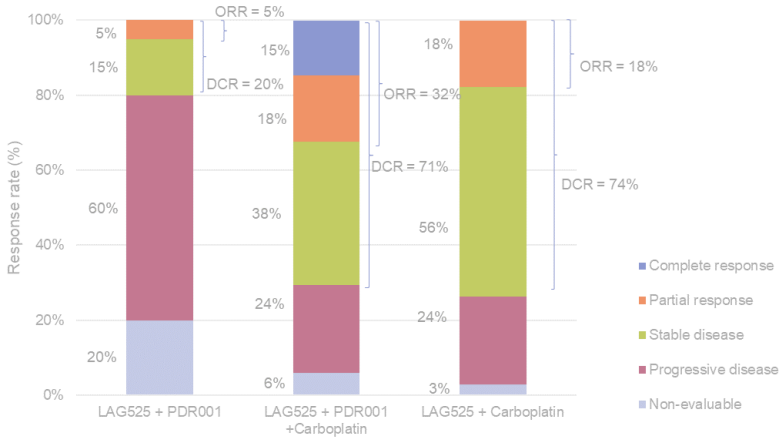
Table A17. Overall response rate (ORR) for Novartis' LAG525 + spartalizumab Phase II advanced malignancies program.

ORR (90% CI)					
Anti-PD-1/PD-L1	**NSCLC**	**Melanoma**	**RCC**	**Mesothelioma**	**TNBC**
sample size (n)	*20*	*20*	*19*	*41*	*42*
Naïve	15%	15%	26.3%	17.1%	9.5%
	(4.2-34.4)	(4.2-34.4)	(11.0-47.6)	(8.2- 29.7)	(3.3-20.5)
Pre-treated	0%	9.1%	5.3%	6.3%	0%
	(0.00-12.7)	(1.6-25.9)	(0.3-22.6)	(0.3-26.4)	(0.0-19.3)

Source: Lin et al. (2020)

mTNBC data highlights efficacy of triplet combo including LAG525. The most recent data presented form the LAG525 program was at ESMO this year (Sept 2021)[88] from the Phase II metastatic triple negative breast cancer (TNBC) program, again evaluating LAG525 in combo with spartalizumab but also carboplatin chemotherapy. The trial evaluated different combinations of the three compounds with the triple combination producing the greatest effect (ORR 32.4%) and the LAG525 + spartalizumab arm the least (ORR 5.0%). The LAG-3/chemo arm was intermediate in effect (ORR 17.6%). See **Figure A22.** Despite this, none of the arms met the proof of preliminary efficacy criteria (ORR ≥ 35%) suggesting this program is unlikely to progress further from here. We understand spartalizumab is the key impediment in this Novartis program and not LAG525.

Figure A22. Clinical responses from LAG525 Phase II study in TNBC.



Source. Carey et al. (2021), Wilsons.

Other triple combos underway. In parallel, Immutep are now progressing an Efti triple combo trial (Efti/anti-PD-1/chemo) in solid tumours (INSIGHT-003) in addition to an Efti triple-combo Phase II in NSCLC (preparation).

Two milestones received. Immutep (nee Prima Biomed) received the first licensing milestone in August 2015 associated with LAG525 entering clinical phase trials (undisclosed $). A second milestone was received by Immutep in July 2017 likely associated with successful data readout from the Phase I/II study of LAG525 in combination with spartalizumab (NCT02460224) that was later presented at ASCO 2018[89].

Costs lie with Novartis. Under the terms of their license agreement, Novartis are responsible for all development costs associated with Ieramilimab. Immutep are eligible to receive milestone payments and potential future commercial royalties should it gain marketing authorisation. The details of this license agreement are not public. We assess a royalty in the order of 3-6% would be a typical range for such a transaction.

LAG525 not in current valuation. We do not model any explicit revenues associated with the LAG525 program, nor does it factor into our SOTP valuation at this time.

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[86] Lin et al. 2020. A Phase II, multicentre study of the safety and efficacy of LAG525 in combination with spartalizumab in patients with advanced malignancies. *Journal for ImmunoTherapy in Cancer*. 8(s3). Abstract #387.
[87] Hong et al. 2018. Phase I/II study of LAG525 ± spartalizumab (PDR001) in patients (pts) with advanced malignancies. *Journal of Clinical Oncology*. 35 (S15); 3012.
[88] Carey L et al. 2021. A Phase 2 study of LAG525 in Combination with Spartalizumab (PDR001), PDR001 and Carboplatin (Carbo), or Carbo, as First- or Second-Line Therapy in Patients (Pts) with Advanced (Adv) Triple-Negative Breast Cancer (TNBC). POSTER 275P. Accessed online here.
[89] Hong et al. 2018. Phase I/II study of LAG525 ± spartalizumab (PDR001) in patients (pts) with advanced malignancies. *Journal of Clinical Oncology*. 35 (S15); 3012.

A3.2 IMP731 (GSK2831781)

GSK licensing deal signed in 2010. In December 2010 GSK entered into an exclusive licensing deal with Immutep SA (pre-Prima acquisition) for the rights to develop and commercialise IMP731. The deal included an upfront payment (undisclosed) with the deal (upfront + milestones) totaling £64M (~A$118M). We understand at present there is still £54M (~A$100M) in outstanding milestones based on development progression of the program (with an upfront in 2010 and two milestones in 2015 & 2019 now paid). Importantly, these are not tied to any one indication (i.e. not impacted by recent UC trial termination). The deal also includes scope for royalties (single-digit, tiered) on any future commercial revenues from IMP731.

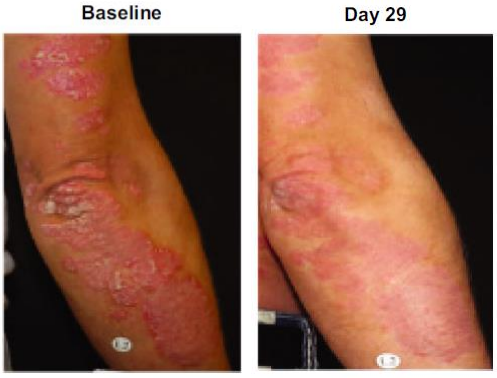
Mechanism of action is unique. IMP731 is a depleting antibody of LAG-3, meaning it is cytotoxic to LAG-3 expressing, recently activated T-cells and destroys these cells in a targeted fashion. This is a unique mechanism to that of the other IMM assets (Efti, IMP701, IMP761). There are two signalling mechanisms employed in order to kill these LAG-3 expressing T cells; complement-dependent cytotoxicity (CDC) or antibody dependent cellular cytotoxicity (ADCC). Put simply, via either pathway, the problematic LAG-3 expressing activated T cells which are perpetuating the autoimmune response via inflammatory signalling are removed from the chain of events, thus reducing the disease perpetuation. This approach could be disease modifying over time if complete removal of activated LAG-3 T cells was achieved.

GSK2831781 derived from IMP731 IP. In a similar case to LAG525, the GSK asset under development is GSK2831781, which was derived from the IMP731 asset that was licensed by Immutep to GSK. Immutep still retain the IP rights in relation to IMP731 and GSK2831781 within their patent families.

Autoimmune conditions the target. Please see **section A3.3 overleaf** for further detail. LAG-3 signaling has been shown to be involved in autoimmune disease (AID) processes. In this case specifically, upregulation and expression of LAG-3 on activated T cells forms part of the pathogenic process that support the overstimulation of the immune system supporting the disease symptoms. Removal of these cells aids in halting the disease cascade as a novel therapeutic approach to driving immunosuppression in AIDs.

