Immutep Ltd (IMMP)

Initiation Report

LifeSci Investment Abstract

Immutep (NasdaqGM: IMMP) is a clinical-stage biotechnology company focused on developing LAG-3 related immunotherapeutics for cancer and auto-immune disease. The Company's 4 candidates are designed using its LAG-3 technology that leverages the unique immunostimulatory and immunoinhibitory properties of LAG-3. LAG-3 has received strong attention as a therapeutic target following Phase I/IIa oncology data with Bristol-Myers Squibb anti-LAG-3 antibody, relatlimab. Immutep's lead candidate, IMP321, is being developed in three combination approaches for oncology: a chemo-IO combination, an IO-IO combination, and as a vaccine adjuvant. Multiple Phase I and II clinical trials are ongoing with IMP321. Immutep has secured several potential revenue-generating partnerships and collaborations, including 2 out-licensed clinical assets to Novartis and GlaxoSmithKline.

Key Points of Discussion

- **Diverse Portfolio of LAG-3 Candidates has Generated Interest from Multiple Big Pharma Companies.** Immutep has successfully leveraged the immunostimulatory and immunoinhibitory properties of LAG-3 to develop 4 unique LAG-3 product candidates for autoimmune disease and oncology. The Company has out-licensed two of their clinical-stage assets, IMP701 and IMP731 to two big pharma companies. IMP701 was out-licensed to Novartis (NYSE: NVS) for a significant but undisclosed amount in upfront and milestone payments. IMP731 was out-licensed to GlaxoSmithKline (NYSE: GSK) in an agreement that makes Immutep eligible for up to £64M in milestones and single-digit tiered royalties. Immutep also has clinical trial collaborations with other large pharma companies.

- **IMP321 is a Soluble Formulation of LAG-3 for Metastatic Breast Cancer and Melanoma.** IMP321 is a soluble dimeric fusion protein consisting of the Fc portion of the IgG1 human antibody and the four-extracellular domains of LAG-3. By engaging MHC Class II expressed on the surface of antigen presenting cells (APCs), soluble LAG-3 induces the functional maturation of dendritic cells, the most powerful of antigen-presenting cells. This immunostimulatory response has the potential to enhance the activity of the standard of care treatments currently used for both metastatic melanoma and breast cancer.

  Preliminary data from the Phase I TACTI-mel melanoma trial demonstrated a 61% (11/18) overall response rate and the Phase IIb AIPAC breast cancer study demonstrated at 87% (13/15) disease control rate upon preliminary analysis. Immutep anticipates final PFS data from AIPAC in H1 2019. The Company additionally plans to begin 2 studies in 2018 combining their candidates with PD-(L)1 inhibitors.

Expected Upcoming Milestones

- Q4 2018 – Initiation of TACTI-002.
- Q4 2018 – Initiation of INSIGHT-004.
- Q4 2018 – Data from the fourth patient cohort in TACTI-Mel.
- H1 2019 – Final progression free survival data from AIPAC.
- 2019 – Preliminary Data Readout from TACTI-002.

Analysts

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Market Data

Price	$3.13
Market Cap (M)	$96
EV (M)	$80
Shares Outstanding (M)	30.8
Fully Diluted Shares (M)	39.7
Avg Daily Vol	139,296
52-week Range:	$1.25 - $4.21
Cash (M)*	$16.8
Net Cash/Share	$0.55
Annualized Cash Burn (M)	$10.0
Years of Cash Left	1.7
Short Interest (M)	0.31

**As of June 30th*

Financials

FY Jun		2017A	2018A	2019A
EPS	H1	(0.19)	(0.18)	NA
	H2	NA	NA	NA
	FY	(0.41)	(0.49)	NA

For analyst certification and disclosures please see page 35

- **Strong Interest Surrounding Therapeutic Application of LAG-3.** LAG-3 has recently garnered interest in the oncology industry. Its simultaneous immuno-suppressive and immuno-stimulatory properties also opens up the possibility for LAG-3 application in auto-immune disorders. The number of patients evaluated with LAG-3 candidates steadily rose from less than 1,000 in 2013 to approximately 6,700 in 2018 alongside the growth in the number of clinical trials studying LAG-3 therapeutics. Prevailing big pharma interest is highlighted by Immutep securing a licensing agreement with Novartis, Bristol-Myers Squibb's development of relatlimab, and other big players like Merck and Regeneron developing their own LAG-3 inhibitors. Bristol-Myers Squibb's relatlimab is the furthest along in clinical development, currently being evaluated in a Phase II/III trial. Phase I/IIa data from the *Opdivo* + relatlimab combination in patients with relapsed or refractory melanoma was presented at ESMO 2017, demonstrating an overall response rate of 11.5%, which increased to 18% when analysis was conducted amongst patients with LAG-3 expression in at least 1% of tumor-associated immune cells within the tumor margin. Immutep is positioned as one of the leaders in the development of LAG-3 therapies with 3 programs in clinical development, two of which are out-licensed through partnerships with Novartis and GlaxoSmithKline.

- **Final Progression Free Survival Data from AIPAC is Expected in H1 2019.** AIPAC is an ongoing Phase IIb study using IMP321 in combination with standard chemotherapy (paclitaxel) for patients with metastatic breast cancer. The study enrolled 15 patients in the phase I safety run-in portion and is anticipated to enroll an additional 226 in the double-blind Phase II portion. The Company announced that the mid-point of patient enrollment was reached in June 2018. Preliminary results from the safety run-in portion were presented at ASCO 2018. Overall, both the 6mg and the 30mg doses of IMP321 in combination with paclitaxel were safe and well-tolerated, with the only serious treatment-related adverse event being grade 1 cytokine release syndrome. The primary endpoint for the phase II portion will be assessment of progression free survival for a time period of up to 37 months. Key secondary endpoints include safety and tolerability of IMP321, assessment of the change in quality of life, evaluation of objective response rate and evaluation of stable disease. Efficacy-related endpoints will be analyzed solely on patients enrolled in Stage 2. Progression free survival data are anticipated in H1 2019.

- **Three Potential Areas of Application for LAG-3.** Immutep is developing its LAG-3 therapeutics with three pivotal areas of application- as part of a chemotherapy-immunotherapy combination, as part of an IO-IO combination and as a potential vaccine adjuvant. The potential for chemo-IO combination regimens has been demonstrated by the approval of pembrolizumab with chemotherapy for NSCLC. The co-administration of IMP321 with chemotherapy has the potential to demonstrate additive effects by increasing the circulating presence of activated DCs ready to uptake tumor antigens from cells dying as a result of chemotherapy-induced immunogenic death.

  The rationale behind the IMP321/anti-PD-(L)1 combination can be thought of as "taking the brakes off the immune system" while simultaneously "pushing the accelerator". The anti-PD-(L)1 checkpoint inhibitor treatment method combats the loss of immunogenicity by increasing immune detection of cancer cells masked by PD-(L)1 inhibitory receptors. The co-administration of IMP321 could increase the population of primed circulating CTLs ready to attack the "unmasked" tumor cells, enhancing the efficacy of checkpoint inhibitors. Lastly, cancer vaccine adjuvants can boost the desired response to otherwise weak antigens that also have associated tolerance mechanisms. One mechanism to overcome these immunosuppressive barriers is the potent recruitment and activation of antigen presenting cells that will either prime or activate a pre-existing adaptive immune response- a potential key function of IMP321.

Financial Discussion

Full Year 2018 Financial Results. Immutep reported revenue equal to A$2.63M (USD 1.88M) for the year ended June 30th, 2018 (referred to as FY2018), attributed to two significant milestone payments from Novartis and EOC Pharma. Research and development expenses were A$10M (USD 7.14M), as compared to A$7.5M (USD 5.4M) in FY2017. Corporate and administrative expenses increased from A$4.3 M (USD 3.07M) in FY 2017 to A$7.2 M (USD 5.14M) in FY 2018. After-tax loss was A$12.74 M (USD 9.1M), as compared with an after-tax loss of A$9.37 M (USD 6.7M) in FY 2017, translating into a diluted loss per share of A$0.49 (USD 0.35) in FY2018 compared with a diluted loss per share of A$0.41 (USD 0.29) in FY 2017. The Company had cash and cash equivalents of A$23.48 M (USD 16.8M) as of June 30th, 2018.

Second Quarter 2018 Financing and Share Purchase Plan. In March 2018, Immutep announced the successful completion of the placement of 326,192,381 ordinary shares to various Australian and US institutional investors, including Platinum Asset Management, Australian Ethical and Ridgeback Capital Investments. The placement generated a total of A$6.85 M (USD 4.9M) prior to transaction-related expenses. Subsequently, the Company announced the close of its Shared Purchase Plan in April 2018. The SPP successfully placed 300,561,089 new ordinary shares, at A$0.021 (USD 0.015) per share, generating A$6.31M (USD 4.5M) before transaction-related expenses. Together, the two financing events raised a total of A$13.16M (USD 9.4M).

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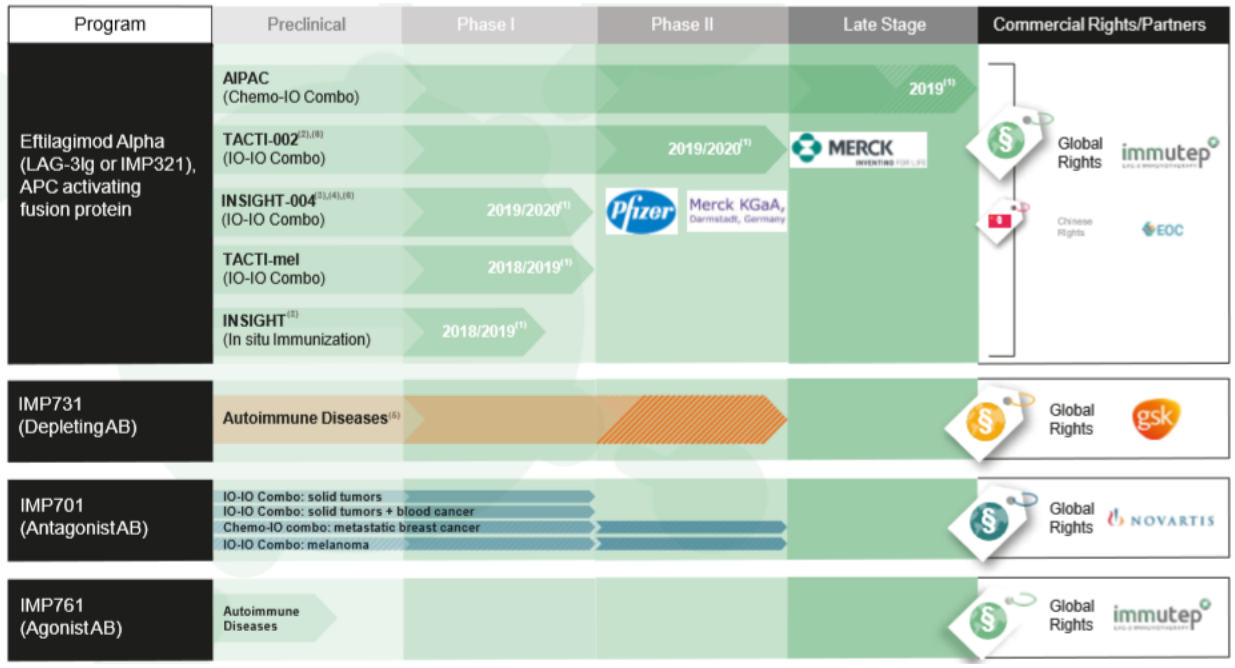
Company Description

Immutep (NasdaqGM: IMMP) is a clinical-stage biotechnology company focused on the development of LAG-3 related immuno-therapeutics. Lymphocyte activation gene 3 (LAG-3) was originally discovered by the Company's Chief Medical and Scientific Officer, Frédéric Triebel, and has since been characterized as a powerful antigen-presenting cell activator as well as a negative regulator of T-cells. Pre-clinical and clinical studies have shown that soluble LAG-3 induces potent maturation of APCs, reduces tumor burden, and increases the presentation of tumor antigens on APCs, in the context of a cancer vaccine adjuvant. The Company is developing its lead LAG-3 therapeutic eftilagimod alpha in three pivotal areas: a chemo-immunotherapy combination, an immunotherapy-immunotherapy combination, and as a vaccine adjuvant. The unique immuno-stimulatory and immuno-suppressive properties of LAG-3 have allowed Immutep to develop 4 unique product candidates for immuno-oncology and autoimmune diseases, and the Company's developmental pipeline is shown in **Figure 1**.

