Wednesday, 13 October 2021

RESEARCH REPORT

CORPORATE CONNECT

Immutep Limited

A Truly Undervalued Company

Share Price & Estimated Fair Value Price

Fair Value Price	$2.20
Current Price	$0.535
Implied Increase/Dec	311%

In May 2021, we published a comprehensive research report (CRR) on Immutep Ltd. We were so impressed that we felt it imperative that a follow-up report valued the company, because the market was not seeing what we did: eftilagimod alpha (efti). This drug was giving a solid signal of activity as a monotherapy in a large breast cancer trial and extremely strong signals of clinical activity when used in combination with pembrolizumab (Keytruda®, Merck) to treat previously untreated/unresectable PD-1/L1 naïve non-small cell lung cancer and as a second-line treatment for PD-1/L-1 naïve recurrent head and neck cancer. Additionally, we saw a first-rate management team - an absolute requirement for a successful drug development company.

Recent Events: Immutep presented updated numbers from TACT-002 Groups A & C at this year's American Society of Clinical Oncology (ASCO) meeting. In both cases, the clinical data continued to reflect the extremely strong data we analysed in our CRR. Significant new insights indicated **efti was improving the durability of responses and producing encouraging progression-free survival data**.

Presentations of final results from INSIGHT-004 **concluded signals of efficacy were seen**, even though only 12 patients were in the trial.

Two new trials have been planned/started since our CRR, the major benefit of both being that Immutep will be free to share the data with potential partners.

The market has been informed that final overall survival (OS) from the AIPAC (Active Immunotherapy PAClitaxel) trial will be delivered at a conference in November 2021. At the last interim analysis of AIPAC, there was a strong trend favouring the efti arm, with 40% of events remaining. A positive trial result will underscore efti's utility as monotherapy, greatly enhancing its value.

Valuation: We valued Immutep using comparables for many reasons. **The primary one was transparency**. Readers can see all of the information and reasoning behind the valuation, easily access further information and adjust the valuation to make it more in line with their thinking.

We scanned ~50 companies with an interest in immunotherapy and eventually chose six that were fairly valued and that we could reasonably compare Immutep to, providing us with a value ladder on which to slide Immutep.

Three of the companies were US-based, two Canadian and one German, giving us a reasonable geographic spread. All were NASDAQ listed.

Our assessments were based on enterprise values (EVs), calculated by removing cash and equivalents from the companies' market capitalisations.

As a final step, we looked at Nektar Therapeutics (NASDAQ:NKT), which we noted in our CRR was highly similar to Immutep.

In most cases, it was easy to determine whether Immutep should have a higher/lower value than a particular company. **In one case, we found it difficult to separate Immutep from a company.** This company had the second highest EV of the companies we looked at (AUD1.75B). In the end, the dynamics in the immune checkpoint inhibitor space, backed by some solid examples, led us to give Immutep a slightly higher valuation than this company. **We settled on an EV for Immutep of AUD1.75B**.

After adding cash back to our EV estimate and dividing by the total number of issued shares, the fair value of an Immutep share was $2.20.

Marc A. Sinatra, BSc(Hons), MBA

Company Information

ASX Ticker	IMM
NASDAQ Ticker	IMMP
NASDAQ Price	USD3.87
Shares on Issue	851M
Fully Diluted Shares on Issue	888M
Market Capitalisation	$469M
ASX Vol. (Shares/Day)*	2.3M

* Shares per Day for the Last 20 Trading Days.

Cash Sufficiency

	$ Million
Cash at Last 4C	60.6
Last Quarter Burn	5.7
Cash Inflows Post Last 4C	53.5
Estimated Current Cash	**114.1**