Initial safety and efficacy data supportive in psoriasis. The initial first in human Phase I/IIs study[90] included both healthy volunteers (n=40) and patients with psoriasis (n=27) evaluating GSK2831781 at five ascending doses vs. placebo (3 doses in psoriasis cohort). The drug was well tolerated and safe with no drug-related serious adverse events. The study showed improvement of psoriasis symptoms (reduced inflammatory markers and presentation) in patients with mild-to-moderate disease (vs placebo) with LAG-3+ cell levels measurably reduced in blood and lesion areas highlighting efficacy of the approach (**Figure A23**). This provides a basis for further work in psoriasis but also other AIDs. This first clinical study supported the progression of GSK2831781 into a Phase II in ulcerative colitis.

Figure A23. Comparison of psoriasis lesions at Baseline vs Day 29 after treatment with 1.5mg/kg GSK2831781.



Source: *Ellis et al. (2020).*

Recent Phase II study in ulcerative colitis terminated due to lack of efficacy. Earlier this year (Jan 2021) GSK announced they had terminated their Phase II trial of GSK2831781 in ulcerative colitis (NCT03893565). Futility, following a planned interim analysis, was noted as the reason behind this decision to end the trial early. Whilst this is a negative step we don't write off the potential of GSK2831781 given the heterogeneity of autoimmune diseases, and the potential for this drug asset to show efficacy in another key indication in which LAG-3 signaling has been shown to be involved in disease development (i.e. psoriasis, Type 1 diabetes, multiple sclerosis, rheumatoid arthritis).

*See **section A3.3** for further detail and references on LAG-3 involvement in autoimmune disease.*

Granted patents in major jurisdictions. IMP731 is covered by granted patents that relate to specific antibody sequences, its use to deplete LAG-3 expressing T cells and the mechanisms related to this action. The patent family covers the use of IMP731 for the treatment and/or prevention autoimmune conditions and organ transplant rejection. First patent rights were granted in 2010 for IMP731. Patents are granted in Europe, USA, Canada and Japan with an expiry in April 2028.

*See **section A4** for further detail.*

[90] Ellis et al. (2020). Depletion of LAG-3+ T cells translated to Pharmacology and Improvement of Psoriasis Disease Activity: A Phase I Randomized Study of mAb GSK2831781. *Clinical Pharmacology & Therapeutics*. 109(5): 1293-1303.

Two milestones received to date. The first milestone was paid by GSK in early 2015 (single digit million dollar sum) correlating to the first patient being dosed in the First-in-Human Phase I of GSK'781 trial (NCT02195349) evaluating safety and tolerability, in addition to PK/PD in healthy patients and those with plaque psoriasis (autoimmune condition). The second milestone payment of £4M (~A$7.4M) was received in September 2019 associated with the first patient being dosed in GSK's Phase II ulcerative colitis study with GSK2831781.

All development costs lie with GSK. Akin to LAG525, GSK assumes all responsibility for the clinical development and potential commercialisation of GSK2831781, including all associated costs.

IMP731 not in current valuation. We do not model any explicit revenues associated with the IMP731 program, nor does it factor into our SOTP valuation at this time.

R&D pipeline

A3.3 IMP761

The forgotten child. The IMP761 asset is an interesting one, and the second asset of Immutep's that remains entirely inhouse. IMP761 is the earliest stage asset in clinical development within their pipeline and therefore we appreciate why there is limited focus on this asset at present. We assess IMP761 has the potential to be as important to Immutep's valuation as Efti in time, with a far-reaching indication TAM in autoimmune disorders (AIDs), again taking a novel approach to this set of disorders.

IMP761 mechanism of action. Regulatory T cells exerting cytotoxic actions leading to the destruction of the body's own healthy cells occurs in autoimmune diseases. LAG-3 is a checkpoint that modulates the activities of T cells. Deficient LAG-3 signalling has been shown to be linked to AID development. IMP761 is a selective, humanised monoclonal antibody, LAG-3 agonist that binds to LAG-3 receptors expressed on the surface of T cells to promote an inhibitory immune response (immunosuppressive). Activation of LAG-3 receptors on T cells is a homeostatic mechanism that keeps the immune system in check; when agonised it generates a more robust inhibitory block to autoimmune T cells which is positive in conditions were the immune system is over stimulated and attacking itself (this is the opposite mechanism to tumour attack in which the immune system is stimulated to attack tumour cells). IMP761 is a first in class LAG-3 agonist.

AIDs are caused by immune overstimulation. Immunosuppressive drugs are required to manage the disease.

Rationale for LAG-3 involvement in Autoimmune disorders has been shown both pre-clinically and correlates to clinical observations. Studies have shown that LAG-3 signalling is involved in the development of autoimmune disorders including Type 1 Diabetes (T1D)[91], psoriasis & related conditions[92], inflammatory bowel disease (IBD)[93], multiple sclerosis (MS)[94] and rheumatoid arthritis (RA)[95]. LAG-3 has been shown to play a key role in the prevent of autoimmunity development and deficiency of LAG-3 has experimentally been shown to increase susceptibility to autoimmune disease[96]. We could perhaps think of LAG-3 signalling as a contributing "brake" on the immune system that when removed or lessened causes immune overstimulation leading to pathogenesis. Reinstalling this 'brake' mechanism (i.e. the deficiency in LAG-3 signalling) may be therapeutic in returning the immune system to normal functioning levels.

IMP761 a disease-modifying treatment, as opposed to symptomatic. Modulation of LAG-3 signalling represents a disease-modifying strategy in AID, as opposed to inhibition of inflammatory response that is induced further downstream as a result of T cell activation, which is symptomatic (i.e. Humira blocks TNFα which is produced as a result of T cell activation downstream). Targeting the root cause of AIDs in a manner than can prevent downstream sequelae is a more a complete way in which to promote immunosuppression and disease control, hence why IMP761's MOA is extremely interesting in the realm of AIDs which currently lack effective disease-modifying treatments.

IP protection secured. Immutep were granted a patent for IMP761 covering the European market in Oct 2020 with an expiry in 2036. This patent captures use of IMP761 in a vast range of AIDs. Patents in the US and other major markets are not yet granted (still pending).

*See **section A4** for more details relating to granted patents.*

Initial preclinical safety & efficacy data positive. Non-human primate safety studies of IMP761 have shown it can bind with high affinity to the correct LAG-3 expressing T cells and exert immunosuppressive effects. Proof-of-concept in non-human primate models of delayed type hypersensitivity (DTH) has recently been published that highlights the early potential of IMP761 in modulation of regulatory T cells in order to suppress a deleterious antigen-induced T-cell response [97]; an immunosuppressive response relevant for therapeutic treatment of AIDs.