Figure 1. Immutep's Developmental Pipeline



Source: Company Presentation

Eftilagimod alpha, or IMP321, is a soluble LAG-3 fusion protein that is currently being evaluated in multiple clinical trials-AIPAC, TACTI-mel, and INSIGHT. AIPAC is evaluating the combination of IMP321 and chemotherapy in the treatment of metastatic breast cancer while TACTI-mel is evaluating the co-administration of IMP321 and anti-PD-1 therapy in metastatic melanoma. Preliminary data, although early, support the continued evaluation of the agent. Preliminary data from the melanoma trial demonstrated a 61% (11/18) overall response rate and the breast cancer study demonstrated at 87% (13/15) disease control rate upon preliminary analysis. In March 2018, Immutep entered into a clinical trial collaboration and supply agreement with Merck (NYSE: MRK) to initiate TACTI-002, a phase II trial assessing the combination of IMP321 with

Keytruda in HNSCC and NSCLC. The trial is anticipated to initiate in Q4 2018. More recently, the Company announced another clinical trial collaboration and supply agreement with Pfizer and Merck KGaA to initiate INSIGHT-004, a phase I trial assessing IMP321 in combination with PD-L1 inhibitor *Bavencio* (avelumab) in various solid tumors. While Immutep has exclusive world-wide rights to the development of IMP321 in the US and EU, EOC Pharma holds the exclusive rights to develop and commercialize the product in mainland China, Hong Kong, Taiwan and Macau as part of a milestone and royalty-based licensing agreement. EOC Pharma initiated a Phase I study of IMP321 in metastatic breast cancer in China. Immutep has also secured multiple big-pharma licensing agreements surrounding two of their clinical-stage assets, IMP701 and IMP731. IMP701 was out-licensed to Novartis (NYSE: NVS) for a significant but undisclosed amount in upfront and milestone payments. IMP731 was out-licensed to GlaxoSmithKline (NYSE: GSK) in an agreement that makes Immutep eligible for up to £64M in milestones as well as single-digit tiered royalties.

Collaborations and Partnerships

Immutep has secured an extensive number of partnerships and collaborations surrounding their 4 LAG-3 product candidates. They have multiple licensing agreements and collaborations related to their lead asset, IMP321. While Immutep has exclusive world-wide rights to the development of IMP321 in the US and EU, Eddingpharm (private) held the exclusive rights to develop and commercialize the product in mainland China, Hong Kong, Taiwan and Macau as part of a licensing agreement established in 2013. The agreement was transferred to EOC Pharma, an affiliate of Eddingpharm, in 2015. Under the agreement, Immutep is eligible for milestone payments and royalties, although concrete details remain undisclosed. The Company received their first milestone payment from EOC Pharma in February 2018 totaling $1 M.

In 2017, Immutep announced a collaboration agreement with Cytlimic, a spin-off from the NEC corporation (PINX: NIPNF), to test IMP321 in combination with a cancer peptide vaccine. Under the new material transfer agreement that will be revenue-generating for Immutep, the Company will provide IMP321 for a formulation development to be used in clinical and pre-clinical trials conducted by Cytlimic.

Additionally, Immutep has a strategic supply partnership with WuXi Biologics, a subsidiary of WuXi AppTech Co. Ltd (Shanghai: 603259.SS), who will be the exclusive manufacturer of IMP321. In March 2018, the Company entered into a clinical trial collaboration and supply agreement with Merck to conduct TACTI-002, a new Phase II clinical trial evaluating the combination of IMP321 with *Keytruda* for patients with HNSCC and NSCLC. Additionally, in September 2018, Immutep announced another clinical trial collaboration and supply agreement with Merck KGaA and Pfizer to assess the efficacy of IMP321 in combination with avelumab, an anti-PD-L1 antibody, in patients with advanced solid malignancies. This collaboration will serve as an amendment to the currently ongoing INSIGHT study.

The Company's two other clinical-stage assets are out-licensed to two big pharma companies. IMP701 was initially out-licensed to CoStim Pharmaceuticals in 2012, which was acquired by Novartis in 2014. As part of the original agreement, Novartis holds exclusive world-wide rights to the development of IMP701 for cancer and Immutep is eligible to an undisclosed amount in upfront and milestone payments as well as royalties based on world-wide sales. Novartis has paid out two milestone payments to date. In 2011, the Company executed a licensing agreement with GlaxoSmithKline granting GSK exclusive world-wide rights to the development of IMP731 for autoimmune disorders. The agreement makes Immutep eligible for up to £64M (~$100M) in

upfront and milestone payments as well as single-digit tiered royalties. The Company received their first milestone payment from GSK for the initiation of a Phase I clinical trial of IMP731 and anticipates another potential upcoming milestone payment based on GSK's public announcement to initiate a clinical proof of concept study with IMP731 in colitis.

LAG-3 Technology

Lymphocyte activation gene-3 (LAG-3) is a membrane-protein and an MHC Class II ligand that is responsible for multiple roles within the immune system that include T-cell inhibition and regulation of dendritic cell function. It is structurally and genetically related to the CD4 protein but possesses some differentiating characteristics. LAG-3 binds MHC Class II molecules with higher affinity than CD4 and does not transduce signals through the protein tyrosine kinase *lck*. LAG-3 expression is induced in activated $CD4^+$ and $CD8^+$ T-cells and is correlated with their ability to secrete interferon-γ (IFN-γ), making it one of the few known markers expressed only on the surface of activated T-cells. Immutep has designed multiple unique approaches to the therapeutic use of LAG-3, leveraging both its immunostimulatory and immunoinhibitory properties. Soluble LAG-3 (LAG-3Ig) has been shown to possess immunostimulatory properties modulated through to the activation of antigen presenting cells (APCs). On the other hand, natural LAG-3 is an established co-inhibitory receptor whose expression on activated T-cells is known to potentiate an inhibitory effect on these cells, translating to an overall immunoinhibitory response. These unique characteristics give LAG-3 targeting agents the potential for application across both oncology and auto-immune diseases.

LAG-3 as an Immuno-Stimulator. Tumor cells have developed a variety of cellular mechanisms to evade and suppress elimination by the immune system. One such mechanism is the loss of antigenicity, which has several causes.[1] Loss of antigenicity can result from defects in antigen presentation, deriving from lack of tumor antigen expression, downregulation of MHC molecules or alteration to MHC-antigen loading. It can also be caused by the downregulation of costimulatory molecules CD80 and CD86, which results in hampered MHC signaling to T-cells.[2]

The immuno-stimulatory effects of LAG-3 come from its role as an APC activator. Although all nucleated cells are considered antigen-presenting cells, only mature APCs can initiate specific immune responses by priming naïve T-cells. Specifically, dendritic cells are regarded as the most-powerful of antigen-presenting cells for their unique ability to induce primary immune responses. The soluble recombinant fusion LAG-3Ig protein has been shown to induce the phenotypic maturation of immature dendritic cells through ligation to MHC class II. Mature APCs have increased expression of both MHC class I and MHC class II molecules, as well as increased expression of co-stimulatory molecules CD80, CD86 and CD40.[3] Although $CD8^+$ cells generally only recognize antigens presented on MHC Class I, mature APCs can also present MHC Class II- associated exogenous antigens to CD8+ T-cells through cross-presentation. Therefore, LAG-3Ig induced increases in mature dendritic cells with CD80 and CD86 up-regulation results in a physiological improvement in antigen

[1]Beatty, G. L. and Gladney, W.L., 2015, "Immune Escape Mechanisms as a Guide for Cancer Immunotherapy", *Clinical Cancer Research",* 21(4), pp. 687-692

[2]Charette, M. et al., 2016, "Turning tumor cells into antigen presenting cells: the next step to improve cancer immunotherapy?", *European Journal of Cancer,* 68, pp. 134-147

[3]Andreae, S. et al., 2002, "Maturation and activation of dendritic cells induced by lymphocyte activation gene-3", *Journal of Immunology,* 168, pp. 3874-3880

presentation to $CD8^+$ cells. This has the potential to counteract the loss of antigenicity that tumors utilize as an evasion mechanism.

LAG-3 as an Immuno-Suppressor. Aside from the loss of antigenicity, loss of immunogenicity and the generation of an immuno-suppressive tumor microenvironment have also been widely accepted as alternative mechanisms for tumor immune evasion. This can be propagated by tumors upregulating certain immune checkpoints, such as PD-L1 and CTLA-4, leading to inhibition of T cell activity. Immune checkpoints have been implicated as the key contributors to T-cell exhaustion in cancer, resulting in impaired tumor killing ability. Checkpoint inhibitor therapies have become promising therapeutic targets for harnessing the immune system in the fight against cancer and identifying cancers that are potentially susceptible to immunotherapy. However, diminished efficacy of current ICIs has led to an increased need to pinpoint other immune checkpoint molecules and negative regulatory markers.

While soluble LAG-3 has a role as an APC activator, natural LAG-3 is emerging as a relevant checkpoint molecule for its involvement as a negative regulator of T-cells. The process of T-cell activation is marked by biochemical/biophysical reprogramming to meet the higher energetic demands associated with an activated state.[4] One such reprogramming requirement is the change in metabolic status, as shown by the distinct metabolic states characterizing naïve and mature T-cells. Ligation of TCRs by peptide/MHC complexes stimulates multiple signaling cascades, including one that results in the downstream mobilization of calcium. As a result, calcium signaling is thought to play a key role in modulating the downstream pathways that are involved in this metabolic shift. The simultaneous cross-linking of LAG-3 with the CD3/TCR complex has been shown to hamper this increase in calcium flux, confirming its negative regulatory activity.[5] Although, the exact signaling pathways evoked in this interaction remain unclear, LAG-3's unique and universally conserved KIEELE motif has been shown essential for inhibitory function. The proteins that bind this particular motif have yet to be elucidated.

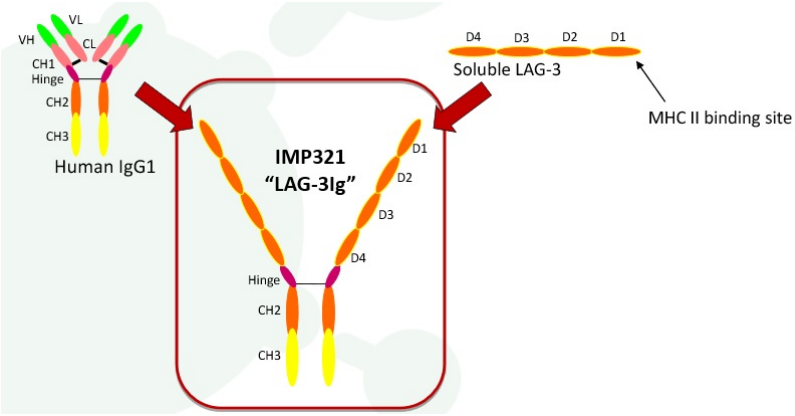
Eftilagimod Alpha (IMP321): APC Activator for The Treatment Cancer

Mechanism of Action. Eftilagimod alpha (IMP321) is a soluble, recombinant formulation of LAG-3 known as LAG-3Ig. It is a dimeric fusion protein consisting of the Fc portion of the IgG1 human antibody and the four-extracellular domains of LAG-3. **Figure 2** depicts the structure of IMP321. The key role of soluble LAG-3 is the activation of antigen presenting cells, thereby producing an immunostimulatory response.

[4]Fracchia, K.M. et al., 2013, "Modulation of T-cell metabolism and function through calcium signaling", *Frontiers in Immunology,*

[5]Anderson, A.C. et al., 2016, "Lag-3, Tim-3 and TIGIT: Co-inhibitor receptors with specialized functions in immune regulation", *Cell: Immunity,* 44(5), pp. 989-1004

Figure 2. Recombinant Fusion Protein LAG-3Ig



Source: Company Presentation

IMP321 was shown to induce the phenotypic and functional maturation of dendritic cells, the most powerful of antigen-presenting cells, confirming its role as an APC activator. IMP321 uniquely binds to a subset of MHC Class II molecules localized in cholesterol-rich lipid rafts which presumably contain transducer proteins that facilitate downstream MHC class II signaling. This binding induces the upregulation of CD80 and CD86 as well as morphological changes, confirming the transition from immature to mature dendritic cells.

A key secondary component to DC maturation is the migration of DCs to secondary lymphoid organs where they acquire potent immunostimulatory properties and go on to sensitize naïve antigen-specific T-cells, thereby promoting a primary immune response. IMP321 has shown the ability to induce the secretion of cytokines essential to this migratory process.[6] IMP321 induced-maturation results in the upregulation of DC receptors for CCR7, a constitutive chemokine essential for homing to the lymph nodes, while simultaneously down-regulating the receptors for inflammatory cytokines. Additionally, IMP321 results in the up-regulation of the costimulatory molecule Signal 2 which is involved in determining whether a naïve antigen-specific T-cell becomes immune or tolerant. This up-regulation may therefore increase the immunogenicity of antigen-loaded mature DCs and lead to more efficient antigen-presentation.

