immutep
LAG-3 IMMUNOTHERAPY

11

Investor Update

An exciting year ahead for Immutep's two first-in-class agonists designed to fight cancer and autoimmune disease:

- **Efti (MHC Class II Agonist)** – Upcoming Pivotal Phase III in Non-Small Cell Lung Cancer
- **IMP761 (LAG-3 Agonist)** – On Track to Launch First-in-Human Clinical Trial by Mid-2024

IN THIS ISSUE:

Message from the CEO .....
Efti: A First-in-Class MHC Class II Agonist with Differentiated Efficacy/Safety in Oncology 2
PD-L1 Expression Levels and Why They Matter in Non-Small Cell Lung Cancer (NSCLC) 3
Positive Efficacy & Safety in 1L NSCLC from TACTI-002 and INSIGHT-003 Clinical Trials 4
Potentially Improving the Survival Curve in Non-Small Cell Lung Cancer 6
IMP761: A First-in-Class LAG-3 Agonist Designed to Tackle Autoimmune Diseases 7
Summary 8

Message from the CEO

As we recently announced our Q2 FY2024 results, I am proud of what the team at Immutep has accomplished to date and enthusiastic about what lies ahead. The positive clinical data with our lead clinical candidate eftilagimod alpha (efti) in combination with immune checkpoint inhibitors (ICI) like anti-PD-1 therapy has provided us with meaningful momentum in oncology. We are excited about the remainder of 2024 with our upcoming Phase III in first line non-small cell lung cancer, and multiple data updates from our clinical pipeline including TACTI-003 in first line head and neck cancer and AIPAC-003, which is evaluating efti in combination with chemotherapy in metastatic breast cancer.

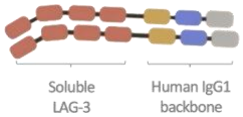
"Immutep's differentiated immuno-oncology (IO) approach is yielding the sought-after alignment of efficacy and safety with mature clinical data."

With the pivotal Phase III in non-small cell lung cancer being one of the most significant events in the Company's journey, this update will walk through what makes efti unique in this important indication and the clinical data that has emerged over the past 18 months. The non-small cell lung cancer drug market is expected to grow to US$48 billion in 2031, with ICIs expected to reach over half these sales[1]. Additionally, this newsletter will cover our innovative immunotherapy for autoimmune diseases called IMP761, which is on the verge of reaching the clinical stage. To our knowledge, IMP761 is the first agonist LAG-3 antibody ever developed, and we are driven by its potential to restore balance to the immune system and help patients with a variety of autoimmune disorders including rheumatoid arthritis, Type 1 diabetes, and more.

Before moving on, I would like to again thank all of our shareholders for their support. With our solid cash position providing a runway to early CY2026, we are in a strong position to reach multiple milestones and catalysts to create shareholder value.

Efti: A First-in-Class MHC Class II Agonist with Differentiated Efficacy/Safety in Oncology

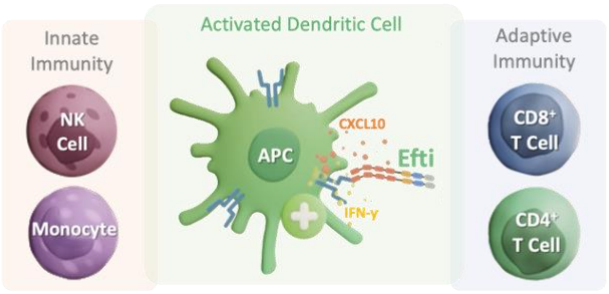
Immutep's differentiated immuno-oncology (IO) approach is yielding the sought-after alignment of efficacy and safety with mature clinical data. From the late-breaking oral presentation at the Society for Immunotherapy of Cancer in November 2022 that centered on response rates, progression free survival, and durability, to the compelling overall survival data presented at ESMO Congress in October 2023, we are motivated by the potential of efti in combination with anti-PD-1 therapy to make a meaningful difference in the treatment landscape of first line non-small cell lung cancer (1L NSCLC).



Efti - A first-in-class soluble LAG-3 fusion protein (LAG-3Ig) with high affinity for MHC Class II on antigen-presenting cells such as dendritic cells.

What sets the immuno-oncology (IO) combination of efti with anti-PD-1 therapy apart from anti-PD-1 in combination with ICIs is our novel approach that targets both dendritic cells (DC) via efti and T cells via anti-PD-1 therapy.

Efti complements other IO therapies through its unique activation of dendritic cells that bridge adaptive/innate immune systems



DCs are potent antigen-presenting cells (APC) and master regulators of the immune response that play an essential role in effectively tackling multiple diseases including cancer[2]. This makes them ideal therapeutic targets and in particular for combination with other immunotherapies and/or with chemotherapy.