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[91] Bettini *et al.* 2011. Cutting Edge: Accelerated Autoimmune Diabetes in the Absence of LAG-3. *Journal of Immunology*. 187: 3493-3498.
[92] Gertel S *et al.* 2020. LAG-3+ T Cells are diminished in Active Psoriatic Arthritis Patients and their restoration in vitro is mediated by TNF inhibitors [abstract]. *Arthritis Rheumatol.* 72(S10).
[93] Bauché *et al.* 2018. LAG3+ Regulatory T Cells Restrain Interleukin-23-producing CX3CR1+ Gut-Resident Macrophages during Group 3 Innate Lymphoid Cell-Driven Colitis. *Immunity*. 49: 342-352.
[94] Jones B *et al.* 2021. T cells in relapsing-remitting multiple sclerosis demonstrate diminished expression of LAG-3. *J Immunol.* 206 (S1): 51.10.
[95] Nakachi *et al.* 2017. Interleukin-10-producing LAG3+ regulatory T cells are associated with disease activity and abatacept treatment in rheumatoid arthritis. *Arthritis Research & Therapy*. 19: 97.
[96] Jha V *et al.* 2014. Lymphocyte Activation Gene-3 (LAG-3) Negatively Regulates Environmentally-Induced Autoimmunity. *PLOS One*. 9(8): e104484.
[97] Angin et al. 2020. A LAG-3-Specific Agonist Antibody for the Treatment of T Cell-Induced Autoimmune Diseases. Journal of Immunology. Doi/10.4049/jimmunol.1900823.

Humira the best drug predicate when thinking about IMP761 opportunity. Abbvie's blockbuster anti-TNFα drug, Humira, is a mainstay therapy in many AID indications including IBD (~$1.2B sales) and rheumatoid arthritis (RA) (~$6B sales), with annual sales totalling US$19.8B in 2020. This is however expected to erode further as more Humira biosimilars enter the market, which should also continue to support and reinvigorate new R&D into the AID space. Abbvie's follow on answer for RA launched in 2020 is RINVOQ, a JAK inhibitor (a drug class riddled with safety concerns), that has already seen sales of US$681M in 1H21. These figures highlight the significant opportunity for effective drugs with superior safety and tolerability profiles, given the blockbuster incumbents struggle on this front yet still achieve >$1B annual revenues in these AID indications.

Next steps. The completion of GMP and preclinical development studies (including toxicology) is the next step for Immutep in advancing IMP761 closer to the clinic, ahead of a Phase I safety study. We understand that there are plans to prepare an IND package for an IMP761 Phase I study within the next two years, meaning we may see this asset in the clinic by CY23.

Most recent capital raise highlights near term investment. We would expect to see significant investment by Immutep into this program in the coming years once the advanced Efti programs (TACTI-003, AIPAC-II) are underway. We note that capital was earmarked at the July 2021 raise to progress IMP761 to IND stage and understand that the necessary preclinical and manufacturing work to support an IND package are being prepared signalling active investment and development of this program by Immutep.

Another asset with partnering optionality; not in current valuation. Whilst Immutep have not out-licensed IMP761, as they can add further value to this asset given its early stage, it provides them with an additional out-licensing opportunity akin to the path taken with their Novartis and GSK partnered assets. This could provide a further deal opportunity including upfront payments (plus milestones and royalties) which could assist in providing non-dilutive capital for Immutep in the future. IMP761 does not contribute to our current SOTP valuation at this time.

A3.4 LAG-3 Diagnostics

Immutep have access to this area via LabCorp partnership. Late last year (Oct 2020) Immutep entered into a collaborative agreement with LabCorp, a large US-based clinical laboratory provider and diagnostics developer, to lend their expertise and knowledge of LAG-3 to support development of LAG-3 targeted diagnostics. We would expect to see the assessment of LAG-3 expression status for tumours become more standard practice as the first potential anti-LAG-3 therapies are clinically adopted (i.e. relatlimab). This partnership provides Immutep with access to the IO diagnostics market with no risk and potential upside should they aid in development of a successful diagnostic programs that support new drug and/or indication approvals.

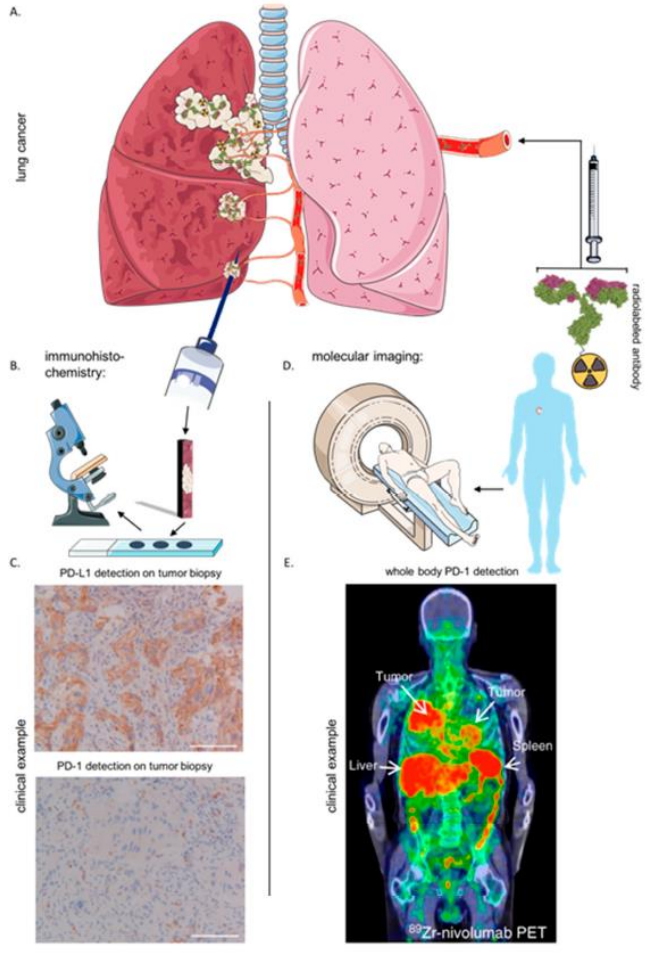
LabCorp working with BMS to develop LAG-3 diagnostic tests. We note that LabCorp are also collaborating with the other LAG-3 leaders in the IO space, BMS, in order to develop LAG-3 tumour expression diagnostic assays that can be used to define LAG-3 expression status of tumours on a standardised combined positive score (CPS) scale. A recent presentation at the American Association for Cancer Research (AACR) meeting in April[98] highlighted early work from this collaboration evaluating LAG-3 and PD-1 expression levels in various tumour types and the associated correlations via newly developed immunohistochemistry assays.

Several FDA approvals of ICIs predicated on companion diagnostic use; LAG-3 could follow in PD-L1's footsteps. The use of targeted immunotherapies (i.e. anti-PD-1) has brought about the need for specific companion diagnostics to define eligible patients based on the approved tumour biomarker subsets. In **Figure A3** we previously highlighted the number of ICI approvals (≥13) that require use of an FDA-approved companion diagnostic (CDx) across a range of ICIs and indications. It is foreseeable that future LAG-3 targeted therapies may follow this same path with FDA approvals premised on companion diagnostic tests. This supports the future growth trajectory of this segment which is in its infancy.

Regeneron developing companion diagnostic alongside their LAG-3/PD-1 bispecific; focused on whole of body imaging. In metastatic cancer, where secondary tumours can be diffuse the use of a whole of body approach to identify biomarker expression (i.e. using PET) is superior to localised expression being evaluated from the tumour biopsy via immunohistochemistry techniques (**Figure A24** shows example with PD-L1 expression).