Safety Profile. Overall, treatment with IMP321 appears to be safe and well-tolerated. No dose-limiting toxicities or treatment-related discontinuations have been reported. The most common adverse events related to IMP321 across both conducted clinical trials was grade 1/2 local erythema and injection site reactions. The 6mg and 30mg doses appear to be well-tolerated when administered in combination with paclitaxel. All 3 doses levels appear to be well-tolerated when administered in combination with pembrolizumab. In the AIPAC trial, grade 1 cytokine release syndrome was the only serious treatment-related adverse event reported, and helps confirm the immunostimulatory effects of IMP321. 4 patients (27%) in the AIPAC trial and 4 patients (33%) in the TACTI-Mel trial experienced grade 3/4 adverse events. Pre-clinical toxicology studies assessing the three

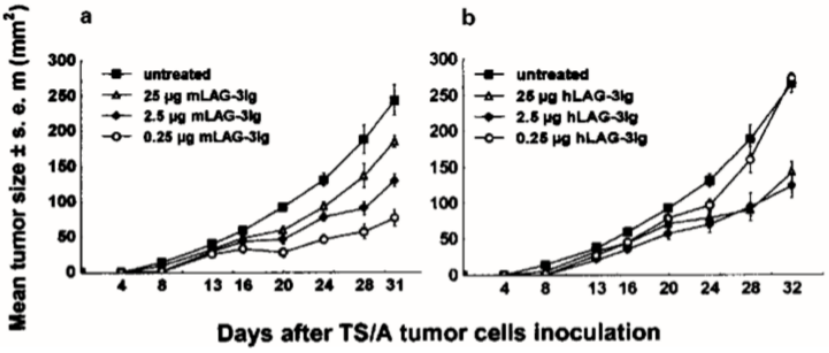
[6]Buisson, S. and Triebel, F., 2003, "MHC Class II engagement by its ligand LAG-3 (CD223) leads to a distinct pattern of chemokine and chemokine receptor expression by human dendritic cells", *Vaccine,* 21(9-10), pp. 862-868

injections of IMP321 at 3000x the maximal dose per kg used in Phase I trials did not lead to detectable toxicity or signs of inflammation.[7]

Preclinical Data Discussion

***In Vivo* Efficacy of IMP321 for Treating Cancer**. The B7.1-ICAM-1- non-immunogenic undifferentiated spontaneous mammary adenocarcinoma TS/A cell line was used as a tumor model. Different concentrations of recombinant soluble human LAG-3 (hLAG-3Ig) and mouse LAG-3 (mLAG-3Ig) were tested. Statistically significant growth rate reductions ($p<0.01$) were observed when wild-type tumor cells were injected with 2.5 µg or 0.25 µg mLAG-3Ig, but interestingly the 25 µg dose performed worse.[8] When administering hLAG-3Ig at higher doses, statistically significant growth reductions ($p<0.01$) were seen at the 2.5 µg and 25 µg dose level. The effect of LAG-3Ig administration on tumor growth is depicted in **Figure 3**. Dosing variation between mouse and human results could be due to protein folding and half-life differences between hLAG-3Ig and mLAG-3Ig. This data demonstrated that LAG-3 has the potential to induce anti-tumor effects in non-immunogenic tumors.

Figure 3. Effect of LAG-3Ig Administration on Tumor Growth



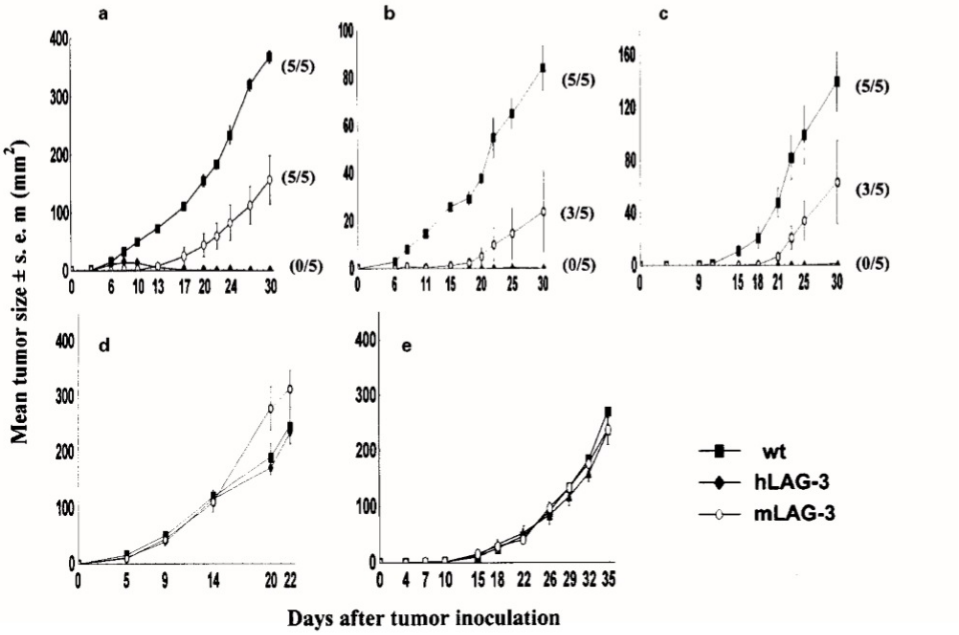
Source: Prigent et al., 1999

To assess whether LAG-3 cell surface expression could affect tumor growth, three tumor lines were transfected with the cDNA of hLAG-3 or mLAG-3. The three tumor lines were MCA 205, TS/A and RENCA (immunogenic renal adenocarcinoma). C57BL/6, BALB/c and T-cell deficient BALB/c *nu/nu* mice were subcutaneously injected with the minimum tumorigenic dose (MTD) of either wild-type or transfected tumor cells. Wild-type tumor lines grew progressively in either of the three mouse models. In contrast, hLAG-3/MCA 205, hLAG-3/TS/A and hLAG-3/RENCA cells did not form palpable tumors in immunocompetent mice. hLAG-3/TS/A and hLAG-3/RENCA cell lines grew progressively in immune-deficient *nu/nu* mice at levels similar to wild-type cells. In a significant portion of mice, the expression of mLAG-3 contributed to tumor regression and decreased growth from the mLAG-3/MCA 205 cells compared to wild type. Tumor growth reduction associated with tumor cell LAG-3 expression is shown in **Figure 4**.

[7]Fougeray, S. et al., 2006, "A soluble LAG-3 protein as an immunopotentiator for therapeutic vaccines: preclinical evaluation of IMP-321", *Vaccine,* 24(26), pp. 5426-5433

[8]Prigent, P. et al., 1999, "Lymphocyte Activation gene-3 induces tumor regression and anti-tumor immune response", *European Journal of Immunology,* 29, pp. 3867-3876

Figure 4. Tumor Cell LAG-3 Expression Decreases Tumor Growth



(a) C57BL/6, MCA 205; (b) BALB/c, TS/A; (c) BALB/c, RENCA; (d) BALB/c nu/nu, MCA 205; (e) BALB/c nu/nu, TS/A

Source: Prigent et al., 1999

BALB/c mice were injected with 1 x MTD of wild type TS/A or RENCA cells in order to assess the efficacy of treatment with irradiated LAG-3+ tumor cells. Mice were treated at day 6 with 5 x MTD of either hLAG-3+ or mLAG-3+ TS/A or RENCA cells. Reduction of tumor growth was seen in all cases across both tumor types, with 3 cases demonstrating complete regression when injected with irradiated hLAG-3+ tumor cells.

IMP321 Demonstrates Potential as a Vaccine Adjuvant. C57BL/6 and BALB/c mice were subcutaneously injected with the minimal tumorigenic dose of either MCA-205 mouse fibrosarcoma cells or metastatic mouse adenocarcinoma TS/A cells. Mice were treated by subcutaneous injection of irradiated tumor cells as a source of antigens with or without 0.1 μg or 1 μg mLAG-3Ig. Treatments were administered either once on day 6 or twice on days 6 and 14. The co-administration of mLAG-3Ig reduced tumor growth ($p < 0.01$) in both tumor models as opposed to treatment with irradiated cells alone or PBS. Results between mice treated once and mice treated twice were similar. Re-challenge of mice at day 30 with 5 x minimum tumorigenic dose of wild-type tumor cells showed specific tumor-immune responses were maintained. Tumor growth was lowered in C57BL/6 mice previously injected with hLAG-3/MCA 205 cells. Protection against re-challenge was also observed in TS/A and RENCA cells ($p<0.01$). Similar studies testing the potential of LAG-3Ig as a vaccine adjuvant demonstrated that IMP321 induced similar maturation levels when compared to a known inducer of APC activation, sCD40L. IMP321 has a potential safety advantage over sCD40L as the clinical development of sCD40L has been hampered by its associated risk of thrombosis.[9]

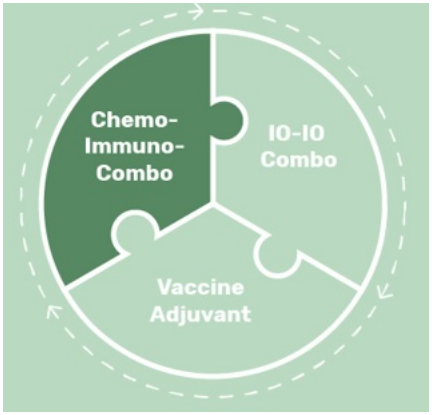
[9]Fougeray, S. et al., 2006, "A soluble LAG-3 protein as an immunopotentiator for therapeutic vaccines: preclinical evaluation of IMP-321", *Vaccine,* 24(26), pp. 5426-5433

IMP321 Induced Tumor Rejection was Mediated by CD8+ T-cells. 10-mm diameter tumors were excised at day 8 from normal hosts injected with 5 x MTD of hLAG-3 MCA 205 and hLAG-3 TS/A cells. The percentage of $CD8^+$ cells was about 31% in hLAG-3 MCA 205 tumors, as compared to 4% in wild type MCA 205 tumors. The respective contribution of $CD4^+$ and $CD8^+$ cells to the anti-tumor response was measured by depletion of the individual subsets. Depletion of $CD4^+$ cells lead to partial abrogation of tumor protection. Depletion of $CD8^+$ cells led to a complete loss of tumor cell rejection. Additional studies demonstrated that the peptide-specific $CD8^+$ T-cells generated in the presence of IMP321 were endowed with strong cytotoxic activity and enhanced release of type 1 cytotoxic (Tc1) cytokines, such as IFN-γ, as well as being characterized by a final effector memory phenotype.[10]

Potential Combinations with LAG-3 Immunotherapy

Through its diverse functionality and unique mechanism of action, LAG-3 has the potential to be used in various combination therapies. As shown in **Figure 5**, the Company is currently developing IMP321 in three potential combinations: chemo-IO combination, IO-IO combination and as an adjuvant to cancer vaccines.

Figure 5. IMP321 Areas of Application



Source: Company Presentation

Chemotherapy-Immunotherapy Combo. The potential for chemo-IO combination regimens has been demonstrated by the approval of pembrolizumab with chemotherapy for NSCLC. Chemotherapeutic agents induce the immunogenic death of tumor cells- a type of cell death that primes an anti-cancer immune response. Immunogenic cell death (ICD)-induced by chemotherapeutics generally begins with ER stress that promotes the translocation of calreticulin (CRT) to the plasma membrane as a pre-apoptotic signal.[11] This is succeeded by the release of damage-associated molecular pattern (DAMP) molecules alongside various tumor antigens

[10]Casati, C. et al., 2006, "Soluble human lag-3 molecule amplifies the *in vitro* generation of type 1 tumor-specific immunity", *Cancer Research,* 66(8), pp. 4450-4460

[11]Wang, Y. et al., 2018, "Immunogenic effects of chemotherapy-induced tumor cell death", *Genes and Diseases,* pp. 1-10, available online at : https://www.sciencedirect.com/science/article/pii/S2352304218300679

from dying tumor cells. DAMP molecules stimulate the recruitment of dendritic cells that play a pivotal role in uptake, processing and presentation of the released tumor-antigens to prime cytotoxic T-lymphocytes, effectively mounting an anti-tumor immune response. The co-administration of IMP321 with chemotherapy has the potential to demonstrate additive effects between the two therapies by amplifying the immune response already generated with chemotherapy alone. IMP321 is a powerful activator of antigen-presenting cells that can increase the circulating presence of activated DCs ready to uptake tumor antigens from dying tumor cells, resulting in a physiological increase in antigen presentation to CTLs.