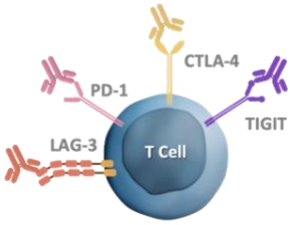
Once these powerful immune cells are uniquely activated through MHC Class II agonism via efti, DCs enlist multiple anti-cancer cells from the adaptive and

(1) Nature Reviews Drug Discovery 22, 264-265 (23 Jan 2023) doi: https://doi.org/10.1038/d41573-023-00017-9. (2) Mellman I. Dendritic cells: master regulators of the immune response. *Cancer Immunol Res.* 2013 Sep;1(3):145-9. Doi: 10.1158/2326-6066.CIR-13-0102. PMID: 24777676.

innate immune system, including activated CD8+ T cells, CD4+ T Cells, NK Cells, and monocytes, along with chemokines & cytokines. This broad-based response better enables patients' immune systems to fight cancer.

Conversely when anti-PD-1 is delivered with ICIs, these IO-IO combinations just target T cells and this is repetitive with what anti-PD-1 therapies already do on their own, offering a relatively narrow window to generate a larger immune response than what's already being accomplished with anti-PD-1 monotherapy.

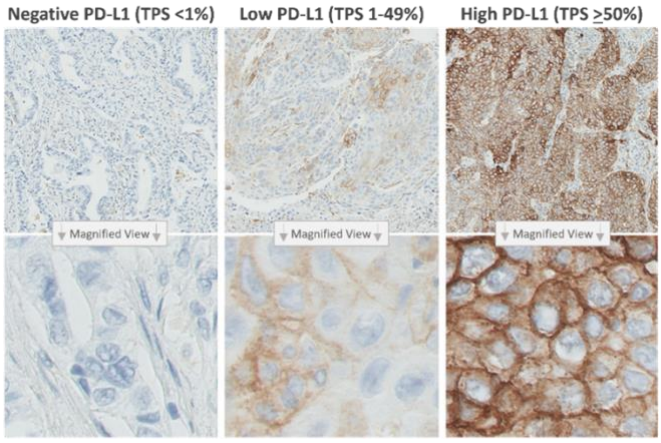
Many IO combinations focus solely on T cells and just target different immune checkpoints on these cells



These IO combinations release the brakes on T cells by blocking the immune checkpoints that they're each named after (e.g. anti-PD-1, anti-CTLA-4, anti-TIGIT, anti-LAG-3). To date, efficacy in NSCLC patients from these IO combinations has been limited to "hot" tumour environments (i.e. inflammatory sites with many infiltrating T cells), where anti-PD-1 monotherapy is already effective. Additionally, blocking two immune checkpoints on T cells leads to increased toxicity versus anti-PD-1 monotherapy, even without adding chemotherapy.[3,4]

PD-L1 Expression Levels and Why They Matter in Non-Small Cell Lung Cancer (NSCLC)

Programmed death ligand 1 (PD-L1) expression is an FDA-approved predictive biomarker of the success of PD-1/PD-L1 inhibitor therapy for patients with non-small cell lung cancer. The method used to assess the level of PD-L1 in NSCLC is three different expression levels: high (TPS ≥50%), low (TPS 1-49%), and negative (TPS <1%). The image here shows tumour samples from NSCLC patients with a TPS of less than 1%, a score of 1 to 49%, and a score of at least 50%.[5] Moving from left to right, the pictures get darker signifying more PD-L1 expression.



PD-L1 staining is shown by the presence of the brown chromogen. Expression of PD-L1 by tumor cells at baseline is known to be correlated with the level of IFN-gamma producing activated T cells at the tumor site and is, therefore, a reflection of a strong pre-existing tumor-specific T cell response.

Generally speaking, the way NSCLC patients are expected to respond to anti-PD-(L)1 therapies is grouped by these three levels of PD-L1 expression: high expressors respond best, low expressors respond sub-optimally, and negative expressors are not expected to respond at all or have negligible responses.

To provide some context to this, the table below shows the regulatory landscape for the only chemotherapy-free ICIs with regulatory approvals in 1L NSCLC in the United States and Europe: pembrolizumab monotherapy (anti-PD-1), atezolizumab monotherapy (anti-PD-L1), and nivolumab (anti-PD-1) combined with ipilimumab (anti-CTLA-4).