Memorial Sloan Kettering are currently evaluating Regeneron's LAG-3 directed PET tracer (^{89}Zn-DFO-REGN3767) in a Phase I clinical trial of diffuse large B cell lymphoma (NCT04566978) to evaluate its biodistribution and optimal imaging time for tumour uptake, as well as accuracy of LAG-3 expression. A second Phase I/II study by Regeneron is looking to combine this PET tracer with an anti-PD-1 in metastatic solid tumours[100]. Regeneron's PET tracer accompanies their anti-LAG-3 mAb (REGN3767) that is currently in an ongoing Phase I of advanced solid tumours (NCT03005782).

Figure A24. Molecular imaging (i.e. PET) allows a whole of body approach vs a biopsy for identification of immune checkpoint expression which is beneficial in metastatic cancers that are diffuse (PD-L1 NSCLC example).



Source: Lecocq et al. (2021)[99]

[98] Dillon et *al.* 2021. Distribution and prevalence of LAG-3 expression in samples of melanoma and gastric/gastroesophageal junction cancer [Abstract] AACR 2021 Annual meeting. April 10. Poster 1625. https://www.abstractsonline.com/pp8/#!/9325/presentation/2726
[99] Lecocq et *al.* 2021. The Next-Generation Immune Checkpoint LAG-3 and its Therapeutic Potential in Oncology: Third Time's a Charm. *Int J Mol Sci.* 22:75.
[100] https://clinicaltrials.gov/ct2/show/NCT04706715

Appendix IV: Intellectual Property summary

The majority of IP currently held by Immutep Ltd is via its wholly owned subsidiary Immutep SAS. Immutep SAS was the original company acquired in 2014 by then Prima Biomed, which was formed via a collaborative spin out from the INSERM research institute & Institut Gustave Roussy (Paris) and Merck Serono (subsidiary of Merck KGaA, Germany). **Table A18** below summarises IMM's top-line patent portfolio.

Efti composition of matter IP now lapsed, combination IP guards Efti asset. The initial composition of matter patents for Efti (PCT/FR95/00593) owned by INSERM & Institut Gustave Roussy (Paris) with Frederic Triebel as an inventor are now lapsed (1995-2015) with a know-how license still in place with INSERM and Merck Serono with attached financial obligations (undisclosed). Given the early stage at which this license deal was struck we would expect they are not material (i.e. royalties 2-5%). Immutep's IP strategy has been to insulate Efti via method of use patents. The patent families summarised in **Table A18** highlight the breadth of IP surrounding the use of Efti, importantly with any anti-PD-1 antagonist in an IO-IO combination, with any chemotherapy (IO-Chemo combination) and including triplet combinations (IO-IO-chemo) with expiries of key anti-PD-1 patents out to 2036. We understand there is scope for up to a 5-year patent term extension in some cases. Further, Immutep have a wealth of inhouse knowledge and manufacturing trade secrets which support the Efti IP portfolio.

Market and data exclusivities support patent lifetimes. As noted in our **forecasts section (pp21**) Efti represents a novel biologic entity which at the time of approval in either US or EU markets would be eligible for >10year exclusivity periods (US = 12 years total; EU = 10 years total). This would further extend Efti's market exclusivity by 2+ years beyond its current patent term across indications (depending upon the first year of approval). We note the combination of Efti with chemotherapy has a patent expiry of 3 Oct 2028 which is relevant to the AIPAC mBC program. Based on our modelling and the entry of Efti into a registration study in this indication, we would expect a market approval ahead of this expiry. This combination approach (Efti +chemo) would then be protected by the 10-12 year biologics exclusivities granted by regulators extending the exclusivity for this patent family out to ~2036e. Recently however, Immutep have filed a new patent family focused on AIPAC subgroup data with an expiry out to 2041 which further protects the Efti mBC program.

Immutep patents for IMP731 and IMP701 are not negated by subsequent changes to the drugs. In both cases of the out-licensed IMM assts (IMP701 and IMP731), modifications to these drugs have been made by the licensees Novartis and GSK, respectively, and the modified assets are now in clinical development. Importantly, Immutep's IP is retained within these deals and its patents extend to the modified assets (LAG525 and GSK2831781). Immutep's patents are not negated by these modifications as they have claims that are much broader than the patent claims of either Novartis or GSK which are enforceable in these programs. As such, we see limited risk, that should either LAG525 or GSK2831781 make it to commercialisation stage, that Immutep would not be eligible for their agreed royalties for these assets.

Binding assay is potential blocking IP precluding unlicensed biosimilar manufacture. Immutep's patent family includes IP around a LAG-3 binding assay which could be potentially valuable in future at a point of biosimilar drug development which would require this assay in the manufacturing process. These patents are yet to be granted. We note an expiry of Dec 2037. Based on our modelling of Efti market entry we would not expect biosimilar market entry until ~2036 at the earliest (in EU, ~2038 in US), with the first applications being filed from ~2030, allowing a 9-10 year window for this IP to be potentially relevant to Efti biosimilar manufacturers.

IP surrounding BMS' relatlimab includes Johns Hopkins patent EP265898. We highlight this patent in particular given the broad range of claims made with regard to modulation of LAG-3. Key claims include:
Claim 1; An inhibitory agent which binds to CD223 protein or CD223 mRNA and anti-cancer antibodies for use in treating cancer in a mammal.
Claim 2; The inhibitory agent and the anti-cancer antibodies for use according to claim 1, wherein the inhibitory agent and the anti-cancer antibodies increase the number of T-cells in the mammal being treated.
Claim 3; The inhibitory agent and the anti-cancer antibodies for use according to claim 1 or claim 2 wherein the inhibitory agent is an antibody which specifically binds to CD223 protein.

We understand this patent comprises IP relevant to BMS' relatlimab (currently under FDA review), and note it was withdrawn in 2014. We have not conducted any explicit freedom to operate (FTO) analysis but understand that Immutep are comfortable with their FTO in this space (regarding their antagonist).