Immuno-Immunotherapy Combo. The rationale behind the IMP321/anti-PD(L)-1 combination can be thought of as "taking the brakes off the immune system" while simultaneously "pushing the accelerator". Anti-PD-(L)1 checkpoint inhibitors work by blocking the PD-1/PD-L1/2 interactions between T cells and tumors, which leads to the inhibition of T-cell activation. This treatment method combats the loss of immunogenicity-one of the main immune escape mechanisms used by tumors. The co-administration of IMP321 in combination checkpoint inhibitors is designed to simultaneously target another well-established immune escape mechanism-the loss of antigenicity. IMP321 serves as a dendritic cell activator that yields mature dendritic cells with CD80/CD86 upregulation. This increase in the population of mature APCs is intended to increase efficient antigen presentation to CTLs, resulting in an increase in primed circulating CTLs ready to attack the "unmasked" tumor cells.

Adjuvant to Cancer Vaccines. Vaccine adjuvants serve the purpose of enhancing the magnitude and longevity of the specific immune response induced by the antigen present within the vaccine.[12] Specific to cancer vaccines, the use of adjuvants is necessary to boost the desired response to otherwise weak antigens that also have associated tolerance mechanisms. One mechanism to overcome the immunosuppressive barriers that are a hallmark of tumors is the potent recruitment and activation of antigen presenting cells that will either prime or activate a pre-existing adaptive immune response. More specifically, adjuvant formulations yielding a Th1-skewing pro-inflammatory response are centrally vital to effective therapeutic vaccine strategies. IMP321 has demonstrated its potential to generate Type-1 specific immunity in addition to its function as a potent dendritic cell activator. Pre-clinical studies in mouse fibrosarcoma and metastatic adenocarcinoma models demonstrated that co-administration of IMP321 with a vaccine of irradiated tumor cells reduced tumor growth as opposed to the vaccine alone and resulted in a maintained specific tumor-immune response upon re-challenge at day 30. These results support further investigation into IMP321's potential as a vaccine adjuvant.

Market Information for PD-1 Non-Responders

Although IMP321 is initially being studied as a treatment for melanoma and triple-negative breast cancer, its potential utility as a combination treatment with checkpoint inhibitors could expand into other tumor types. Checkpoint inhibitors are effective compared to conventional therapies in several tumor types, but many patients do not respond to treatment, and options are often limited following progression. Broad, response rates to PD-(L)1 inhibitors in approved indications are presented in **Figure 6**, and those that do not respond, or progress could represent a sizeable market opportunity for Immutep with IMP321. PD-(L)1 response rates are based on the prescribing labels and published literature for *Opdivo, Keytruda,* and *Bavencio.*

[12]Dubensky, T.W. and Reed, S.G., 2010, "Adjuvants for Cancer Vaccines", *Seminars in Immunology,* 22(3), pp. 155-161

Figure 6. PD-(L)1 Response Rates in Approved Indications

Indication	PD-1/L1 Response Rate (CR%)
Previously treated RCC	25% (1% CR)
Previously untreated RCC (intermediate/poor-risk)	42% (9% CR)**
Unresectable or metastatic melanoma	44% (15% CR)-58% (19% CR)*
First-line NSCLC with 50% PD-L1 expression	45% (4% CR)
Second-line NSCLC	19-20% (1% CR)
Chemotherapy + *Keytruda* for advanced NSCLC	55% (0% CR)
Relapsed or progressive classical Hodgkin's lymphoma after HSCT	69% (14% CR)
Second-line HNSCC	13% (3% CR)
Locally advanced or metastatic urothelial carcinoma unfit for cisplatin-chemotherapy	29% (7% CR)
Previously treated urothelial carcinoma	21% (7% CR)
Second-line hepatocellular carcinoma	14% (2% CR)
Recurrent gastric cancer	13% (1% CR)
MSI-H/dMMR cancer	40% (7% CR)
Hodgkin's lymphoma	69% (22% CR)
Recurrent or metastatic cervical cancer	14% (3% CR)
Refractory PMBCL	45% (11% CR)
Metastatic Merkel cell carcinoma	33% (11% CR)
3rd line small cell lung cancer	12% (1% CR)
Advanced cutaneous squamous cell carcinoma	47% (4% CR)

*= Includes both anti-PD-1 monotherapy and combination with anti-CTLA-4.
*= combination with anti-CTLA-4

Source: LifeSci Capital

Market Opportunity for Combination Agents Highlighted by Nektar/Bristol-Myers Squibb Collaboration. Due to the vast-number of patients who do not benefit from checkpoint inhibitors, there is great interest from pharmaceutical companies and investors on combination agents, which is highlighted by the collaboration between Bristol-Myers Squibb and Nektar Therapeutics (NasdaqGS: NKTR) that was announced in early 2018 for NKTR-214, a CD-122 (IL-2 receptor beta subunit) biased agonist. Preliminary Phase I/II data with NKTR-214 showed encouraging response rates in treatment naïve melanoma, NSCLC, treatment naïve RCC, and treatment naïve urothelial carcinoma, including in PD-L1 negative tumors. Following these early data, Bristol-Myers Squibb entered into a global development and commercialization collaboration with Nektar for NKTR-214. Under the terms of the agreement, Nektar received an upfront payment of $1.85 billion ($1.0 B cash, and $850 M stock), and is eligible to receive an additionally $1.78 billion in milestones. The Companies will share global profits for NKTR-214, with Nektar receiving 65%, and development costs will also be shared. The two companies will evaluate the combination of NKTR-214 and *Opdivo* in more than 20 indications in 9 tumor types. The size of this collaboration gives an indication of the premium that big pharma is willing to pay for novel therapies.

Metastatic Melanoma Background

Melanoma is a cancer of pigment-producing skin cells, known as melanocytes, and is generally caused by a combination of genetic risk factors and ultraviolet light exposure from the sun. An estimated 91,270 new cases of melanoma will be diagnosed in the US in 2018, and 9,320 patients will die from the disease. An additional 106,995 diagnoses are expected in the EU. Melanoma makes up about 4.5% of the total cancers diagnosed, and accounts for roughly 75% of skin cancer deaths.[13] Although nearly all people with the disease are cured when identified early, the 5-year survival is 64% for patients with Grade III melanoma and 23% for patients with Grade IV disease. Grade III and IV melanoma make up at least 13% of all cases of the disease.

In the US, Caucasian males are historically at the highest risk of melanoma, followed by Caucasian white females. Sun exposure and light skin pigmentation contribute significantly to the development of melanoma; however, melanoma is possible with all types of skin and areas of the body that typically do not receive sun exposure.[14] Certain genes are commonly mutated in melanoma and may be specifically tied to its pathogenesis. The most commonly mutated gene in melanoma, found in over 50% of cases, is BRAF, which encodes an intracellular protein B-Raf.[15] This protein is part of a broader signal transduction pathway, the MAP kinase (MAPK) pathway that is often altered in melanoma.

Treatment of Melanoma. Initial treatment of melanoma generally involves excision of the malignant tissue. Since this type of cancer is very aggressive and invades surrounding tissue, the extent of tissue excised will depend on the stage at which the cancer is found. The surgeon performing the excision will try to remove all cancerous tissue with minimal damage to the surrounding healthy tissue. This generally involves some level of guesswork and due to the need to ensure that no cancer cells remain, the boundaries set by the surgeon tend to be aggressive.

Stage 1 melanoma has a near 100% cure rate due to how well surgery can remove the full lesion. More advanced melanoma is more difficult to treat and usually requires substantial amounts of tissue removal to ensure that the full extent of cancerous tissue is excised. If the melanoma has spread or is inoperable, systemic immunotherapies like Bristol-Myers Squibb's *Opdivo* (nivolumab) +/- *Yervoy* (ipilimumab), or Merck's (NYSE: MRK) *Keytruda* (pembrolizumab) are often used, but these agents also carry substantial costs of roughly $250,000 per year when combined.

In cases where patients progress or do not respond to PD-1 inhibitors, agents such as *Yervoy*, targeted therapy for a specific cancer-causing mutation, chemotherapy, or a drug in clinical trials are recommended. Roughly half of all melanomas have a mutation in the BRAF gene. Patients with this mutation are either prescribed a BRAF inhibitor as a first-line treatment, or following progression on a checkpoint inhibitor. Novartis' (NYSE: NVS) *Tafinlar* (dabrafenib), Roche's (VTX: ROG.VX) *Zelboraf* (vemurafenib), and Array BioPharma's (NasdaqGM: ARRY) *Braftovi* (encorafenib) are the only BRAF inhibitors that are approved as a treatment for melanoma. They are often combined with MEK inhibitors *Mekinist* (trametinib), *Cotellic* (cobimetinib) or *Mektovi* (binimetinib) due to increased efficacy. We also note that a small number of patients receive Amgen's

[13] Siegel, R., et al., 2014. Cancer statistics, 2014. *CA: A Cancer Journal for Clinicians*, 64(1), pp9-29.
[14] NCNN Clinical Practice Guidelines in Oncology: Melanoma. 2014.
[15] Eggermont, AMM, et al., 2014. Cutaneous melanoma. *The Lancet*, 383(9919), pp816-827.

(NasdaqGS: AMGN) oncolytic virus, *Imlygic* (T-Vec), although this use may increase if approved as a combination with anti-PD-1 inhibitors.

Market Information – Melanoma Patients who do not Respond to PD-1 Inhibitors

Epidemiology. The American Cancer Society estimates that 91,270 people in the US will be diagnosed with melanoma in 2018, and 9,320 will die from the disease. In addition, there are an estimated 106,995 cases diagnosed annually in the EU.[16] More than 13% of all melanoma patients are diagnosed with Stage III or IV disease, and we estimate that 90% of eligible patients are prescribed PD-1 inhibitors, making them potential candidates for Immutep's IMP321. The 5-year survival rate is 64% for patients with Stage III melanoma, and 23% for patients with Grade IV disease. We expect these survival rates to improve as more patients receive immunotherapy. Between 42% and 56% of melanoma patients do not respond to frontline PD-1 inhibitors.[17] This translates into between about 4,700 and 6,200 new patients annually who could receive IMP321 in the US, and between around 5,500 and 7,300 in the EU. We also note that the complete response rate to checkpoint inhibitors for melanoma is only between 15% and 19%, and so many patients who initially respond will eventually progress.

Clinical Data Discussion in Melanoma

TACTI-MEL – Two ACTive Immunotherapeutics in MELanoma

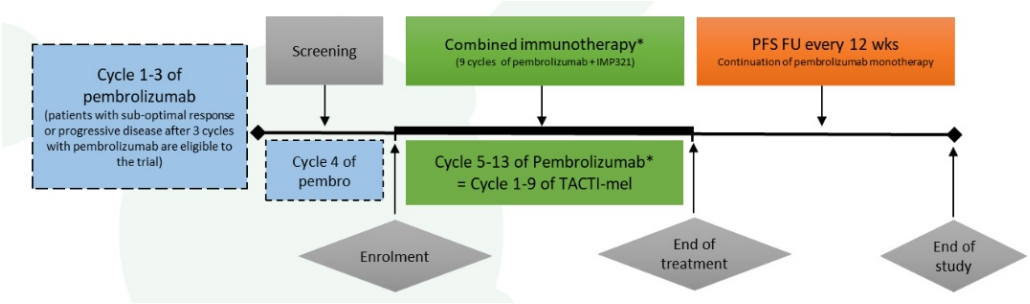
Study Design. This is an open-label, dose-escalation Phase I study of IMP321 in combination with anti-PD-1 therapy (pembrolizumab) for patients with unresectable or metastatic melanoma.[18] The study consists of two parts such that the dose administered in part B will be defined by the dose-escalation conducted in part A. Anticipated enrollment is 24 patients, divided into 4 cohorts of 6 patients. Eligible patients are characterized as those that demonstrate disease progression or suboptimal response to pembrolizumab monotherapy. It is important to note that patient response to pembrolizumab was evaluated after only 3 cycles of treatment even though the median time to response associated with pembrolizumab is approximately 4.5 cycles. Patients enrolled in part A received subcutaneous injections of either 1 mg, 6 mg or 30 mg IMP321 every 2 weeks, beginning at cycle 5 of pembrolizumab treatment. The part A flow diagram is depicted in **Figure 7**. Subsequently, patients enrolled in Part B will receive subcutaneous injections of 30mg of IMP321 every 2 weeks, beginning at day 1/cycle 1 of pembrolizumab treatment. Pembrolizumab treatment will be administered intravenously at a dose of 2 mg/kg every 3 weeks. We note that this previously represented sub-optimal dosing of pembrolizumab with 10 mg/kg being SOC, which was recently amended to a flat 200mg dose. However, 2 mg/kg is the standard dose used in Australia, where the trial is being conducted.