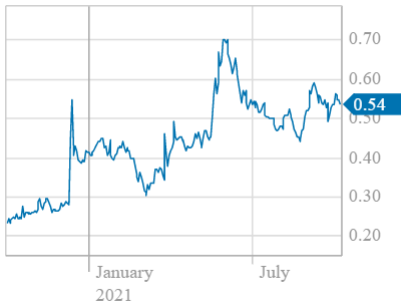
Significant Shareholders

Holder	Holding
FIL	6.21%
Australian Ethical Investments	4.89%

Directors & Key Personnel

Dr Russell Howard	Chairman
Mr Marc Voigt	Executive Director & CEO
Mr Grant Chamberlain	Non-Executive Director
Mr Pete Myers	Non-Exec. Director & Deputy Chair
Dr Frédéric Triebel	Chief Scientific & Medical Officer
Ms Deanne Miller	COO GC & Company Secretary

Chart



Immutep Limited

A Truly Undervalued Company

Introduction

In early May 2021, we published a comprehensive research report (CRR) on Immutep Limited (ASX: IMM). That report can be found here. **We were more than impressed with what we found**. Consequently, we are following up that research report with a post-report update on events relevant to Immutep, before we embark on the major purpose of this report: to derive and justify a value for the company.

Approximately one year before we published the CRR, Immutep started to produce a consistent stream of results from cancer clinical trials from its lead compound, eftilagimod alpha (efti), as both a single agent and in combination with pembrolizumab (Keytruda®, Merck & Co; NYSE: MRK). These results demonstrated unambiguous signals of clinical activity and a side-effect profile that could almost be described as benign. While efti is still some distance from being shown to be safe and effective in appropriate pivotal trials and, then, stamped as such by major regulators (the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)), **we found it extremely hard to develop a cogent argument that Immutep does not have an approvable drug on its hands in efti.** There are unknowns and arguments that can, and will, be had as to the precise indications efti should be targeted at, but the feeling that efti would eventually be approved for some indications was a nearly impossible conclusion to escape. There is also the reality that it is impossible to completely eliminate risk, which is a statistical fact and that, as commercial endeavours go, drug development is one of the riskiest. Still, when you look at the breadth of efti's activity, the science underpinning it, the nature of the market it is in, the revenues that market is currently generating and how those revenues will grow, efti appears almost certain to find itself in several overlapping pivotal programs aimed at an equivalent number of indications. In that scenario, even if a statistical anomaly were to occur and efti were to fail its first pivotal trial, just as Bristol-Myers Squibb's (BMS; NYSE: BMY) nivolumab (Opdivo®), unexpectedly failed an early trial in non-small cell lung carcinoma (NSCLC), efti would get other chances to prove itself.

While the results of clinical trials ultimately determine the fate of a drug, management ultimately determines the fate of a drug development company. The management of a small drug development company like Immutep proves its mettle by successfully managing a company over a linear period of time where the activities of the company and the demands on it are constantly changing relative to the stage of the drug's development. This is most unlike how the management of your average industrial proves itself, which is by demonstrating the ability to improve the company's bottom line over a recurring yearly cycle. Managing the linear, ever-changing requirements of a drug development is also different from managing your average industrial, because rather than having a static workforce as industrials do, drug development companies need to constantly access and manage quite a large number of highly skilled, specialised consultants that the company is likely to require only for the period those specialised skills are needed. Hence, drug development companies tend to rely on a relatively small core group of highly skilled employees. Efti originally was tested for infectious diseases - in a number of phase 1 clinical trials. It's an APC activator i.e. immune booster so is not intended for autoimmune diseases where one needs to down-regulate the immune system. That's what IMP731 (licensed to GSK) & IMP761 aims to do. Now, Immutep is in possession of a drug that appears exceptionally safe and has demonstrated strong signals of efficacy in the clinic. **Immutep's management team is highly suited to drug development, has proved itself and is one of the, if not the, best medtech/drug development management teams in Australia**.

One huge advantage Immutep has, relative to a lot of it peers, is Dr Frédéric Triebel, its Chief Medical Officer (CMO)/Chief Scientific Officer (CSO), who cloned the LAG-3 gene, founded Immutep and is almost certainly the world's expert in the biology relevant to the drugs Immutep is developing. This is an extreme advantage. At Immutep, if Dr Triebel doesn't know the answer to a question or can't provide specialised advice on a certain aspect of drug development involving LAG-3, it is almost certain no else can and, hence, research into finding the answer can begin immediately. At other small companies, it can take weeks, months or years before it's realised that further research in a particular area is/was needed.