Table A18. Current patents assigned to Immutep SAS^

Indication/methodology	Patent (WIPO)	Ownership	Expiry date#	Jurisdictions
Method of use / Combination Therapy of Efti with chemotherapy	**WO 2009/044273**	**Immutep SAS**	**3 Oct 2028**	Granted US (x2), Australia, Europe (x4) & Japan (x2). Pending in US, China & Europe
	The present invention relates to the use of a recombinant LAG-3 or derivatives thereof in order to boost a monocyte-mediated immune response, in particular to elicit an increase in the number of monocytes in blood. This finds use in the development of novel therapeutic agents for the treatment of an infectious disease or cancer.			
Method of use / Combination Therapy of Efti with platinum chemotherapy or topoisomerase I inhibitor	**WO 2015/091970**	**Immutep SAS**	**19 Dec 2034**	Granted in US, Europe, China, Hong Kong, Australia, Japan. Pending in US, Europe, China, Hong Kong, Korea, Japan.
	Combined preparations for the treatment of cancer are described. The combined preparations comprise: (a) LAG-3 protein, or a derivative thereof that is able to bind to MHC class II molecules; and (b) an anti-neoplastic agent, wherein the anti-neoplastic agent is a platinum-based anti-neoplastic agent or a topoisomerase I inhibitor. Methods for the treatment of cancer using the combined preparations are also described.			
Method of use / Efti in combination therapy (AIPAC subgroups)	**PCT/EP21/057588**	**Immutep SAS**	**24 Mar 2041**	PCT application filed.
	Detailed summary not available.			
Method of use / Combination Therapy of Efti with PD-1/PD-L1 therapy	**WO 2016/110593**	**Immutep SAS**	**8 Jan 2036**	Granted in US (x2) and Europe. Pending in Europe, Russia, US, Canada, Mexico, Australia, NZ, China, Hong Kong (x2), Korea, Japan, Brazil, India, Israel.
	Combined preparations, and pharmaceutical compositions, comprising: (a) LAG-3 protein, or a derivative thereof that is able to bind to MHC class II molecules; and (b) a programmed cell death protein-1 (PD-1) pathway inhibitor, are described. The PD-1 pathway inhibitor, such as an anti-PD-1 antibody or an anti-PD-L1 antibody, and a soluble derivative of LAG- 3, acting as an APC activator, together synergistically activate T cells (in particular, CD8+ T cells). Use of the combined preparations and compositions as medicaments, in particular for the treatment of cancer or infection, and to methods for the treatment of cancer or infection, is described.			
Binding assay of Efti	**WO 2018/113621**	**Immutep SAS**	**18 Dec 2037**	Pending in Europe, Russia, US, Canada, Mexico, Australia, NZ, China, Hong Kong, Korea, Japan, Brazil, India, Israel.
	Methods for determining MHC class II binding activity of a preparation comprising lymphocyte activation gene-3 (LAG-3) protein, or a fragment, derivative, or analogue thereof, is described. The methods comprise determining binding of the LAG-3 protein, fragment, derivative, or analogue to MHC class II molecules using bio-layer interferometry (BLI). Such methods can be used as a quality control assay in good manufacturing practice (GMP) grade production of such compounds. Probes and kits for carrying out the methods are also described.			
Composition of matter of IMP761 (LAG-3 agonists)	**WO 2017/037203**	**Immutep SAS**	**1 Sept 2036**	Granted in Europe, South Africa, Nigeria. Pending in Europe, Russia, US, Canada, Mexico, Australia, NZ, China, Hong Kong, Korea, Japan, Brazil, India, Israel, Malaysia, Philippines, Indonesia, Singapore.
	Antibodies, or antigen-binding fragments thereof, that bind to Lymphocyte-activation gene-3 (LAG-3) are described, in particular antibodies, or antigen-binding fragments thereof, that are agonists of LAG-3. The antibodies bind to LAG-3 and inhibit antigen-induced CD4+ and/or CD8+ T cell proliferation, or antigen-induced CD4+ and/or CD8+ T cell activation. The antibodies may be used as medicaments, in particular for the treatment of conditions associated with proliferation and/or activation of CD4+ and/or CD8+ T cells, such as inflammatory and autoimmune disorders.			

Table A18 continued overleaf.

Table A18 continued. Current patents assigned to Immutep SAS^

Indication/methodology	Patent (WIPO)	Ownership	Expiry date#	Jurisdictions
Mechanism of action of IMP761	**WO 2020/221928**	**Immutep SAS**	**1 May 2040**	PCT application filed.
	The present disclosure relates to agonistic anti-LAG-3 (CD223) antibodies which inhibit T cell receptor (TCR)-mediated signal transduction in LAG-3 positive T cells through agonism of LAG-3. The antibodies bind specifically to a discontinuous epitope within the extracellular Ig superfamily domain D1 of LAG-3 protein, wherein the epitope lies outside a 30 amino acid extra-loop sequence of domain D1 of the LAG-3 protein. Use of the antibodies as medicaments is described.			
Discontinuous Epitope binding of LAG-3 (relating to IMP761)	**WO 2020/221927**	**Immutep SAS**	**1 May 2040**	PCT application filed.
	Binding molecules that bind specifically to Lymphocyte-activation gene-3 (LAG-3) are described. The binding molecules inhibit T cell receptor (TCR)-mediated signal transduction in LAG-3 positive T cells through agonism of LAG-3. In some embodiments, the binding molecules bind specifically to a discontinuous epitope within the extracellular Ig superfamily domain D1 of a LAG-3 protein, wherein amino acid residues of the discontinuous epitope lie outside a 30 amino acid extra-loop sequence of the domain D1 of the LAG-3 protein. Use of the binding molecules as medicaments, in particular for the treatment of conditions associated with proliferation and/or activation of CD4+ and/or CD8+ T cells, in particular inflammatory and autoimmune disorders, is also described.			
LAG-3 agonist activity assay (regarding IMP761)	**WO 2020/221924**	**Immutep SAS**	**1 May 2040**	PCT application filed.
	Assays for screening for, or determining activity of, an agonist of lymphocyte-activation gene 3 (LAG-3) are described. According to the assays, a plurality of effector T cells is provided, each effector T cell expressing LAG-3 and a T-cell receptor (TCR) on its surface, and comprising a reporter gene encoding a reporter, wherein expression of the reporter is regulated by LAG-3-mediated inhibition of TCR signaling within the effector T cells. Activity of the agonist is determined from the extent to which expression of the reporter is altered in the presence of the agonist compared with expression of the reporter in the absence of the agonist. The assays may be used for determining the potency of a preparation of the agonist as part of a quality control step in production of the agonist, or for stability testing of a preparation of the agonist. Kits for carrying out the assays are also described.			
Combination therapy with LAG525	WO 2017/019894	Immutep SAS & Novartis AG	28 July 2036	Granted in Europe. Pending in US & Europe.
	Combination therapies comprising antibody molecules that specifically bind to LAG-3 are disclosed. The combination therapies can be used to treat, prevent and/or diagnose cancerous or infectious disorders.			
Composition of Matter for LAG525	WO 2015/138920	Immutep SAS & Novartis AG	13 March 2035	Granted in US (x2), Europe, Australia & Japan Pending in other territories (~50 filed)
	Antibody molecules that specifically bind to LAG-3 are disclosed. The anti-LAG-3 antibody molecules can be used to treat, prevent and/or diagnose cancerous or infectious disorders.			
Composition of Matter for IMP731 (GSK2831781)	WO 2008/132601	Immutep SAS & INSERM	30 April 2028	Granted US, Canada, Europe & Japan (x2) Pending China, US & Europe
	The present invention concerns a molecule binding to LAG-3 protein and causing depletion of LAG-3' activated T cells particularly said molecule is a cytotoxic anti-LAG-3 monoclonal antibody or fragment thereof. It also concerns a method of treating or preventing organ transplant rejection or autoimmune diseases in a mammal comprising administering to said mammal a therapeutically effective amount of said antibody.			

^ *Immutep SAS is a wholly owned subsidiary of Immutep Ltd.*
 # with the possibility for 5-year extension in some instances.

Source: Immutep, WIPO.

Appendix V: Market model summaries

We have developed three market models based on the Efti asset which are the premise to our market forecasts and underpin our ROV valuation of this asset. Each model is based upon addressable markets that are informed by the clinical patient populations in which superior efficacy was observed in existing clinical trial data to date, or where there looks to be adequate supportive data to infer potential addressability of certain cohorts.

A5.1 HR$^+$/HER2$^-$ metastatic Breast Cancer – Efti

We model Efti as a 2nd line therapy in metastatic/advanced recurrent HR+/HER2- breast carcinoma patients to be used in adjunct to paclitaxel chemotherapy. Our model assumes the AIPAC-II Phase III trial will support market approval in late FY25 with first commercial revenues after launch in FY26 in both major markets (USA, EU5).

We have taken a conservative approach to patient population were Efti may be suitable based on a selection of the efficacy subsets identified in the Phase IIb AIPAC study. Those being; a) patients under 65 years of age; and b) Luminal B subtype tumours (high Ki-67 expression).