[16]http://eco.iarc.fr/eucan/Cancer.aspx?Cancer=20#block-table-a

[17]Wolchok, J.D. et al., 2017. Overall survival with combined nivolumab and ipilumumab in advanced melanoma. *The New England Journal of Medicine,* 377, pp1345-1356.

[18]https://clinicaltrials.gov/ct2/show/NCT02676869

Figure 7. TACTI-MEL Part A Study Scheme



Source: Company Presentation

The primary endpoint of the study is assessing the recommended Phase II dose and the safety/tolerability of IMP321. Key secondary endpoints include progression-free survival, overall survival in part B, best overall response rate and time to next treatment. The Company announced completion of patient enrollment for Part B in August 2018, with preliminary data from the fourth cohort anticipated for Q4 2018. Responses were evaluated using immune-related response criteria (irRC) versus traditionally used RECIST v1.1 criteria.

Preliminary Study Results. Preliminary results from part A of the study were presented at SITC 2017. When performing analysis on all results collected after initiation of the combination therapy, the best overall response rate was 33%. When analyzing efficacy from the initial start of pembrolizumab (day 1/cycle 1), the overall response rate is 61%. We note that responses were analyzed using immune-related response criteria (irRC) as opposed to traditionally used RECIST v1.1 criteria. Given that there are some key differences between the two guidelines, it is harder to interpret comparisons between efficacy results of pembrolizumab monotherapy as well as the efficacy results of other clinical trials. The breakdown by degree of response is depicted in **Figure 8**. Tumor shrinkage was noted in 50% of patients, with 2 patients demonstrating complete disappearance of all target lesions.

Figure 8. Response Rate of IMP321 in Combination with Pembrolizumab

Response Type	Response Rate After Start of Combination (Cycle 5 of Pembrolizumab)	Response Rate from Cycle 1 of Pembrolizumab
Immune Related Complete Response (irCR)	6% (n=1)	6% (n=1)
Immune Related Partial Response (irPR)	28% (n=5)	56% (n=10)
Immune Related Stable Disease (irSD)	33% (n=6)	28% (n=5)
Progressive Disease	33% (n=6)	11% (n=2)
Best Overall Response Rate	**33% (n=6)**	**61% (n=11)**

Source: Company Presentation

Of the 12 patients enrolled in the first two cohorts, 3 (25%) demonstrated durable responses for a duration up to 21 months. Treatment and follow-up is still ongoing in the 3rd cohort. 12 patients (66%) were progression free after the start of pembrolizumab. Treatment with IMP321 was generally safe and well-tolerated. A total of 24 severe adverse events were noted, of which only 4 have been deemed as possibly treatment-related. Two treatment-related grade 3/4 adverse events were noted in one patient consisting of grade 3 decreased renal function and grade 3 maculopapular rash. A majority of treatment-related adverse events were grade 1, with the most common ones being local erythema and injection site reactions. No dose-limiting toxicities or AE-related treatment discontinuations were observed.

Metastatic Breast Cancer Background

Breast cancer is the most common form of cancer affecting women worldwide.[19] Breast-cancer type is determined by which specific breast cells are affected. A majority of breast cancers are carcinomas, or tumors that start in epithelial cells that line the organs and tissues of the body. Breast-cancer diagnoses represent approximately 15.3% of all new cancer cases, with an estimated 266,160 diagnoses occurring in the US during 2018. Deleterious mutations within the BRCA1/BRCA2 genes correspond to a significantly higher risk of developing breast cancer. BRCA1 mutations are associated with a lifetime risk of 65%-81% while BRCA2 mutations are associated with a 45%-48% lifetime risk of the disease. Although the 5-year relative survival rate for early-stage breast cancers is almost 100%, the 5-year survival rates drop to 72% with stage III breast cancers and to 22% with metastatic, stage IV cancer.

Breast-cancers are grouped into 4 distinct subtypes by unique gene expression patterns to translate to differing molecular profiles, pathologic features and clinical outcomes. Luminal A tumors are characterized by positive estrogen receptor (ER)/progesterone receptor (PR) expression, negative human epidermal growth factor receptor-2 (HER-2) expression and low Ki-67. Luminal B tumors are characterized by positive ER/PR expression, negative HER-2 expression and high Ki-67. HER-2 enriched tumors exhibit overexpression of the HER-2 receptor. Basal-like tumors, also known as triple-negative breast cancers, are associated with negative expression of ER, PR and HER-2. ER/PR status is the strongest predictive factor for response to endocrine therapy while HER-2 expression is a predictive factor for response to certain therapy options targeting the HER-2/neu receptor. HER-2 is also a known prognostic factor for outcome in node-negative and node-positive patients. Node status is determined by the presence of absence of cancer cells from the breast tumor in the lymph nodes. HER-2 amplification in node-positive breast cancers has shown correlation with earlier relapse and shorter overall survival, in addition to being implicated as an independent indicator of increased risk of recurrent disease in node-negative breast cancers.[20] Although the basal subtype of breast cancer is only found in about 15%-25% of cases, being negative for ER/PR/HER-2 is indicative of poor prognosis as no targeted therapies are currently available for this subtype.[21]

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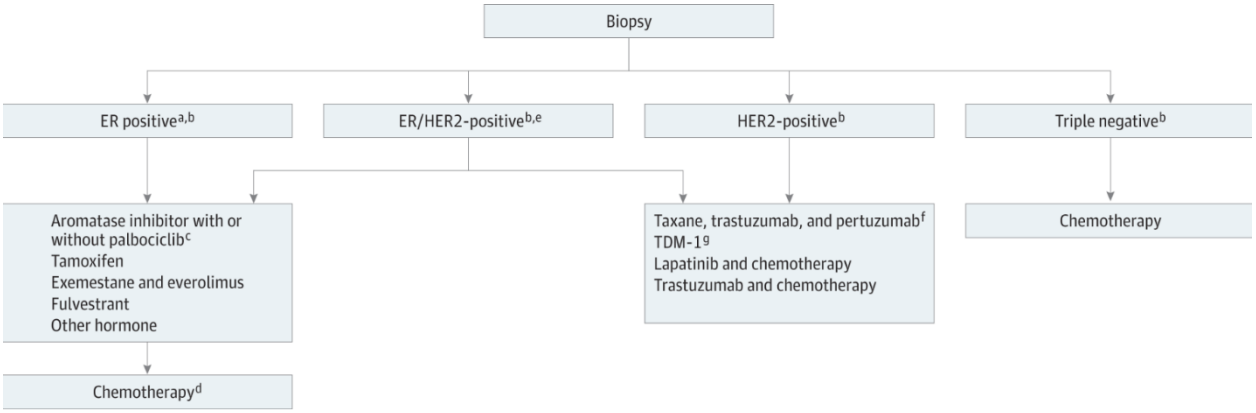
[19]Shah, R. et al., 2014, "Pathogenesis, prevention, diagnosis and treatment of breast cancer", *World Journal of Clinical Oncology,* 5(3), pp. 283-298

[20]Press, M.F. et al., 1993, "Her-2/neu expression in node-negative breast cancer: direct tissue quantitation by computerized image analysis and association of overexpression with increased risk of recurrent disease", *Cancer Research,* 53(20), pp. 4960-4970

[21]Bertucci, F. et al., 2012, "Basal breast cancer: a complex and deadly molecular subtype", *Current Molecular Medicine,* 12(1), pp. 96-110

Treatment Options. After diagnosis, patients are clinically staged using American Joint Commission on Cancer (AJCC) guidelines. Breast-conserving therapy (BCT), which generally consists of conservative lumpectomy followed by radiotherapy, is considered the recommended treatment option for early-stage breast cancer. Absolute contraindications to BCT include multicentric disease, diffuse malignant-appearing calcifications, inflammatory breast cancer and ineligibility to receive radiation. Approximately 30%-40% of US breast-cancer patients are mastectomy candidates, either by choice or through ineligibility for BCT. Appropriate treatment decisions are also influenced by receptor status.[22] A schematic for the standard of care therapeutic options for different breast-cancer subtypes is shown in **Figure 9**.

Figure 9. Standard of Care Therapeutic Options for Breast Cancer



Source: Santa-Maria and Gradishar, 2015

The first-line therapy for triple-negative breast cancers is generally chemotherapy as no target therapy options currently exist for this subtype. Front-line therapy for ER/PR positive tumors is a cyclin-dependent kinase inhibitor and endocrine therapy, specifically Pfizer's (NYSE: PFE) *Ibrance* (palbociclib) in combination with Novartis' (NYSE: NVS) *Femara* (letrozole). Other options for ER/PR positive tumors include alternative combinations of endocrine therapy, chemotherapy and cyclin-dependent kinase inhibitors. The preferred first-line regimen for HER2-positive tumors is a combination of anti-HER2 therapy - Genentech's *Herceptin* (trastuzumab) and Genentech's *Perjeta* (pertuzumab), and chemotherapy consisting of taxane. Patients progressing on this combination are administered Genentech's *Kadcyla* (trastuzumab emtansine (TDM-1)) as the preferred second line treatment. Patients with tumors positive for both ER/PR and HER-2 can be treated with either endocrine or HER-2-targeted therapies as monotherapy or in combination as clinically relevant.

Market Information – Triple-Negative Breast Cancer Patients

Epidemiology. An estimated 266,120 new breast cancer patients will be diagnosed in the US in 2018, representing approximately 15.3% of all newly diagnosed cancer cases. Additionally, an estimated 40,920 patients will die from breast-cancer in 2018. Based on an incidence of 71.1 per 100,000, 363,321 new cases of

[22]Santa-Maria, C.A. and Gradishar, W.J., 2015, "Changing treatment paradigms in metastatic breast cancer", *JAMA Oncology,* 1(4), pp. 528-534

breast cancer will be diagnosed in Europe in 2018. Currently, the 5-year survival rate of individuals with Stage IV breast cancer is 22%. Despite advances for hormone driven breast cancers, there are currently no treatment options besides chemotherapy available for triple-negative breast cancer, which is associated with poor prognosis and unresponsiveness to standard treatment. Although not currently approved in this indication, clinical trials testing the efficacy of immune checkpoint inhibitors in metastatic breast cancer have shown some promise with response rates between 4.7%-23%.[23] Approximately 15%-25% of newly diagnosed breast-cancer patients will be diagnosed with the triple-negative subtype, making them eligible to receive IMP321 to improve treatment efficacy. This translates to an annual patient population of 39,918 - 66,530 in the US and a patient population of 54,498 - 90,830 in the EU.

Clinical Data Discussion for Metastatic Breast Cancer

AIPAC – Active Immunotherapy Paclitaxel

Study Design. This is an ongoing randomized, double-blind, placebo-controlled phase IIb study of IMP321 in combination with standard chemotherapy paclitaxel in patients with metastatic breast cancer.[24] An estimated 241 patients will be randomized 1:1 to receive either paclitaxel + placebo, or paclitaxel + IMP321. All patients will begin treatment with 6 standardized 4-week cycles of chemo-immunotherapy consisting of weekly paclitaxel at days 1, 8 and 15 in combination with either IMP321 or placebo on days 2 and 16 of each cycle. After completion of the 6-cycle chemo-immunotherapy phase, responding or stable patients will continue to receive either IMP321 or placebo every 4 weeks during the maintenance phase for up to 12 additional injections.

The study consists of two stages. Stage 1 was an open-label, safety run-in consisting of 2 cohorts to confirm the recommended phase two dose (RPTD) in combination with paclitaxel. Stage 2 is the placebo-controlled, double-blind randomization stage evaluating paclitaxel with IMP321 at the confirmed RPTD. The primary endpoint of stage one is determination of the RPTD. A key secondary endpoint for stage 1 is the evaluation of pharmacokinetics of IMP321. The primary endpoint in stage 2 is the assessment of progression free survival for a time-period of up to 37 months. Key secondary endpoints include safety and tolerability of IMP321, assessment of the change in quality of life, evaluation of objective response rate and evaluation of stable disease. Efficacy-related endpoints will be analyzed solely on patients enrolled in Stage 2. The Company presented results from the safety run-in stage at *ASCO* 2018 and the study is currently mid-way through enrollment of stage 2.