Chemotherapy-free ICI Therapies in 1L NSCLC	High PD-L1 (TPS ≥50%)		Low PD-L1 (TPS 1-49%)		Negative PD-L1 (TPS<1%)	
	US	Europe	US	Europe	US	Europe
Nivolumab + Ipilimumab	Yes	Yes	Yes	No	No	No
Pembrolizumab Monotherapy	Yes	Yes	Yes[6]	No	No	No
Atezolizumab Monotherapy	Yes	Yes	No	No	No	No

As is shown in the table, all three of these IO therapies have regulatory approvals across both regions for patients with high PD-L1 expression (TPS >50%). However, for low PD-L1 expression (TPS 1-49%) none of these therapies have regulatory approval in Europe, and the picture in the United States is mixed. For negative expressing patients (TPS <1%), none of these chemo-free IO therapies are approved.

(3) Larkin et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma, *N Engl J Med* 2019; 381:1535-1546 DOI 10.1056/NEJMoa1910836; (4) Tawbi et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma, *N Engl J Med* 2022; 386:24-34, DOI: 10.1056/NEJMoa2109970; (5) Garon et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med.* 2015;372:2018–28; (6) NCCN Category 2b treatment option in low PD-L1 versus preferred NCCN Category 1 in high PD-L expression in 1L NSCLC

While ICIs have revolutionised the treatment landscape in NSCLC, the majority of patients do not respond to anti-PD-(L)1 monotherapies. This has driven the biotech industry to search for combinations with anti-PD-(L)1 therapies that can expand the number of patients who respond, improve upon the clinical outcomes for patients who do respond, and also overcome primary or acquired resistance. In treatment of 1L NSCLC, the addition of chemotherapy to ICIs has become the preferred combination therapy for low and negative PD-L1 expressing patients but this comes at a high cost in terms of patient side effects and quality of life.

This is where Immutep can make a difference with efti. The current data from efti in combination with anti-PD-1 in 1L NSCLC, without the use of chemotherapy, has been very encouraging no matter the level of PD-L1 expression, including for patients with negative PD-L1. This ability to potentially help the entire NSCLC patient population regardless of PD-L1 expression is driven by efti's agonism of MHC Class II on dendritic cells. Efti's unique activation of these potent professional antigen-presenting cells leads these "generals of the immune system" to drive an inflammatory anti-cancer response via both adaptive and innate immunity that helps overcome resistance to checkpoint inhibitors such as anti-PD-1 therapy and appears to work synergistically with anti-PD-1 as the clinical data that follows suggests.

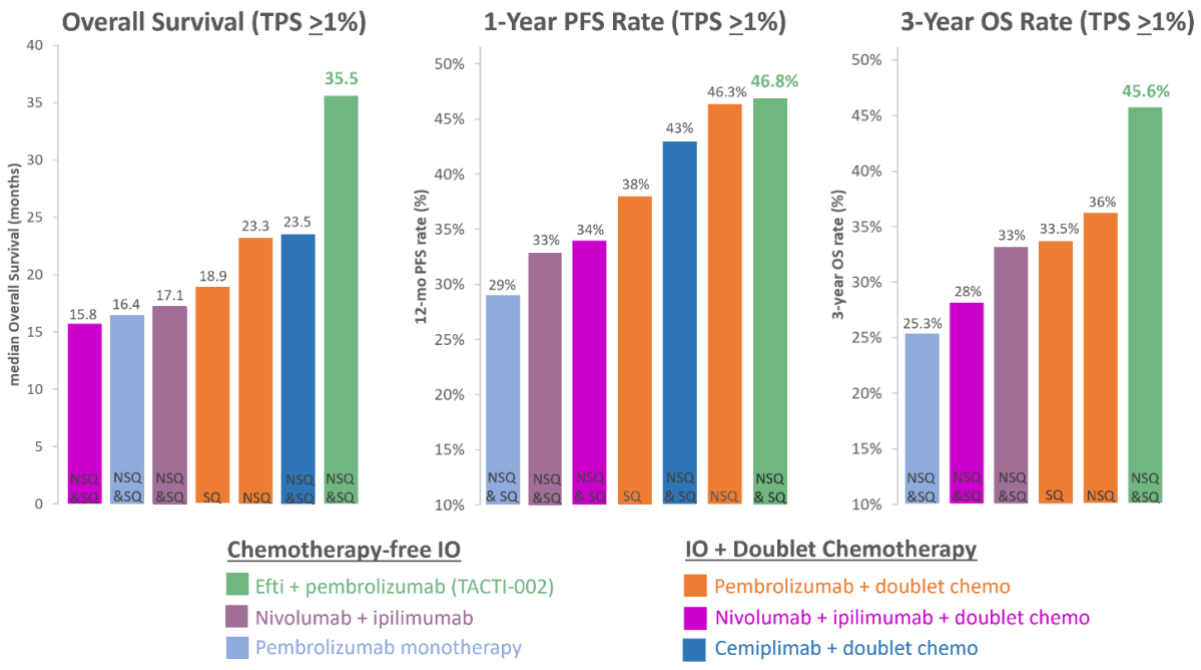
Positive Efficacy & Safety in 1L NSCLC from TACTI-002 and INSIGHT-003 Clinical Trials