Despite efficacy being noted in patients with low monocyte count (<25x10^9 cells/L) we do not view this as a subset that is relevant to treatment course decision making, given it is not a routine assessment conducted and used in this patient cohort unlike PD-L1 expression levels for example, or luminal subtype. We therefore do not include this in our market model TAM assessment.

Addressable patient population estimate of ~46,000 from two major markets. In our addressable population we assume a label indication may be restricted by age alone (<65y) however appreciate an approved treatment could be used off-label for patient subsets where benefits were seen irrelevant of age (i.e. Luminal B subtype) and therefore expand our market size assumptions beyond only those under 65 years of age to include Luminal B subtype tumours (all ages) as a proxy for the potential broadened use of Efti within the HR+/HER2- mBC population.

Table A19. Key Assumptions for mBC model

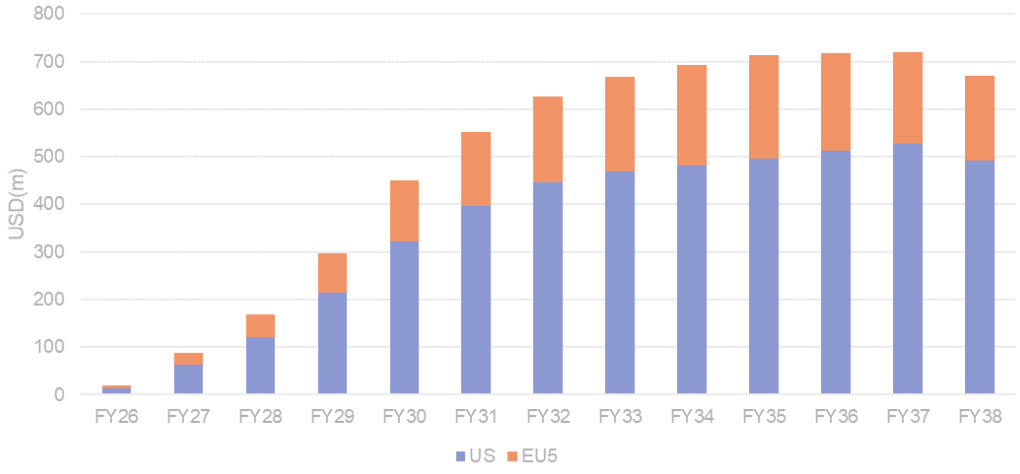
Efti + paclitaxel regimen	US	EU5
Market launch year	FY26	FY26
Biologics exclusivity lost	FY38	FY36
Total addressable patients	29,500	16,500
<65yo patients	20,000	11,500
Luminal B pts	9,500	5,000
Peak market share of addressable cohort (of total HR$^+$/HER2$^-$ mBC)	42% (15%)	42% (17%)
Peak sales year	FY37	FY35
Peak sales estimate (USD)	$530M	$220M
TAM (USD)	$1.25B	$500M
Pricing per dose^ (USD)	$5,000	$3,000
Average net annual price/patient^ (USD)	$51,000	$35,700
Pricing degradation	FY31 (2.5%) ann.	FY31 (2.5%) ann.

^ See **Table 12** *for Efti pricing assumption detail.*

Source: Wilsons

Forecasts restricted to two major markets; further opportunities. We model US and EU5 markets only using published incidence and prevalence estimates for mBC HR+/HER2- and luminal B subtypes. There are sizable opportunities outside of these geographic markets in this indication. As a reminder, Immutep's partnership with EOC Pharma will progress Efti in the mBC indication in China providing potential royalty revenues from another large drug market (>200,000 new mBC cases per year).

Figure A25. Revenue assumptions for Efti in mBC in two major markets (US, EU5)



Source: Wilsons

US$700M peak sales estimate. See **Figure A25**. We model peak market share capture in each geography as ~42% achieved by ~8 years post launch, noting that market share capture >30% is challenging for any drug asset however we believe this level of penetration accurately reflects our fairly restrained addressable population estimates. As a proportion of all HR+/HER2- mBC patients we assume penetration between 15-17% (**Table A19**). We forecast modest loss of market share starting from FY36 and FY38 onwards EU5 and US models respectively, the time around which we estimate market exclusivity would be lost for the Efti in each major market.

Market exclusivities extend into FY38. In each major market there are market exclusivities attached to approvals of new biologics which would apply to an Efti approval in this indication. In the US market this is 12 years from approval under the Biologics exclusivity allowance which provides four years where biosimilar applications are not accepted, and a further 8 years before any such application can be approved for market entry. The EMA provides a total of 10 years data and market exclusivity for NCEs or biologics extending until end of FY35 (working from an FY25 approval estimate). It is important to note these exclusivities are for new biologic approvals and therefore would not be extended for other indications should a supplemental BLA be filed to expand an approval to a new indication (i.e. HNSCC or NSCLC).

A5.2 Head and Neck Squamous Cell Carcinoma (HNSCC) - Efti

Our market model assumes Efti is used in adjunct to pembrolizumab (IO-IO combo) as a 1st line therapy in metastatic HNSCC patients.

We model two major markets only (EU5, USA) with an estimated addressable population of ~ 33,000 patients with first potential revenues in FY28. Notably, Western Europe presents a larger opportunity in HNSCC compared to the US market due to the increased incidence of HNSCC in EU (approx. double the incidence of US associated with differences in cigarette use and HPV prevalence). We assume 8% royalties are paid to MSD (under their existing collaboration agreements) as part of their development partnership with Immutep in this indication.

View on potential label that dictates addressable market. Our assumptions in the HNSCC indication are based on an approved label including;

- 1st line therapy in metastatic HNSCC;
- To be used in combination with pembrolizumab;
- Restricted to PD-L1 positive patients (TPS ≥1) confirmed prior to therapy.

This assumption set is based upon the TACTI-002 Part C results interpolated to a 1st line setting and the fact that PD-L1 positive patients are the focus of the TACTI-003 Phase IIb trial. Further, it assumes that the Efti combination can show superiority over pembrolizumab monotherapy that is already approved (2019) in mHNSCC in the 1st line setting. Recent meta-analyses suggest that ~42% of HNSCC cases are classified at PD-L1 positive [101]. We limit our peak market penetration to 33% in both markets to account for the likely use and approval of other IO combination therapies (in addition to IO-chemo combinations).