Marc Voigt, CEO, has done an excellent job of managing Immutep, getting it publicly listed, establishing an excellent core team of employees, strengthening the company's balance sheet with June's capital raise and, perhaps most importantly, leaving efti completely unencumbered, with the exception of a regional licencing deal for China. Later, we will look at the cash balance of a number of companies similar to Immutep and an unintended benefit of this report will be that Australian investors will begin to genuinely understand how much money a small drug development should have on its balance sheet.

That, in short, is why we like Immutep so much.

A Brief Note on our Valuation Methodology for Immutep

Before we undertake the valuation, below we discuss the methodology we use to value Immutep.

Rather than using the traditional discounted cash flow methodology that Australian investors will be most familiar with, or a risk adjusted DCF (rDCF) methodology that more seasoned medtech investors are familiar with, we value Immutep relative to a basket of comparable companies that we have assembled.

In short, the reasons we have chosen a comparable valuation methodology are as follows:

- Forecasting error for a company with no earnings history
- Reduction of systematic bias (biases which lead you further away from an accurate value, rather than cancelling each other out)
- Making the collective intelligence of the market part of the valuation process
- Transparency – the reader will be able to see everything we have used to arrive at our valuation (and, if they disagree, come up with their own valuation).

Getting Back up to Speed on Immutep

While Immutep boasts development candidates that have been licenced to Novartis AG (SWX: NOVN) in the area of cancer and GlaxoSmithKline plc (GSK; LON: GSK) in the area of autoimmune diseases, as well as an internal autoimmune disease candidate, IMP761 (which is close to commencing clinical trials), the company's primary asset is efti.

Efti is in several current, and many planned, clinical trials. While it could be argued that efti is furthest down the path toward a potential approval for the first-line treatment of hormone receptor positive, HER2 negative, metastatic breast cancer patients, with Immutep having announced phase III trial plans in its June capital raising presentation, there is a real possibility that the compound could obtain an accelerated approval from the FDA for the first-line treatment of head and neck squamous cell carcinoma (HNSCC) in combination with Merck's pembrolizumab, based on the results of a single-arm phase IIb trial (ClinicalTrials.gov Identifier: NCT04811027) on which Immutep and Merck are formally collaborating.

Determining the probability of this latter possibility occurring is more complex than it might seem, the reason for which is positive for Immutep. **The agreement between Immutep and Merck regarding the trials efti has been, or will be, used in combination with pembrolizumab, gives Merck no claim on efti, such that efti is effectively unencumbered**. Immutep and Merck will almost certainly need to come to a commercial agreement before a formal application is made to the FDA for an accelerated approval or, if it takes that long, a standard New Drug Application (NDA) is submitted.

This is quite an unusual position for a company like Immutep to be in, because normally the smaller company would have already licenced its drug candidate to the larger company at this stage of proceedings, and the larger company would be calling the shots. **As a general rule, the closer to a significant regulatory approval the smaller company can take a compound, the more it will be able to command an overall value for a licence from a larger partner for rights to the compound. Generally, the value the smaller company can claim is a lot more**. To put that into the context of an on-market bid for Immutep, the longer Immutep retains the rights to efti, the more a larger company will be willing to bid per share for it.

A further layer of complexity in this is that BMS, which has the second highest selling PD-1 inhibitor on the market in nivolumab, cannot outbid Merck for Immutep and then immediately turn around and look to the FDA for an accelerated approval for the combination of efti and nivolumab. The reason is that despite the fact that both pembrolizumab and nivolumab share the same target within the human, PD-1, the two drugs have different chemical structures. In such situations, the mantra of evidence-based medicine wins out. Thus, the data produced from the efti-pembrolizumab phase IIb trial in the first-line treatment of HNSCC that Immutep and Merck are collaborating on will only be applicable to that specific combination of compounds. **Consequently, developing a scenario where there is competitive tension between Merck and BMS for Immutep, solely based on the potential for an accelerated approval for first-line HNSCC, is not as straightforward as it might seem to the uninitiated**.