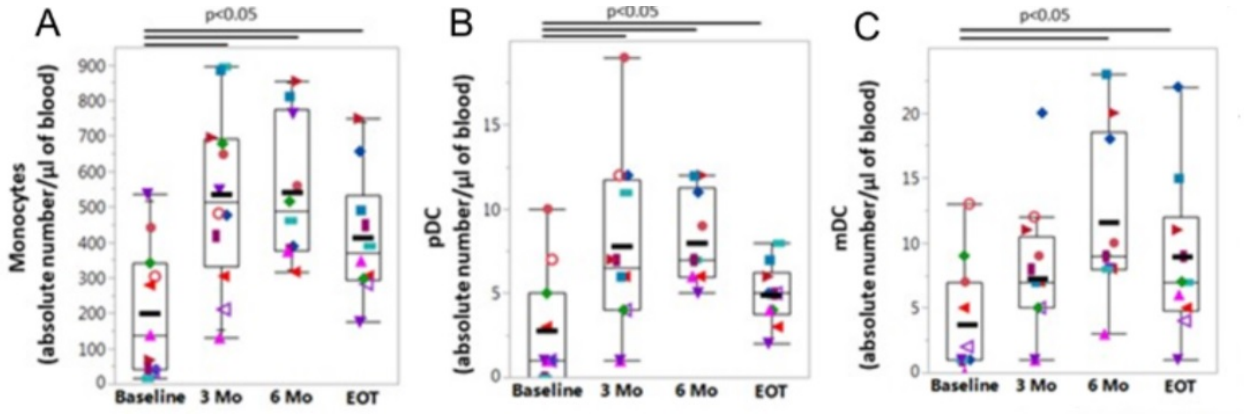
Preliminary Study Results from Stage 1. During the safety run-in stage, 15 patients received between 1-18+ injections of IMP321. Overall, both the 6 mg dose and the 30 mg dose appeared to be safe and well-tolerated in combination with paclitaxel. The only serious treatment-related adverse event was grade 1 cytokine release syndrome. Grade 1 and 2 injection site reactions were the most common adverse events related to IMP321 and 4 patients (27%) experienced an IMP321 related grade 3/4 adverse event.

In terms of efficacy, 7 patients demonstrated a partial response and 6 patients had stable disease, yielding an overall disease control rate of 87% (13/15) and an overall response rate of 47%. Pharmacodynamic analysis

[23]Tan, A.R., 2018, "Checkpoint inhibitors in breast cancer: Changing the therapeutic landscape", *Asco Daily News*
[24]https://clinicaltrials.gov/ct2/show/NCT02614833

validated IMP321's mechanism of action. As shown in **Figure 10**, treatment with IMP321 induced an increase in the number of circulating antigen-presenting cells including monocytes, peripheral dendritic cells and myeloid dendritic cells. Additionally, treatment with IMP321 induced an early and sustainable increase in Th1 biomarkers as well as an increase in the absolute numbers of effector cells including $CD4^+$, $CD8^+$ and activated T-cells.

Figure 10. IMP321 Induced Increase in Circulating APCs



Source: Duhoux, F.P. et al., ASCO 2018

Other Clinical Trials for IMP321

TACTI-002 – Two ACTive Immunotherapeutics in different indications

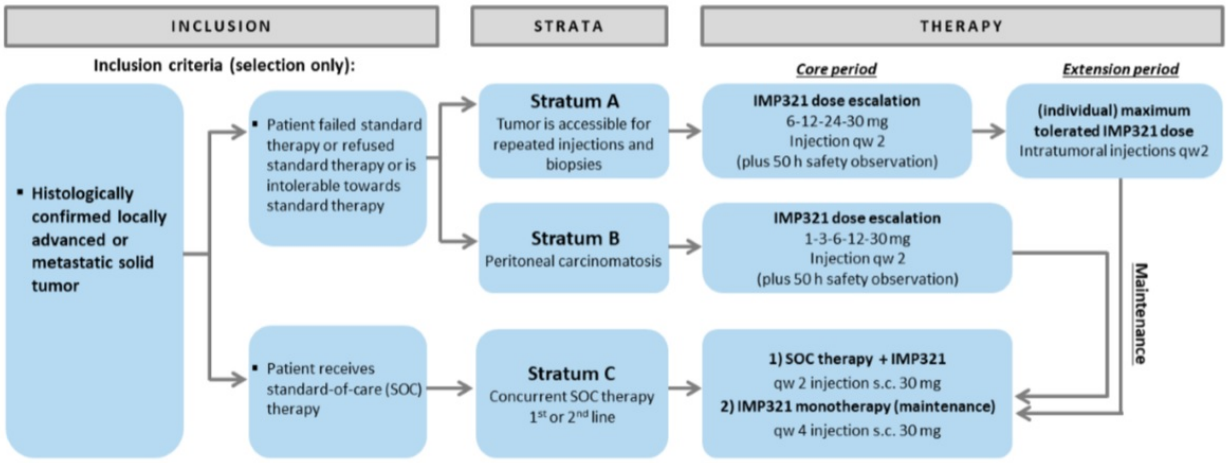
Study Design. This is a multi-center, open-label, single arm Phase II study of IMP321 in combination with pembrolizumab in NSCLC and HNSCC.[25] The study will follow a Simon two-stage design and enroll approximately 110 patients. The three sub-indications are previously untreated unresectable metastatic non-small cell lung cancer, recurrent anti-PD-(L)1 refractory non-small cell lung cancer or metastatic squamous head and neck cancer. All patients will receive pembrolizumab 200mg every 3 weeks in combination with 30 mg of IMP321 every 2 weeks for the first 8 cycles and every 3 weeks starting with cycle 9. The primary endpoint is evaluation of the objective response rate according to iRECIST criteria. Key secondary measures will include the duration, frequency and severity of adverse events, time to response, duration of response, disease control rate, progression free survival, overall survival and response rate. Response-related key secondary endpoints will be evaluated using RECIST 1.1 and iRECIST criteria. The study is being conducted as part of a clinical trial collaboration and supply agreement with Merck. Patient recruitment is anticipated to commence prior to the end of 2018.

[25]https://clinicaltrials.gov/ct2/show/NCT03625323

INSIGHT Investigator-Initiated Clinical Trial

Study Design. This is an open-label, investigator-initiated explorative Phase I study of IMP321 in patients with advanced solid tumors. The study will consist of three strata and the study scheme is shown in **Figure 11**. Strata A/B will include patients who have either failed, refused or are intolerable towards standard therapy. Patients with solid tumor accessible for repeated injections will be part of Stratum A and will receive bi-weekly intra-tumoral injections of IMP321. IMP321 dosing will be done as a dose escalation of 6, 12, 24 and 30 mg in the first cohort. Patients with additional peritoneal carcinomatosis will be part of Stratum B and will receive biweekly intraperitoneal injections of IMP321. IMP321 dosing will be done as a dose escalation of 1, 3, 6, 12, 30 mg in the first cohort. Patients from both cohorts showing a treatment benefit after the last direct injection will be offered a maintenance treatment consisting of subcutaneous IMP321 injections for up to 52 weeks. Stratum C will enroll patients who are receiving standard of care therapy to receive biweekly, subcutaneous injections of 30 mg of IMP321. The primary endpoint of the study is the feasibility rate or the rate of patients receiving treatment without incurring a dose-limiting toxicity. Key secondary endpoints include incidence and severity of AEs/SAEs, objective response rate, progression free survival and overall survival. As of June 2018, 7 patients have been enrolled in Stratum A with dose-escalation accomplished after 3 patients, and 2 patients have been enrolled into Stratum B. Data from single cases in the study will be made available throughout 2018. In September 2018, Immutep entered into another clinical trial collaboration with Merck KGaA and Pfizer to conduct a Phase I study evaluating IMP321 in combination with avelumab that will serve as an amendment to the INSIGHT trial. The recommended phase II dose of IMP321 + avelumab will be studied in patients with advanced solid malignancies under the existing INSIGHT study protocol.

Figure 11. INSIGHT Study Scheme



Source: Mueller, D.W. et al., ASCO 2018

Other Immuno-Oncology Drugs in Development

Following the initial approval of checkpoint inhibitors, the field of immunotherapy drug development has quickly grown. However, their overall lack of efficacy in the majority of patients has driven big pharma interest in the development of combination therapies to provide increased clinical benefit. Currently, there are more than 1,000 combination studies ongoing with checkpoint inhibitors. The only approved immunotherapy combination treatments involve anti-PD-1 + anti-CTLA-4 therapy for melanoma and renal cell carcinoma, and anti-PD-1 + chemotherapy therapy for lung cancer. Several treatments are being developed in combination with checkpoint inhibitors, and ones of interest are listed in **Figure 12**. Notably, some of these therapies are only administered as an intratumoral injection, which could limit their use in some invasive tumor types.

Figure 12. Selected PD-(L)1 Combination Treatments in Development

Company	Drug	Mechanism of Action	Delivery	Indications	Phase of Development
Dynavax (NasdaqCM: DVAX)	SD-101	TLR9 Agonist	Intratumoral	Melanoma, HNSCC	Phase II
Idera Pharmaceuticals (NasdaqCM: IDRA)	IMO-2125	TLR9 Agonist	Intratumoral	Melanoma	Phase III
Checkmate Pharmaceuticals (private)	CMP-001	TLR9 Agonist	Intratumoral	Melanoma	Phase Ib
Bristol-Myers Squibb	Relatlimab	LAG-3 Inhibitor	IV	Multiple tumors	Phase I/II
Bristol-Myers Squibb	*Yervoy*	CTLA-4 Inhibitor	IV	Multiple Tumors	Approved
OncoSec (NasdaqCM: ONCS)	*ImmunoPulse IL-12*	Plasmid IL-12	Intratumoral	Melanoma, Triple negative breast cancer	Phase II
Iovance Biotherapeutics (NasdaqGM: IOVA)	LN-145	TIL	IV	Multiple tumors	Phase II
Merck	Cavatak	Oncolytic virus	Intratumoral	Multiple tumors	Phase II
Syndax Pharmaceuticals (NasdaqGS: SNDX)	Entinostat	Class I HDAC Inhibitor	Oral	Multiple tumors	Phase II
Mirati Therapeutics	Sitravatininb and mocetinostat	Multi-TKI and Class I and IV	Oral	Multiple tumors, but	Phase II

(NasdaqCM: MRTX)		HDAC inhibitor		primarily NSCLC	
4SC (FSE: VSC)	Domatinostat	Class I HDAC	Oral	Multiple tumors	Phase Ib/II
Eisai & Merck	*Lenvima*	Multi-TKI	Oral	Multiple tumors	Phase III
Roche (VTX: ROG.VX)	*Avastin* + chemo	VEGF inhibitor + DNA damage	IV	Multiple tumors	Phase III
Nektar Therapeutics (NasdaqGS: NKTR)	NKTR-214	CD-122 biased agonist	IV	Multiple tumors	Phase II
Eli Lilly (NYSE: LLY)	AM0010	Pegylated-IL10	SQ	Multiple tumors	Phase II
Immutep (NasdaqGM: IMMP)	IMP321	LAG-3Ig	SQ, IP and IT	Multiple tumors	Phase II
Replimune (NasdaqGS: REPL)	RP1	Next-gen oncolytic virus	IT	Multiple tumors	Phase I/II

Source: LifeSci Capital

Competitive Landscape in Oncology

LAG-3 has Gained Increasing Interest as a Therapeutic Target, Including the Development of Bristol-Myers Squibb's Relatlimab. LAG-3 is a co-inhibitory receptor that has received strong therapeutic interest as a novel immune checkpoint to stand alongside PD-1 and CTLA-4. Prevailing big pharma interest is highlighted by Immutep securing a licensing agreement with Novartis, Bristol-Myers Squibb's development of relatlimab, and other big players like Merck and Regeneron developing their own LAG-3 inhibitors. Phase I/IIa data assessing Bristol-Myers Squibb's anti-LAG-3 antibody relatlimab and *Opdivo* in patients with melanoma who were relapsed or refractory to anti-PD-(L)1 therapy was presented at ESMO 2017. Results showed that the overall response rate in 61 evaluable patients was 11.5%- although in patients with LAG-3 expression in at least 1% of tumor-associated immune cells within the tumor margin, the overall response rate was 18% (n= 33) compared to 4% (n= 28) for those with less than 1% LAG-3 expression. 1 patient in the LAG-3 expressing tumors had a CR. Interestingly, PD-L1 expression did not lead to better patient responses. Based on these results and the fact that LAG-3 is an inhibitory checkpoint, we are intrigued in its potential as a target. In terms of safety, treatment was generally well tolerated, and similar to what would be expected with PD-(L)1 inhibition alone. No treatment related deaths were reported, and 4% of patients discontinued treatment due to a treatment related adverse event.