Combining efti with anti-PD-1 therapy in the comparably large TACTI-002 Phase II trial (N=114), which spanned three continents and 18 different trial sites, has shown this chemotherapy-free IO combination is efficacious in first line metastatic NSCLC patients (non-squamous and squamous) across all levels of PD-L1 expression.

Importantly, when measuring Overall Survival (OS), the gold standard in oncology, the mature data from efti and pembrolizumab (KEYTRUDA®) in TACTI-002 reveals:

- Overall Survival of 35.5 months, as compared to 16.4 months published for pembrolizumab monotherapy and 15.8-23.5 months for IO-IO or IO-chemotherapy combinations for patients who express any PD-L1.[7]

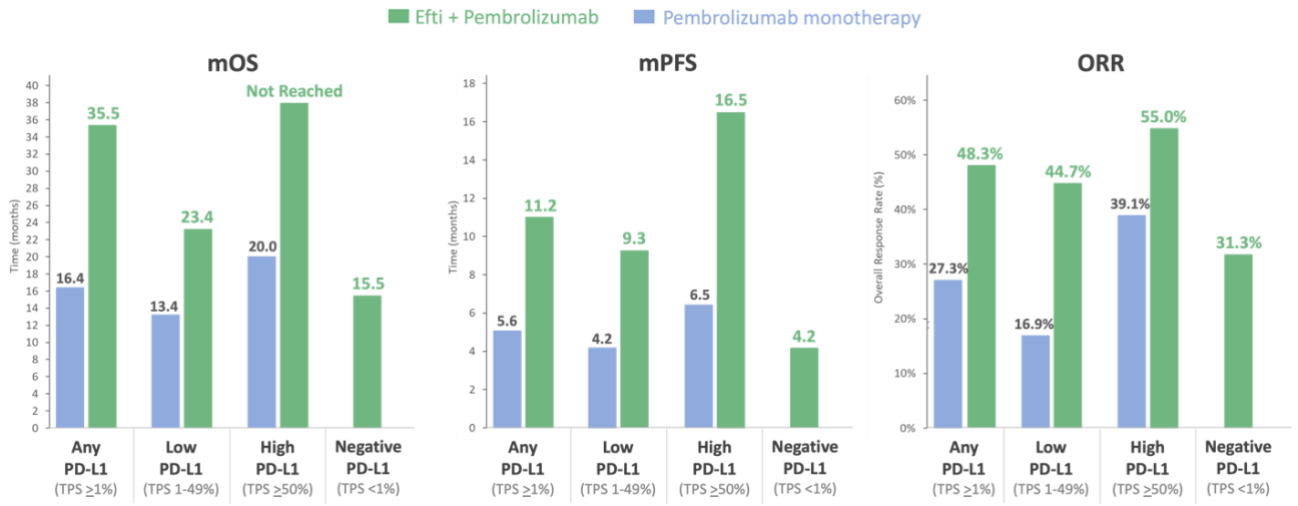
- A 3-year OS rate of 45.6% as compared to typically expected ~25% for pembrolizumab monotherapy and 28-36% for IO-IO or IO-chemotherapy combinations. The 46.8% 1-Year progression-free survival (PFS) rate also compares favorably to pembrolizumab monotherapy and IO-IO and IO-chemotherapy combinations.



(7) Data for standard-of-care therapies from publications/EPAR assessment report of respective registrational trials (e.g., KN-042, KN-189, KN-407, CM-9LA, CM-227, EMPOWER-Lung 3), and comparison of data is from different clinical trials. KEYTRUDA® is a registered trademark of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