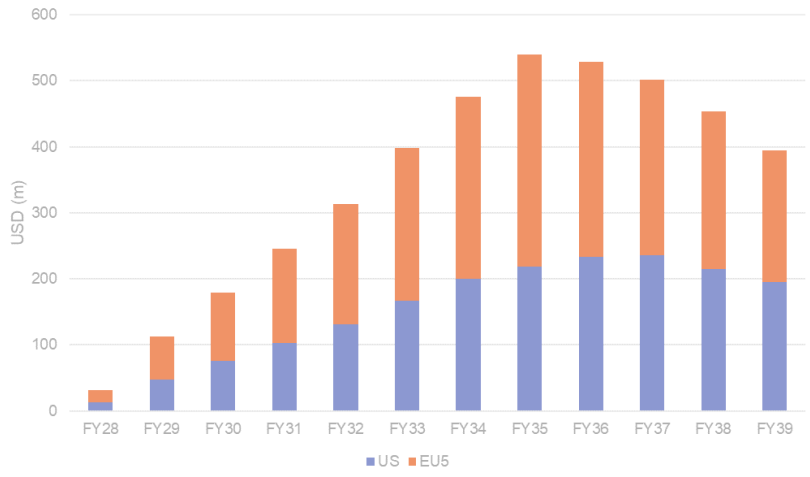
Table A20. Key Assumptions for mHNSCC model

Efti + pembrolizumab regimen	US	EU5
Market approval	FY27	FY27
Biologics exclusivity lost	FY38	FY36
Total addressable patient pool	11,000	22,000
Peak market share of addressable cohort (as % of total mHNSCC cohort)	33% (14%)	33% (13%)
Peak sales year	FY37	FY35
Peak sales estimate (US$m)	191M	265M
TAM (USD)	$710M	$975M
Pricing per dose^ (USD)	$5,000	$3,000
Average net annual price/patient^ (USD)	$63,000	$44,100

^ See **Table 13** *for Efti pricing assumption detail.*

Source: *Wilsons*

Figure A26. Efti revenue assumptions for HNSCC indication in major markets (US, EU5)



Source: Wilsons.

Market exclusivity period shorter based on assumed prior mBC approval. We model entry of Efti biosimilars from FY36 in EU and FY38 in US markets given the loss of Efti market exclusivity in each respective market in these years. The magnitude and impact of biosimilar entry for immune checkpoint inhibitors is an unknown given that we are yet to witness this for this ICI drug class. Ipilimumab is the first ICI candidate for biosimilar market entry with loss of market exclusivity in Europe in 2021 and US in 2023. Based on other monoclonal antibody biosimilar entries (i.e. Herceptin etc) we do not model rapid declines (>30% per annum) akin to generics entry as we have consistently seen a slowed and cautious uptake with regards to biosimilars vs generics particularly in the US market. We include ~9% annual growth declines from loss of exclusivity to manage the entry of biosimilars in this market (FY36-FY39).

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A5.3 Non-Small Cell Lung Cancer (NSCLC) – Efti

Model used as basis for licensing deal assumptions. Our NSCLC market model is the basis for our partnering analysis for this indication (**Table A21**). In our model we assume Efti approval in FY26 with first revenues in FY27 in both major markets. Our Efti revenue estimates for Immutep in NSCLC are premised on a deal in 2H FY23 including upfront payments, milestones and royalties (summarised in **Table 3; p12** of this report). These royalties and milestones are premised on our market model assumptions for what Efti success in NSCLC looks like.

We assume use of Efti in a 1st line metastatic/advanced recurrent NSCLC setting in combination with pembrolizumab. Consistent with other indications, we only model US and EU5 geographic markets. The incidence of NSCLC in each major market is relatively consistent. We assess an addressable patients pool of ~125,000 across US and EU5 markets.

Addressable cohorts reflect a PD-L1 all comers approach. We construct our addressable cohorts based on an all-comers approach with respect to PD-L1 expression. We note that currently pembrolizumab monotherapy in the 1st line setting is restricted to PD-L1 positive (≥ 1% TPS) patients (~65% total NSCLC) in US and only those with high PD-L1 expression (≥50% TPS) in Europe (~30% total NSCLC). The existing data evaluating Efti in combination with pembrolizumab from the TACTI-002 Part A and Part B cohorts supports our assumption that Efti could be approved without a PD-L1 expression restriction. This is premised on its continued efficacy in the TACTI-002 Part A study (extension phase) with a follow-on Phase III showing superiority to pembrolizumab monotherapy.

PD-L1 negative and anti-PD-1 refractory patients; likely integral to deal attractiveness. The ability to expand the use of pembrolizumab into PD-L1 negative patients (<1% TPS) and those with low expression in Europe is a key attraction of this asset in the NSCLC indication where it has the opportunity to expand the addressable market by ~2 fold (compared to current existing approvals across US and EU5).

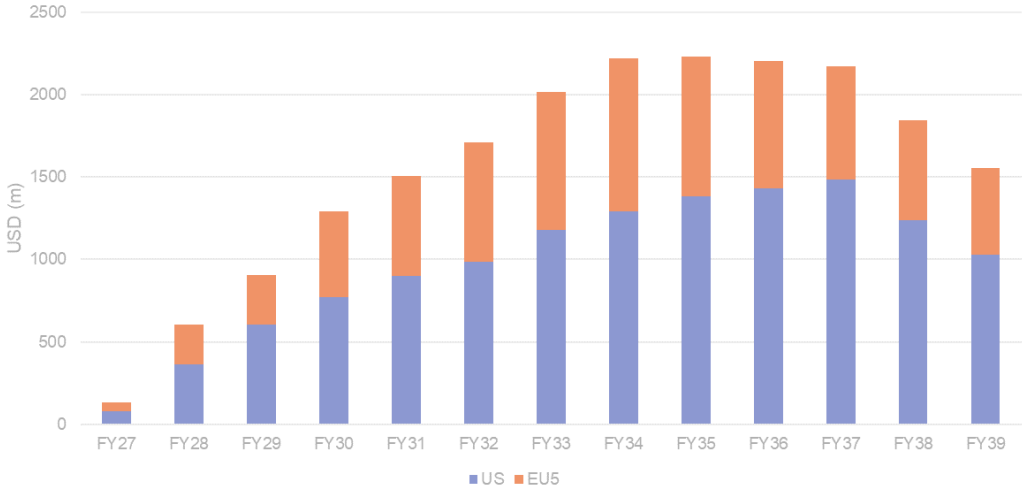
Table A21. Key Assumptions for mNSCLC model

Efti + pembrolizumab regimen	US	EU5
Market approval	FY26	FY26
Exclusivity lost	FY38	FY36
Total addressable patient pool	65,000	64,000
Peak market share of addressable cohort (% of total NSCLC)	35% (35%)	33% (33%)
Peak sales year	FY37	FY34
Peak sales estimate (USD)	$1.48B	$930M
TAM (USD)	$4.2B	$2.8B
Pricing per dose^ (USD)	$5,000	$3,000
Average net annual price/patient^ (USD)	$63,000	$44,100

^ See **Table 13** *for Efti pricing assumption detail.*

Source: Wilsons

Figure A27. Efti revenue assumptions for NSCLC indication in major markets (EU5, US)



Source: Wilsons.

Appendix VI: Board and Management

A6.1 Board of Directors

Dr Russell Howard. Non-Executive Chairman

Dr Howard joined the Immutep board in late 2017. Dr Howard is a scientist and serial entrepreneur as an inventor of five patents and >150 scientific publications. His scientific expertise is centred around molecular parasitology and molecular biology. He was the co-founder and prior CEO of NASDAQ listed biotechnology company Maxygen as well as developer of CleanTech company Oakbio Inc. Russell also currently serves on the board of a privately held biotech NeuClone and was director of ASX listed Circadian Technologies from 2013-2015. Russell holds a PhD in biochemistry from the University of Melbourne.

Marc Voigt. Executive Director

Marc joined Immutep in 2012 (then Prima Biomed) as CFO and CBO. He was appointed CEO in 2014 just prior to the Prima acquisition of French biotech Immutep SA. Marc has been instrumental in leading the pivot of the company from its cancer vaccine focus (2001-2014 Prima Biomed) to its current LAG-3 Immuno-oncology focus (2016-). Marc has experience in investment banking and was an investment manager at a midsized healthcare venture capital fund alongside a range of executive positions within private German biotech companies prior to joining Immutep. Marc holds an MBA from Freie Universitat of Berlin and is based in Europe.