Activity of IMP321 May be Better Understood in Future Studies Based on TACTI-Mel Trial Design. Immutep presented updated preliminary data from their TACTI-Mel study in May 2018. The study is evaluating the combination of IMP321 with pembrolizumab in patients with metastatic melanoma and reported an overall response rate of 61% (11/18) and a progression-free rate of 66% at 6 months. The eligible patient population for the study was intended to be patients that were demonstrating suboptimal responses to *Keytruda* monotherapy. Eligibility screening was conducted after patients received 3 cycles of *Keytruda* treatment. However, it is important to note that the median time to response reported for *Keytruda* is approximately 4.5 treatment cycles. Additionally, the trial utilized 2 mg/kg dosing of *Keytruda*, which previously represented suboptimal dosing. The 61% reported overall response rate showed marked improvement from the 33% overall response rate encountered with 10 mg/kg *Keytruda* monotherapy. Notably, TACTI-Mel response rate analysis was conducted in the context of immune-related response criteria (irRC), which differs from the traditionally used RECIST v1.1 criteria. irRC guidelines make it more difficult to demonstrate complete and partial responses but simultaneously have looser interpretation of stable and progressive disease, which presents an obstacle when placing the results with IMP321 in context with other clinical trials.

Subcutaneous Administration of IMP321 May Offer a Preferential Method of Delivery. We previously noted that some of the combination therapies in development use an intratumoral delivery method which could limit their use in certain tumor types. Additionally, the majority of other approaches in development utilize intravenous drug delivery. Immutep is pursing the development of IMP321 as a subcutaneous injection, as well as studying intratumoral and intraperitoneal injections. Patient-preference studies revealed that patients clearly preferred subcutaneous delivery, highlighting that this delivery method could provide a positive point of differentiation for IMP321.

Other APC Activation Approaches Being Developed. Other approaches being developed to activate antigen presenting cells include CD40 agonists, Toll-like receptor (TLR) agonists, Stimulator of interferon Genes (STING) agonists and oncolytic viral therapies. The STING pathway is involved in sensing foreign DNA and facilitating the generation of a type I interferon immune response. Binding of a ligand to the STING protein results in the secretion of type I interferons (IFNs) and pro-inflammatory cytokines that act downstream to activate antigen-presenting cells. Another approach studied for the activation of APCs is the use of CD40 antibodies and soluble CD40 ligands. Binding of the CD40 costimulatory molecule by either antibody or ligand strongly activates APCs. This approach is also associated with increased safety concerns as sCD40L has previously been implicated to increase the risk of thrombosis.[26] TLR-agonists have a similar mechanism of action in which binding of the TLRs results in stimulation of antigen presenting cells and leads to the production of pro-inflammatory cytokines that activate cytotoxic T-lymphocytes and B-lymphocyte immune response.

IMP701: LAG-3 Antagonist for the Treatment of Cancer

IMP701 (LAG-525) is a humanized IgG4 monoclonal antibody that binds LAG-3 and inhibits the LAG-3/MHC class II interaction. LAG-3 is a cell-surface marker expressed on the surface of activated T-cells that is implicated in negatively regulating T-cell signaling and function. High levels of LAG-3 expression are associated with the development of exhausted T-cells characterized by variable deficits in proliferation and

[26]Srinivasa-Prasad, K.S. et al., 2003, "Soluble CD40 ligand induces β3 integrin tyrosine phosphorylation and triggers platelet activation by outside-in signaling", *PNAS,* 100(21), pp. 12367-12371

effector functions that are typically seen in cancer. The immunosuppressive effects of LAG-3 are thought to be mediated by simultaneous cross-linking between LAG-3 and the CD3/TCR complex yielding a decrease in calcium flux and inhibition of T-cell proliferation. Other inhibitory receptors, such as PD-1 and CTLA-4, have been a central focus in the development of immune checkpoint inhibitor therapy. However, their efficacy is only realized in a subset of patients, which has driven increased interest in other inhibitory receptors and combination therapies. LAG-3 is emerging as a novel immune checkpoint inhibitor with potential for additive benefit when combined with PD-(L)1 co-blockade. Novartis received exclusive world-wide rights to IMP701 through a licensing agreement under which Immutep is eligible for an undisclosed amount in regulatory and development milestones as well as royalties based on world-wide sales of LAG-525 in the case of approval. The Company has received two milestone payments related to the development of LAG-525 to date. LAG-525 is currently being evaluated in 4 ongoing clinical trials run by Novartis.

Phase I/II Study of IMP701 with PDR001 in Advanced Solid Tumors

This is a two-part, open-label phase I/II study to characterize the safety, tolerability and preliminary efficacy of LAG-525 (IMP701) as a single agent and in combination with Novartis' anti-PD-1 monoclonal antibody PDR-001 (spartalizumab).[27] The study will enroll approximately 515 adult patients, with part A enrolling patients with advanced solid tumors and Part B enrolling patients with a variety of cancers including NSCLC, melanoma, RCC, mesothelioma and TNBC. Part A of the study is the dose-escalation phase to determine either the maximum tolerated dose (MTD) or the recommended phase two dose (RPTD). Part B of the study is a dose expansion phase that will study LAG-525 as a single agent or in combination with PDR-001 at the MTD or RPTD. As a single agent, LAG-525 was dosed as either 1-15 mg/kg (or 240/400mg) every two weeks or as 3-10 mg/kg (or 400mg) every 4 weeks. Dosing in combination with spartalizumab was conducted at 15 dose levels/schedules ranging from 0.3 mg/kg LAG-525 + 1 mg/kg spartalizumab every two weeks to 1,000 mg LAG-525 + 400 mg spartalizumab every 4 weeks. The primary endpoint of part A is the incidence of dose-limiting toxicities. The primary endpoint for part B is the overall response rate according to RECIST v1.1 criterion. Key secondary endpoints across both phases include additional safety measures, pharmacokinetic and pharmacodynamic measures, disease control rate, progression free survival and duration of response.

Preliminary Results. As of January 15th, 2018, 131/134 (97.8%) patients receiving LAG-525 monotherapy and 107/121 (88.4%) patients receiving the combination therapy discontinued treatment. Treatment discontinuation was primarily due to progressive disease, represented by 83.6% in the single-agent arm and 71.9% in the combination therapy arm.[28] 4 patients in each study arm experienced a dose-limited toxicity, as shown in **Figure 13**. Common adverse events were fatigue (9.0%) and nausea (8.2%) in the single-agent arm and fatigue (19.0%), diarrhea (15.7%) and nausea (12.4%) in the combination arm. Serious treatment-related AE's were noted in 5.2% and 5.8% of patients in the single-agent arm and the combination arm, respectively.

[27]https://clinicaltrials.gov/ct2/show/NCT02460224

[28]Hong, D. et al., 2018, "Phase I/II Study of LAG525 ± Spartalizumab (PDR001) in Patients with Advanced Malignancies", *Abstract #3012 presented at ASCO 2018*

Figure 13. Incidence and Characterization of Dose-Limiting Toxicities

Treatment Arm	Dose	Dose-Limited Toxicity
LAG-525 Monotherapy	1 mg/kg Q2W	Grade 3 Intra-abdominal Fluid Collection
	5 mg/kg Q2W	Grade 3 Lipase Increase
	5 mg/kg Q2W	Grade 3 Vomiting
	10 mg/kg Q4W	Grade 4 Acute Kidney Injury
LAG-525 + Spartalizumab Combination	LAG-525 80 mg Q2W + spartalizumab 400 mg Q4W	Grade 3 Hyperglycemia
	LAG-525 400 mg + spartalizumab 400 mg Q4W	Grade 3 Pneumonitis
	LAG-525 600 mg + spartalizumab 300 mg Q3W	Grade 3 Brain Tumor Edema
	LAG-525 1000 mg + spartalizumab 400 mg Q4W	Grade 3 Autoimmune Hepatitis

Source: Hong et al., ASCO Abstract #3012, 2018

In terms of efficacy, complete or partial response was observed in 10% (12/121) of evaluable patients with one complete response ad 11 partial responses. The complete response was noted in a thymoma patient treated with LAG-525 240 mg + spartalizumab 300 mg Q3W. Partial responses were seen in the following indications: mesothelioma (2), triple-negative breast cancer (2), nasopharyngeal carcinoma (1), adrenocortical carcinoma (1), cervical cancer (1), urothelial carcinoma (1), gastric cancer (1), prostate cancer (1) and unknown primary (1). Responses were noted across a broad range of dose levels and schedules, although there was no apparent dose dependent correlation. We also note that no responses were noted in patients treated with LAG-525 monotherapy, whereas immune checkpoint inhibitors against PD-(L)1 and CTLA-4 have shown single agent responses. The Part B portion is ongoing, evaluating the combination of LAG-525 with spartalizumab in select indications including triple negative breast cancer and mesothelioma.

Phase II Study of PDR001 + IMP701 in Patients Relapsed/Refractory to SOC

This is an open-label, parallel-cohort Phase II study of the IMP701 + PDR-001 (spartalizumab) combination in multiple tumor types that are relapsed/refractory to the available standard of care.[29] The targeted sub-indications are small-cell lung cancer, gastric adenocarcinoma, esophageal adenocarcinoma, castration-resistant prostate adenocarcinoma, soft-tissue sarcoma, ovarian adenocarcinoma, advanced well-differentiated neuroendocrine tumors and diffuse large B-cell lymphoma. The study will initially enroll 7 indication-specific cohorts, 5-10 patients in each. Cohorts will be expanded up to 30 patients contingent on satisfying pre-determined expansion criteria. All patients will receive IMP701 (400mg) + PDR-001 (300mg) as an intravenous infusion over 30 minutes once every 3 weeks for a maximum treatment time of 2 years. The two primary

[29]https://clinicaltrials.gov/ct2/show/NCT03365791

endpoints are clinical benefit rate evaluated at 24 weeks and progression free survival up to 24 months. Key secondary endpoints include safety/tolerability and time to response, overall response rate, duration of response and time to progression up to 24 months. 58 patients have been enrolled as of May 21st, 2018. Futility analysis will be conducted after 24-week clinical benefit rate data is available for ≥5 patients in a cohort.

Additional Phase II Studies with LAG-525

In April 2018, Novartis announced the initiation of two additional studies that will include LAG-525 among other evaluable combination treatments. One is an open-label, three-arm, multi-center phase II study evaluating three potential combinations of LAG-525, PDR-001 and carboplatin in patients with advanced triple-negative breast cancer.[30] 96 patients will be randomized to receive one of three combinations: LAG-525 at 400mg every 21 days + spartalizumab 300mg every 21 days, LAG-525 at 400mg every 21 days + spartalizumab 300mg every 21 days + carboplatin dosed per AUC 6 every 21 days, or LAG-525 at 400mg every 21 days + carboplatin dosed per AUC 6 every 21 days. The primary endpoint is the overall response rate in a 24-month time-frame, as measured by RECIST v1.1 criterion. The other study is an open-label, phase II trial assessing various PDR-001 combinations in previously treated unresectable or metastatic melanoma, one of which will be the combination of PDR-001 with LAG-525.[31] The LAG-525 +spartalizumab treatment arm will receive LAG525 with 400 mg spartalizumab intravenously every 4 weeks. The primary endpoint is overall response rate in a 28-month time frame, as measured by RECIST v1.1.

Other LAG-3 Candidates in Development

Recently, LAG-3 has garnered interest in the oncology industry. However, its simultaneous immuno-suppressive and immuno-stimulatory properties open up the possibility for LAG-3 application in auto-immune disorders as well. As the number of clinical trials studying LAG-3 therapeutics grows, the number of patients evaluated with LAG-3 candidates rose from less than 1,000 in 2013 to approximately 6,700 in 2018. Immutep is positioned as one of the leaders in the development of LAG-3 therapies with 3 programs in clinical development, two of which are out-licensed through partnerships with Novartis and GlaxoSmithKline. **Figure 14** presents an overview of other LAG-3 candidates in development. Bristol-Myers Squibb's *Relatimab* is the furthest along in clinical development, currently being evaluated in a phase II/III trial.