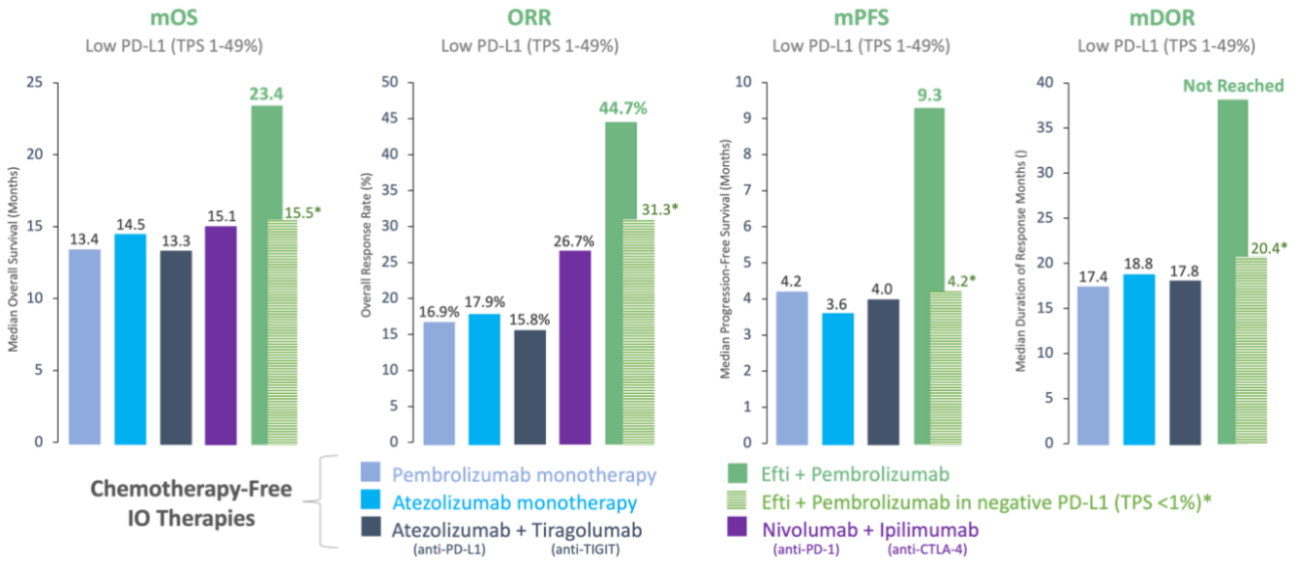
In addition to this OS data, our conviction in the potential of efti with anti-PD-1 therapy in metastatic 1L NSCLC is strengthened by the following efficacy results from TACTI-002:

1. Efti in combination with pembrolizumab (KEYTRUDA®), which became the world's top selling drug in 2023 exceeding $25 billion in sales, is generating durable response rates and PFS that exceed historical results from pembrolizumab monotherapy in high, low, and negative PD-L1 expressing patients, and doing so with a favorable safety profile.[8,9]



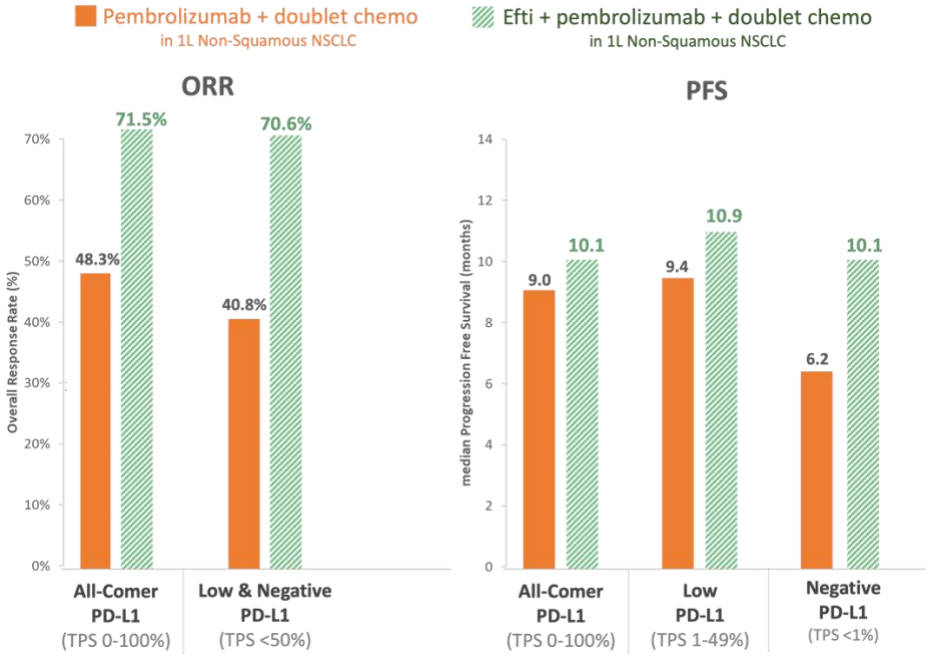
Given the lack of historical results in negative PD-L1 expressing 1L NSCLC patients who received pembrolizumab monotherapy, the chart only has data from patients in TACTI-002 with negative PD-L1 expression. As shown above, even the efficacy in low and/or negative PD-L1 expressing patients in TACTI-002 compares favorably to patients receiving pembrolizumab monotherapy with any PD-L1 (TPS ≥1%), which would not typically be expected.