Pete Meyers. Non-Executive Director & Deputy Chairman

Pete joined the Immutep board in 2014. Pete has previously held CFO positions at several pharmaceutical companies including Eagle Pharmaceuticals, Motif BioSciences, TetraLogic Pharmaceuticals and currently at Slayback Pharma LLC. He has over 18years experience in healthcare investment banking including as Co-Head of Global Healthcare investment banking at Deutsche Bank Securities. Pete holds a Bachelor of Science (Finance) from Boston College and an MBA from Columbia Business School.

Grant Chamberlain. Non-Executive Director.

Grant joined the Immutep board in 2017. Grant is a Partner at One Ventures, a leading venture capital firm in Australia and has over 20 years of corporate advisory and investment banking experience, with particular expertise in M&A from time at Bank of America Merrill Lynch, Nomura Australia and Deutsche Bank. Grant holds a Bachelor of Laws (Hons) and Bachelor of Commerce from the University of Melbourne.

A6.2 Management

Marc Voight. Chief Executive Officer

See above.

Dr Frederic Triebel. Chief Scientific Officer & Chief Medical Officer

Prof Triebel has served as CSO and CMO of Immutep since 2014. Dr Triebel founded Immutep S.A., the acquired company, in 2001, following his years as an immunologist at Institut Gustave Roussy in Paris and discovery of the LAG-3 gene in 1990. This discovery spurred research leading to the development of Efti and other LAG-3 assets now within the Immutep portfolio. He continues to manage and drive Immutep's clinical development of their LAG-3 focused portfolio and is an international KOL on LAG-3. He is a trained clinical haematologist (MD) and holds a PhD in Immunology from the Paris University and is based in Europe.

Deanne Miller. Chief Operating Officer, General Counsel & Company Secretary

Deanne has been the COO of Immutep since 2016 after first joining as General Counsel and Company Secretary in 2012. She has extensive legal experience as well as experience in investment banking, advisory and compliance roles within Australia. Deanne holds a Bachelor of Law (Hons) and Bachelor of Commerce, Accounting and Finance from University of Sydney. Deanne is an admitted solicitor in NSW and is based in Sydney.

Christian Mueller. VP of Strategic Development.

Christian joined Immutep in 2016 and is integral to their clinical trial and asset development strategy given his prior experience in clinical development of oncology drugs including monoclonal antibodies. His clinical trial experience extends from leadership and development of Phase I out to Phase IIb trials. He holds a Masters of Science (Biotechnology) from the Technical University Berlin and is based in Europe.

Dr Claudia Jacoby. Director of Manufacturing

Dr Jacoby has been with Immutep since 2015 coming from 15+ years in the biotech industry which included head roles in Biochemistry and Manufacturing at various European biotech companies. She is responsible for management and development of GMP manufacturing practices for Immutep assets using her expertise in protein expression and purification and analytical chemistry. Dr Jacoby holds a Masters in Biochemistry and PhD in Biochemistry from the Martin-Luther University of Halle-Wittenberg in Germany.

Dr James Flinn. Director of Intellectual Property and Innovation

Dr Flinn joined Immutep in 2017 to manage their IP portfolio, after 20+ years' experience within the pharmaceutical and biotech industry including GSK where he was Senior Patent Counsel for their dermatology business unit. James is a qualified Patent attorney and holds a PhD from University of Melbourne focused in peptide chemistry and structural biology and is based in Australia.

David Fang. Finance Director & Assistant Company Secretary

David joined Immutep in 2018 after experience as Group finance manager at Kazia Therapeutics (ASX:KZA). David worked as a Auditor at PWC alongside other accounting/auditor experience across the biotech/healthcare industry. He holds a Masters of Professional Accounting from Western Sydney University, Masters of Commerce (IT systems and technology) from Macquarie University and is a CPA.

Immutep Limited (IMM)

Business description

Immutep (IMM:ASX) (formerly Prima Biomed) is a clinical stage Australian biopharma operating in the immuno-oncology (IO) sector with their portfolio of LAG-3 directed biologics which were first acquired in 2016. Immutep have four assets under development, all with strong IP protection; two of which are out-licensed (LAG525, IMP731) to major development partners (Novartis, GlaxoSmithKline) and have attached milestone and royalty revenue optionality, with the remaining two (IMP321 or 'Efti' and IMP761) being developed in-house for a range of oncology and autoimmune indications. Efti, being Immutep's lead asset in development, is preparing to enter the first registration level Phase III study in metastatic breast cancer advancing its timeline to the clinic. Efti differentiates from other LAG-3 assets in development given its unique mechanism of action. Immutep has strong in-house expertise with their CMO/CSO Dr Frederic Triebel being the one who discovered the LAG-3 checkpoint which is now the basis for a new wave of checkpoint inhibitor development. Immutep has depository listings (ADRs) traded on the NASDAQ (IMMP).

Investment thesis

We initiate on Immutep (IMM) with an OVERWEIGHT recommendation and a $0.91 per share risked PT. Immutep is an Australian clinical stage biopharmaceutical company whose clinical assets focus on a new immuno-oncology (IO) target, the immune checkpoint molecule LAG-3. This is the perfect time to engage with LAG-3 directed assets now that Bristol Myers Squibb has filed the first LAG-3 directed drug for FDA approval. Immutep's clinical programs explore every therapeutic aspect of this multifaceted drug target. IMM's lead product Efti soon advances to Phase IIb & III trials aiming to enhance and extend IO blockbusters including Merck's (MSD) Keytruda. A wealth of pharma partnerships explore utility in oncology and autoimmune disease. We see a valuation disconnect between IMM and their opportunities in these markets with significant TAMs in metastatic cancers (breast $2.3B, head & neck $2.2B, lung $8B) where unmet need is high and partnership with existing blockbusters (Keytruda) sets them up for an immediacy of clinical adoption with future approvals. Our unrisked PT of $2.33/share highlights this.

Revenue drivers

Market approvals (long term)

Licensing deals (upfront and milestone payments)

Balance sheet

Net cash of ~$106M as of end 1Q FY22.

Margin drivers

Not applicable

Board

Dr Russell Howard – Non-Executive Chairman

Marc Voight – Executive Director

Pete Meyers – Non-Executive Director and Deputy Chairman

Grant Chamberlain - Non-Executive Director

Key issues/catalysts

Clinical trial results

Market approvals

Regulatory interactions with EMA and FDA

Competitor development progress

Indication expansion opportunities

Corporate activity (licensing deals, M&A)

Management

Marc Voight – Chief Executive Officer

Dr Frederic Triebel – Chief Scientific Officer and Chief Medical Officer

Deanne Miller – COO, General Counsel and Company Secretary

Christian Mueller – VP of Strategic Development

Dr Claudia Jacoby – Director of Manufacturing

Dr James Flinn – Director of IP and Innovation

David Fang – Finance Director and Assistant Company Secretary

Risk to view

Unfavourable regulatory reviews

Failure to show adequate clinical efficacy to support approvals

Competition within a busy IO space

Changes in SOC landscape making existing trial programs less relevant (i.e. regarding pembrolizumab, paclitaxel)

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Disclaimers and Disclosures

Recommendation structure and other definitions

Definitions at wilsonsadvisory.com.au/disclosures.

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