The main reason we have raised this issue is because it is generally accepted practice to evaluate a company in the order of most advanced asset/indication (i.e., closer to a major regulatory approval) to least advanced. We have decided to maintain consistency with the structure of our CRR of Immutep to make it easier for readers to refer between the two documents, irrespective of the potential for an argument as to the indication for which efti is most advanced.

Eftilagimod Alpha

1) First-Line Use in the Treatment of Hormone Receptor Positive, HER2 Negative, Metastatic Breast Cancer Patients (The AIPAC Trial)

The latest data release from this trial is contained in our May report and is discussed commencing on page 8.

The topline result will be an improved overall survival (OS) of 2.7 months in the efti + chemotherapy arm, compared to chemotherapy alone. At the time of data cut-off (September 2020), that difference was a strong trend (p=0.14) in favour of the efti + chemotherapy combination and **since 60% of events (patients deaths) have occurred, that median OS advantage should be considered firm.** Strictly speaking, where the yet-to-be-determined upper 95% confidence interval (CI) on the OS estimate lands will determine the final outcome of the trial. With 40% of events outstanding, there is a strong chance that the efti + chemotherapy combination will be shown to be significantly superior to chemotherapy alone.

Having said that, AIPAC is not a hypothesis-testing trial (i.e., pivotal trial), but one whose overall aim is to provide information to enable Immutep (and its Chinese partner, EOC Pharma) to design the well-controlled pivotal trial(s) the major regulators will want to

see if they are ging to support efti's approval. Immutep has not made a big song and dance about its future plans for efti, but a portion of its circa AUD67M raising in June 2021 is earmarked for a 500-patient phase III registrational trial in hormone receptor positive, HER2 negative, metastatic breast cancer "based on AIPAC". Immutep has flagged to the market that a another analysis looking at OS will be undertaken at some point during the current half (i.e., 2H, CY21) and, if the p-value of the trial at that point is ≤, the trial can be reasonably called positive at that point. If that does occur it should act as a strong catalyst for Immutep's share price. Beyond that, Immutep continues to expand its intellectual property around efti, announcing the issuance of a Chinese patent covering chemotherapy-immunotherapy combinations for the treatment of cancer in late May 2021.

The big date for this trial has now been set. The OS results from the phase IIb AIPAC Study will be presented at the Society for Immunotherapy of Cancer Annual Meeting to be held from 10 to 14 November 2021.

2) The TACTI-002 Trials (First and Second Line Non-Small Cell Lung Carcinoma, Second-Line Head and Neck Squamous Cell Carcinoma)

Where the TACTI-002 trial stood can be found on page 11 of our CRR.

The big event concerning this trial, and the cohorts of patients within it, were two abstracts presented at the American Society of Clinical Oncology (ASCO) conference in June 2021.

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

Table 1. Interim Study Results From TACTI-002, Group A, First-Line NSCLC Presented at SITC on 10 November 2020 and ASCO on 4 June 2021.

Tumour Response Best Overall Response (BOR) per iRECIST	SITC, 2020 N (%) N = 36	ASCO, 2021 N (%) N = 36
Complete Response (CR)	2 (5.6)	2 (5.6)
Partial Response (PR)	11 (30.6)	13 (36.1)
Stable Disease (SD)	11 (30.6)	10 (27.8)
Progressive Disease (PD)	9 (25.0)	6 (16.7)
Not Evaluable	3 (8.3)	5 (13.9)
Disease Control Rate (DCR; CR+PR+SD/N)	24 (66.7)	25 (69.4)
Objective Response Rate (ORR)	13 (36.1)	15 (41.7)
ORR in Evaluable Patients	13 (39.4), N = 33	15 (48.4), N = 31

Sources: Immutep Limited, ASX announcement, 10 November 2020 and ASX announcement, 4 June 2021

Table 1 provides a comparison of the data as it stood at the interim analysis included in our May report, which was presented at the 2020 Society for Immunotherapy of Cancer (SITC) Conference, and the data reported at ASCO in June (2021). No new patients were recruited into the study between the two interim analyses, giving us a nice view of how the data varied over time.