2. Efti combined with pembrolizumab provides differentiated efficacy as compared to multiple approved & investigational chemotherapy-free approaches in low PD-L1 expressors (TPS 1-49%)[10]. Notably, the negative PD-L1 expressing patients (TPS <1%) who received efti and pembrolizumab had response rates, OS, PFS, and durability of responses that matched or exceeded results from these other therapies in patients with low PD-L1 expression, which would not typically be expected.



(8) Pembrolizumab monotherapy data from publications/EPAR assessment report of KN-042 registrational trial. In patients with any PD-L1 expression (TPS ≥1%), TACTI-002 has 66% patients with TPS 1-49% and 34% with TPS ≥50%, which compares to KN-042 with ~53% patients with any PD-L1 and ~47% patients with PD-L1 TPS ≥50%; (9) KEYTRUDA sales figures from MSD's Q4 FY2023 report; (10) Pembrolizumab monotherapy data from KN-042 registrational trial , Atezolizumab and Tiragolumab + Atezolizumab data from CITYSCAPE Phase II trial. Ipilimumab + Nivolumab from CM-227 registrational trial.

Beyond TACTI-002, the addition of chemotherapy to efti and pembrolizumab in the INSIGHT-003 trial is driving superior responses as compared to other IO-chemotherapy and IO-IO-chemotherapy combinations as well. Early results from this Phase I trial, in which 81% of patients have low or negative PD-L1 expression, show a 71.4% Overall Response Rate, 90.5% Disease Control Rate, 10.1-month median PFS, and median Overall Survival that has not been reached.[11]



While we are certainly encouraged, these early results are from a small number of patients (N=21). INSIGHT-003 has now enrolled and dosed 30 out of a planned 50 patients and we look forward to more mature data from a larger patient pool, with a keen focus on how these initial results evolve. Of note, the patient segment in 1L NSCLC that has a higher need for new solutions are these negative and low PD-L1 expressing patients. This is where we have concentrated our efforts with our unique triple combination therapy in INSIGHT-003.

Potentially Improving the Survival Curve in Non-Small Cell Lung Cancer

The differentiated efficacy and safety profile of efti with anti-PD-1 therapy positions this novel combination well, especially as compared to other IO combinations targeting 1L NSCLC. Its unique positioning as the only MHC Class II agonist in the clinic today is yielding results that have exceeded our own expectations. We are firm believers that efti has significant potential to improve the survival curve in NSCLC, one of the largest indications in all of oncology.

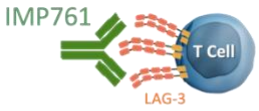
The Company's progress around our planned TACTI-004 registrational trial continues. We have been pleased with the regulatory feedback we have received to date and are thankful for their support in evaluating efti in combination with an anti-PD-1 therapy either in a chemotherapy-free regimen or as a triple combination approach including chemotherapy. Additional interactions with the FDA, other local European regulators, as well as with other stakeholders and potential partners are ongoing.

(11) INSIGHT 003 evaluating feasibility of eftilagimod alpha (soluble LAG-3) combined with 1st line chemo-immunotherapy in metastatic non-small cell lung cancer (NSCLC) adenocarcinomas – a multicenter early phase trial – Abstract #1042P, ESMO Congress 2023. Pembrolizumab + doublet chemo data from KN-189 trial.

IMP761 – A First-in-Class LAG-3 Agonist Designed to Tackle Autoimmune Diseases

Immune checkpoint agonists, including for CTLA-4, PD-1, and LAG-3, are increasingly gaining recognition in the healthcare industry for their inherent ability to treat autoimmune diseases.[12,13] These immune checkpoint receptors play key roles in maintaining balance within our immune systems, and when that balance goes off-center it can lead to autoimmune disorders. Several companies are active with PD-1 agonists targeting different autoimmune diseases including Eli Lilly, Johnson & Johnson, AnaptysBio, and Gilead Sciences through their acquisition of MiroBio, a private company focused on checkpoint agonists targeting PD-1 and BTLA.

Like PD-1, CTLA-4 and BTLA, LAG-3 has been identified as a promising target in autoimmune diseases due to its ability to switch off activated T cells that are damaging tissue or creating inflammatory responses. Unlike these other immune checkpoints, to our knowledge Immutep is the only company that has successfully developed an agonist antibody to LAG-3. This first-in-class immunotherapy is called IMP761 and its development was no small feat. It took our CSO Frédéric Triebel, M.D., Ph.D., and our research team years to design.