Figure 14. Other LAG-3 Candidates in Development

Company	Drug	Delivery	Indications	Phase of Development
Bristol-Myers Squibb (NYSE: BMY)	BMS-986016	IV	Melanoma, Hematologic Cancers, RCC, Solid Tumors	II/III
Immutep (Nasdaq: IMMP)	Eftilagimod Alpha	SQ, IT, IP	Breast Cancer, Melanoma, Solid Tumors	IIB

[30]https://clinicaltrials.gov/ct2/show/NCT03499899?term=LAG525&rank=2
[31]https://clinicaltrials.gov/ct2/show/NCT03484923?term=LAG525&rank=4

Novartis AG (NYSE: NVS)	LAG-525	IV	Breast Cancer, Solid Tumors	II
Boehringer Ingelheim (private)	BI-754111	IV	Solid Tumors	I
F-star Alpha (private)	FS-118	IV	Cancer	I
GlaxoSmithKline (NYSE: GSK)	GSK-2831781	IV	Psoriasis, Colitis	I
MacroGenics, Inc. (Nasdaq: MGNX)	MGD-013	IV	Solid Tumors	I
Merck (NYSE: MRK)	MK-4280	IV	Solid Tumors	I
Regeneron Pharmacueticals (Nasdaq: REGN)	REGN-3767	IV	Cancer	I
Tesaro, Inc. (Nasdaq: TSRO)	TSR-033	IV	Solid Tumors	I

Source: LifeSci Capital

LAG-3 in Auto-Immune Disease

Proper functioning of the immune system relies on maintaining the fine balance between immune-activation and immune-inhibition. Insufficient inhibition of the immune response can result in the development of autoimmune disorders. In a healthy individual, self-reactive T-cells are supposed to be inactivated or deleted through a process known as thymic selection, which would predict that the presence of auto-reactive T-cells is highly unlikely. However, auto-reactive $CD4^+/CD8^+$ T-cells can be produced by the body through the attenuation of TCR signal intensity, resulting in decreased sensitivity to thymic negative selection and escape from this thymic selection mechanism.[32] Auto-reactive Th1 cells, a subset of $CD4^+$ T-helper cells, are specifically implicated in the pathogenesis of organ-specific autoimmune disorders. Th1 T-helper cells produce IFN-γ and IL-2, well-characterized pro-inflammatory cytokines, and their pathogenic activity can be attributed to the evocation of a strong and chronic inflammatory reaction if improperly regulated.[33] Activated T-cells are associated with the expression of LAG-3, one of the few markers identified to date that are present solely on activated T-cells. As a result, Immutep believes LAG-3 to be a viable marker for targeted immunosuppression that could eliminate pathogenic activated T-cells while minimizing the impact on resting T-cells.

[32]Ito, Y. et al., 2014, "Detection of T-cell responses to a ubiquitous cellular protein in autoimmune disease", *Science,* 346(6207), pp. 363-368

[33]Emmi, L. and Romagnami, S., 2006, "Chapter 7: Role of Th1 and Th2 cells in Autoimmunity", from *The Autoimmune Diseases (Fourth Edition)*, pp. 83-101

LAG-3 is additionally highly expressed on a subpopulation of naturally occurring $CD4^+CD25^+$ T-cells known as natural regulatory T-cells (T-regs). T-regs are central in ensuring peripheral tolerance to potentially auto-reactive T-cells that managed to slip past thymic selection. They exert their immuno-suppressive functions through direct cell-cell contact dependent manners. Two events related to the initiation and persistence of auto-immune disease are the altered generation of T-regs and inadequate inflammatory suppression, generally a direct result in an imbalance of circulating T-regs. LAG-3 has been elucidated to confer T-reg regulatory activity and be an important contributor to the function of these cells. This makes LAG-3 expression on T-regs to be a potential target for the selective manipulation of T-reg activity for the treatment of autoimmune disease.

IMP731: LAG-3 Depleting Antibody for Autoimmune Disease

IMP731 is a humanized monoclonal antibody specific to lymphocyte-activation gene 3 (LAG-3). The antibody possesses antibody-dependent cellular cytotoxicity (ADCC) properties mediated by afucosylation, which has been shown to enhance ADCC.[34] IMP731's intended mechanism of action is the destruction of LAG-3 expressing activated T-cells presumed to be involved in autoimmunity. We note that LAG-3 is expressed on activated natural regulatory T-cells, which are central to regulating self-reactive T-cells, at higher levels than activated effector T-cells. However, in tissues where NK cells are less present, ADCC mediated death on T-regs may occur at a much lower rate than in the blood. GlaxoSmithKline received exclusive world-wide rights to IMP731 (GSK2831781) as part of a license agreement in which Immutep is eligible to receive up to £64M in regulatory and development milestones as well as royalties. Immutep has previously received a milestone payment upon the initiation of a Phase I study of IMP731 in plaque psoriasis, which has since been completed. No data has been reported, however, the Company anticipates upcoming milestone payments in light of GlaxoSmithKline's publicly announced plans to conduct a clinical proof-of-concept trial of IMP731 (GSK2831781) in colitis.

IMP761: Humanized LAG-3 Agonist Antibody

IMP761 is a humanized IgG4 monoclonal LAG-3 agonist antibody being developed for therapeutic use in autoimmune disease. It is positioned to be a first-in-class product for this therapeutic area. The agonist antibody is intended to amplify the immunosuppressive effects LAG-3 exerts on activated T-cells The Company intends to pursue the development of IMP761 in multiple autoimmune indications, including inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis. In September 2018, the Company announced that it will commence cell-line development and associated manufacturing steps for IMP761, signaling progress toward clinical development.

[34]Pereira, N.A. et al., 2018, "The "less is more" in therapeutic antibodies: Afucosylated anti-cancer antibodies with enhanced antibody-dependent cellular cytotoxicity", *mAbs,* 5, pp. 693-711

Intellectual Property

Immutep's lead asset, IMP321, is protected by 4 patent families which include patents for dosage regimens, for methods of treatment, for different assays and for combination therapy. These patents expire between 2028 and 2036. IMP701 (LAG-525) is protected by 2 patent families consisting of patents for composition of matter, patents for methods of treatment and for combination treatment that expire between 2035 and 2036. IMP731 is protected by one patent family that expires in 2028 and includes patents for composition of matter and for methods of treatment. The Company's pre-clinical asset, IMP761, is protected by one patent family that includes patents for composition of matter and for methods of treatment, which expires in 2036. The Company notes that all these patents are eligible for a 5-year extension term made available in certain circumstances to compensate for delay in obtaining regulatory approval.

Management Team

Marc Voigt
Chief Executive Officer

Mr. Voigt has served as our Chief Financial Officer and Chief Business Officer since 2012 and was appointed as CEO and Executive Director in July 2014. He has extensive experience in the corporate and biotechnology sectors. He has previously worked as a personal assistant to a member of the Executive Board of Allianz Insurance. Mr. Voigt has also worked for German investment bank, net.IPO.AG, in the area of business development and German securities offerings. In the early 2000's he was investment manager in a midsize healthcare venture capital fund. In the biotech sector, he has held different executive positions, foremost in private German biotech companies. He has a Masters Degree in Business Administration from the Freie Universität of Berlin and is a member of the judging panel of Germany's largest business plan competition.

Frédéric Triebel, MD/Ph.D
Chief Scientific Officer and Chief Medical Officer

Frédéric Triebel, MD Ph.D. founded Immutep S.A. in 2001 and served as its Scientific and Medical Director from 2004. He was appointed as Immutep's (formerly Prima BioMed) Chief Medical Officer and Chief Scientific Officer following the acquisition of Immutep S.A by Prima BioMed in December 2014. Before starting Immutep, he was Professor in Immunology at Paris University. While working at Institut Gustave Roussy (IGR), a large cancer centre in Paris, he discovered the LAG-3 gene in 1990 and in subsequent research identified the functions and medical usefulness of this molecule. He headed a research group at IGR while also being involved in the biological follow-up of cancer patients treated in Phase I/II immunotherapy trials. He was Director of an INSERM Unit from 1991 to 1996. First trained as a clinical haematologist, Prof. Triebel holds a Ph.D. in immunology (Paris University) and successfully developed several research programs in immunogenetics and immunotherapy, leading to 144 publications and 16 patents.

Deanne Miller
Chief Operating Officer

Ms. Miller joined Immutep as General Counsel and Company Secretary in October 2012 and was promoted to the role of Chief Operating Officer in November 2016. She has broad commercial experience having held legal, investment banking, regulatory compliance and tax advisory positions, including, Legal Counsel at RBC Investor Services, Associate Director at Westpac Group, Legal & Compliance Manager at Macquarie Group, Regulatory Compliance Analyst at the Australian Securities and Investment Commission, and Tax Advisor at KPMG. She joined Prima as General Counsel and Company Secretary in October 2012. She has a Combined Bachelor of Laws (Honours) and Bachelor of Commerce, Accounting and Finance (double major) from the University of Sydney. She is admitted as a solicitor in NSW and member of the Law Society of NSW.

Jay R. Campbell
Vice President, Business Development and Investor Relations

Mr. Campbell joined Immutep in February 2017. He was previously Senior Director of Business Development and Investor Relations at Kolltan Pharmaceuticals, Inc., a privately-held biotechnology company developing biologic therapeutics targeting receptor tyrosine kinases for oncology and immunology, which was acquired by Celldex Therapeutics, Inc. in December 2016. Prior to Kolltan, Mr. Campbell spent over 13 years working in the financial services industry and as an independent business development consultant, the majority of which was as an investment banker focusing on the life sciences industry. During this time, Mr Campbell was a business development consultant to ISTA Pharmaceuticals, Inc. in connection with the company's review of strategic alternatives that culminated in the sale of the company to Bausch & Lomb in 2012. Mr. Campbell previously worked at Maxim Group, Royal Bank of Scotland, ABN AMRO, Rothschild, and Schroders. Throughout his career, he has worked on over 25 successful financing, licensing, and M&A transactions representing more than $13.0 billion. Jay serves as a member of the board of directors of Update Pharma, Inc., a privately held clinical-stage small molecule company focused on developing overlooked or underutilized anti-cancer drugs. He received a BSBA in Management from Bucknell University and minored in Spanish.

Christian Mueller
Director of Clinical Development and Regulatory Affairs

Mr. Mueller, MSc BBA, has worked in the field of clinical development of oncology drugs for more than a decade and joined Immutep in 2016. After completing his Master of Science in Biotechnology at the Technical University Berlin, he joined Medical Enzymes AG where he focused on therapeutic enzymes for the treatment of cancer. He was responsible for all deliverables of clinical phase I and II studies, built up a clinical team and took over the responsibilities for the strategic clinical development of the lead compound. Since 2012 he worked with Ganymed Pharmaceuticals AG. in developing ideal monoclonal antibodies in the field of immune oncology. He was responsible for the clinical development program of the lead antibody and the setup and management of the clinical team. He successfully completed a multinational randomized phase IIb study with 200+ patients investigating the lead antibody in combination with chemotherapy in patients with advanced metastatic gastric cancer. The study was the core asset of a 1.2 billion USD trade sale deal with Astellas. His efforts in the field of clinical development have led to several publications and patents.

Claudia Jacoby, Ph.D
Director of Manufacturing

Dr Jacoby joined Immutep in 2015 with more than 15 years' experience in the biotech industry. Prior to her current role, she held various positions at pre-clinical and clinical-stage pharmaceutical companies, where she gained comprehensive experience in protein expression and purification as well as in analytical and preclinical development. As Head Biochemist and Head of Manufacturing at different European biotech companies, she developed and supervised manufacturing processes conducted according to "Good Manufacturing Practice" (GMP) of biologicals and small molecules in interaction with Contract Manufacturing Organisations ensuring the supply of clinical trials up to Phase II. In parallel Dr Jacoby was acting as an independent Medical Writer supporting companies in regulatory interactions for clinical trial applications. Dr Jacoby has a Master degree in Biochemistry and completed her PhD at the Institute for Biotechnology of the Martin-Luther-University of Halle-Wittenberg, Germany.

Michael Buchholz, Ph.D
Director of Manufacturing

Dr. Buchholz joined Immutep in June 2018 and has over 15 year's experience working in the biotechnology industry. Michael brings to Immutep extensive experience in biotechnology manufacturing as well as relationship management with technology suppliers, contract manufacturers and research organizations. After completion of his PhD at the University of Bath, UK, he started his career as project manager in cell therapy manufacturing on the contract manufacturing organization (CMO) site at the Fraunhofer Institute for Immunology and Cell Therapy, Leipzig, Germany where he gained significant experience in "Good Manufacturing Practice" (GMP). In 2012 he joined Prima BioMed as Project Manager Manufacturing with focus on cell therapy manufacturing at CMOs in the US, Australia and Germany. In 2014 Michael was promoted to the role of Director Manufacturing overseeing GMP compliance and recombinant protein production at a CMO in China. In 2016 Michael joined Cell Medica as Site Head for Cell Medica`s GMP manufacturing facility in Berlin, Germany, with focus on cell therapy manufacturing. In parallel Michael is acting as an independent lecturer for Good Manufacturing Practice with focal point on Biologics and Cell Therapy manufacturing. Michael holds a PhD in regenerative medicine from the University of Bath, UK, and a MSc in Biochemistry from Free University Berlin, Germany.

Risk to an Investment

We consider an investment in Immutep to be a high-risk investment. Immutep is a development stage company with no history of taking a treatment to market, and currently with no FDA approved drugs in its portfolio. There are several other companies trying to target the same indications as Immutep, and the cancer treatment pipeline is especially crowded with competitors. Immutep lead program has not yet generated pivotal data and has limited clinical data to date. Furthermore, early indications of efficacy do not necessarily translate into positive late-stage results. As with any company, Immutep may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any drug and Immutep may not receive FDA approval for its candidates despite significant time and financial investments. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet the expectations of investors.

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