IMP761 - A first-in-class LAG-3 agonist antibody targeting the root cause of autoimmune diseases to restore balance to the immune system.

Our proprietary IMP761 immunotherapy has been designed to restore balance to the immune system. It does so by silencing self-antigen-specific memory T cells, which are the underlying cause of many autoimmune diseases. Encouraging *in vivo* and *in vitro* preclinical studies were published in the *Journal of Immunology*. The results show IMP761 inhibits antigen-induced T cell proliferation/activation as well as T cell receptor (TCR)-induced NFAT (nuclear factor of activated T cells) activation. Regarding the latter, IMP761's inhibition of this TCR signalling was shown to be dose-dependent.

Additionally, IMP761 inhibited the antigen-specific skin T cell reaction in animal studies using an antigen-specific delayed-type hypersensitivity (DTH) model. This immunosuppressive effect was also supported by a gene expression profiling study (Figure A, B).

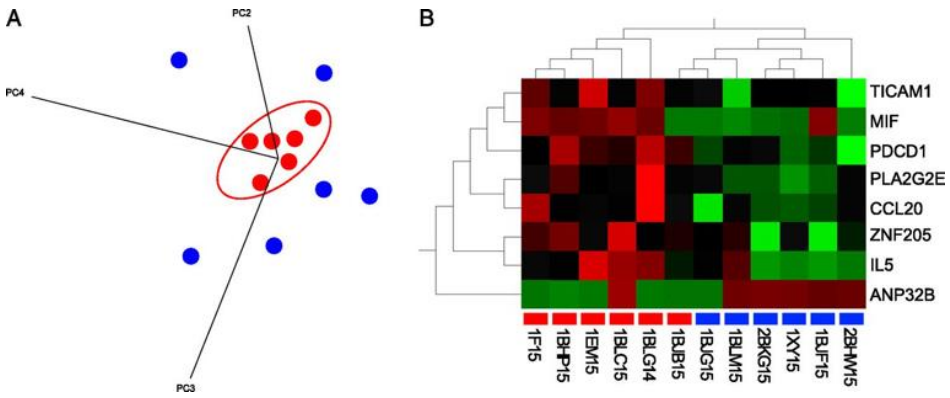


Figure A – Principal component analysis revealed that IMP761-injected animals did not cluster with PBS-injected animals, demonstrating that IMP761 can change the immune gene expression profile at the tuberculin skin test site.

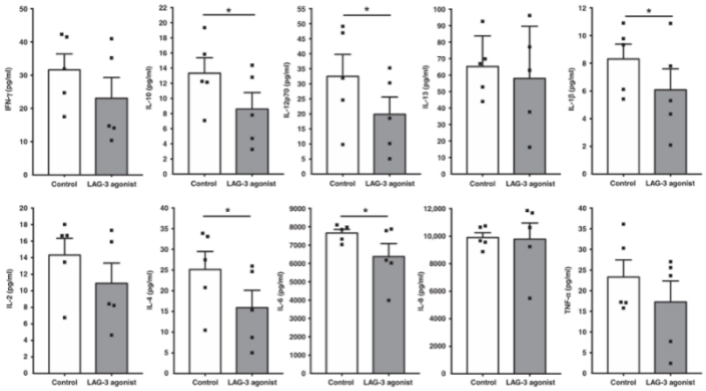
Figure B – Gene ontology analysis revealed that among the seven genes downregulated after IMP761 injection, five were linked to the inflammatory response biological process (CCL20, IL-5, MIF, PLA2G2E, TICAM1) and one (PDCD1) encoded PD-1, which can also be considered an immune activation marker following activation of the IFN-γ cascade. ANP32B, linked to dampening inflammation, was upregulated in the IMP761 group.

These *in vivo* and *in vitro* preclinical studies provided early proof-of-concept that IMP761, a novel LAG-3 agonist antibody, can drive immunosuppression and target the antigen-induced T cell responses that are the cause of many autoimmune diseases.

Subsequently, preclinical data in oligoarticular juvenile idiopathic arthritis (o-JIA) was published in *Pediatric Research*. This work was led by Erdal Sag, MD, MSc, and a team of rheumatologists in Denmark and Turkey who designed an *ex vivo* disease model for o-JIA, examined the effects of co-inhibitory receptors in this model, and demonstrated that these co-inhibitory receptors might contribute to the pathogenesis of the disease.

(12) Grebinoski S, Vignali DA. Inhibitory receptor agonists: the future of autoimmune disease therapeutics? *Curr Opin Immunol.* 2020 Dec;67:1-9; (13) Hu S, Liu X, Li T, Li Z, Hu F. LAG3 (CD223) and autoimmunity: Emerging evidence. *J Autoimmun.* 2020 Aug;112:102504

The peer-reviewed publication details how IMP761 leads to a decrease in a broad spectrum of effector cytokines in just 48 hours (depicted in image to the right). The decreased secretion of IL-10, IL-12, IL-1β, IL-4, and IL-6 reached the level of statistical significance ($p < 0.01$). Additionally, this study showed children with o-JIA have a skewed LAG-3 metabolism and suggests they can benefit from agonistic LAG-3 activity.



Treatment with agonist LAG-3 antibody and control (*$p<0.05$).

IMP761's ability to enhance LAG-3's natural downregulation of auto-reactive memory T cells opens the door to potentially address rheumatoid arthritis, Type 1 diabetes, and many other autoimmune diseases. One particularly interesting aspect to LAG-3 agonism is several motifs in the LAG-3 intracellular region have not been reported for other inhibitory coreceptors before (e.g. PD-1), indicating that LAG-3 inhibits T cell activation using nonredundant inhibitory mechanisms with the other inhibitory co-receptors.

Immutep is finalising its preclinical work on this LAG-3 agonist antibody and currently remains on track to bring IMP761 to the clinic by the middle of 2024. We look forward to providing more information as we approach this important milestone.

Summary

In summary, I am excited about what the future holds for Immutep and these two first-in-class agonist immunotherapies in oncology (efti) and autoimmune disease (IMP761). The potential impact on patients' lives by stimulating their own immune systems against cancer or suppressing immune responses to target the root cause of autoimmune disorders is substantial. We are focused on bringing these therapeutics to market in a timely and efficient manner.

In oncology, there is a clear need for combination therapies that can safely improve the rate, depth, and duration of responses to ICIs (e.g. anti-PD-1 therapy). Efti's differentiated efficacy and safety profile in combination with anti-PD-(L)1 therapies has attracted warranted attention throughout academia and industry, and we continue to move forward to drive value for our shareholders and to successfully deliver our innovative therapeutic solutions to patients in need.

There is a great deal of news ahead for Immutep, including the trial design for our upcoming pivotal TACTI-004 Phase III trial in 1L NSCLC, the initiation of the first-in-human Phase I study of IMP761, as well as numerous clinical data updates in oncology in first line head and neck squamous cell carcinoma (TACTI-003), first line non-squamous non-small cell lung cancer (INSIGHT-003), metastatic breast cancer (AIPAC-003), soft tissue sarcoma (EFTISARC-NEO), and urothelial cancer (INSIGHT-005). The foundation is set for 2024 to be an exciting year.

Upcoming Milestones & Clinical Data

Non-Small Cell Lung Cancer
TACTI-004 trial design and preparations for study start

Non-Small Cell Lung Cancer
Updates from triple combo INSIGHT-003 trial

Metastatic Breast Cancer
Update from AIPAC-003 study

Head & Neck Squamous Cell Carcinoma
Data in 1H2024 from TACTI-003

Soft Tissue Sarcoma & Urothelial Cancer
Updates from investigator-initiated EFTISARC-NEO & INSIGHT-005 studies

Autoimmune Diseases
IMP761 forward to clinical development in mid-2024

IMMUTEP

FAST FACTS

Listings
Australian Securities Exchange (ASX), NASDAQ

Stock Codes
ASX: IMM, NASDAQ: IMMP

Issued Capital – Ordinary Shares
1,188,834,559 (as of 31 January 2024)

Market Capitalisation
A$404 million / US$273 million
(as of 16 February 2024)

Cash & Term Deposits
A$103.7 million / ~US$67.8 million
(as of 31 December 2023)

FOLLOW IMMUTEP'S PROGRESS

Immutep is dedicated to maintaining consistent and clear communications with our investors. In addition to our newsletter, we encourage our shareholders to continue following Immutep's progress in a number of ways:

- Our website is a good source of information for those in search of details about our company, our management team, and archived information. We encourage everyone to check it out regularly. www.immutep.com
- Immutep registers all of our clinical trials, and the details of participating doctors, on the www.clinicaltrials.gov website, a service of the United States National Institutes of Health. This register is the largest such repository of clinical trial information around the world.
- Immutep's social media channels including Twitter, LinkedIn and Facebook.

Immutep Limited, Level 32, Suite 32.07, Australia Square, 264 George Street, Sydney NSW 2000

This investor update was authorised for release by Marc Voigt, the CEO of Immutep Limited.
ABN: 90 009 237 889