Largely, the data presented at SITC is consistent with that presented at ASCO and provides a hint to one of the key questions that is being asked of efti: Does the addition of efti to pembrolizumab in the treatment of NSCLC improve just the response rate or does it improve the duration of response as well? Efti's proposed mechanism of action (MOA) suggests that this is exactly what should happen and these results are consistent with what would be expected if efti were doing so. Essentially, the data is consistent with the view that efti + pembrolizumab was:

- Improving response rates relative to pembrolizumab alone
- Having little influence on the safety profile relative to pembrolizumab alone
- Producing an ORR comparable to that seen when pembrolizumab is combined with chemotherapy
- Increasing the duration of the response relative to pembrolizumab alone.

The newest data released was that the efti + pembrolizumab combination was estimating median progression-free survival (PFS) at 8.2 months. KEYNOTE-024 found that pembrolizumab monotherapy produced a PFS of 10.3 months, but the patients in that trial

were restricted to those with a tumour proportion score for PD-L1 expression of ≥ 50% (Reck et al N Engl J Med 375: 1823-1833). These are the patients most likely to respond to pembrolizumab. TACTI-002 did not restrict patient entry into the trial based on PD-L1 expression, which is why a PFS of 8.2 months is impressive relative to the PFS finding from KEYNOTE-024. Moreover, if you look at the subgroup of patients in TACTI-002 Part A who had a TPS of ≥ 50%, the PFS was 11.8 months.

As a reminder, Immutep and Merck agreed to increase the size of TACTI-002 by 74 patients in November 2020, bringing the total to be recruited into the trial up to 110. As of 1 September 2021, 43 out of the expansion stage had been recruited to Part A of TACTI-002, indicating recruitment for this expansion group is proceeding well.

Overall, the updated Group A results are consistent with the previous data Immutep released on the group and, importantly, with efti's proposed mechanism of action. The key pieces of new data out of the ASCO interim analysis were that efti + pembrolizumab were improving the duration of responses relative to pembrolizumab alone and that a PFS of 8.2 months was seen in the trial despite the patients being unselected for PD-L1 expression.

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

Updated data was also presented at ASCO for efti for Group C patients. That data, presented by Dr Irene Brana of the Vall d'Hebron Institute of Oncology, Barcelona, Spain, is provided in table 2, along with the data we looked at in our CRR from the SITC presentation.

Table 2. Interim Study Results From TACTI-002, Group C, Second-Line HNSCC, Stages 1 and 2 Presented at SITC on 10 November 2020 and ASCO on 4 June 2021.

Tumour Response Best Overall Response (BOR) per iRECIST	SITC, 2020 N (%) N = 28	ASCO, 2021 N (%) N = 37
Complete Response (CR)	3 (10.7)	5 (13.5)
Partial Response (PR)	7 (25.0)	6 (16.2)
Stable Disease (SD)	3 (10.7)	3 (8.1)
Progressive Disease (PD)	10 (35.7)	17 (45.9)
Not Evaluable	5 (17.9)	6 (16.2)
Disease Control Rate (DCR; CR+PR+SD/N)	13 (46.4)	14 (37.8)
Objective Response Rate (ORR)	10 (35.7)	11 (29.7)
ORR in Evaluable Patients	10 (43.5), N=23	11 (35.5), N=31

Sources: Immutep Limited, ASX announcement, 10 November 2020 and ASX announcement, 4 June 2021

An additional nine patients have been recruited into this study since data cut-off for the previous analysis. While one might look at the data and be tempted to read a weak trend toward a decline in response rates between analyses, it needs to be remembered that these additional nine patients are also the group of patients who have been on the drug for the shortest period of time. This trial began in February 2019 and the data cut-off for each analysis was 8 October 2020 for SITC and 16 April 16 2021 for ASCO. Therefore, while the data on the patients for the SITC analysis was collected over 18 months, the data that has been added from the nine new patients is no more than six months old.

We found data from two studies of pembrolizumab in HNSCC patients, which reported time to response data, KEYNOTE-012 (Mehra et al (2018) Br J Cancer) and KEYNOTE-055 (Baumi et al (2017) J Clin Oncol), however, comparing the time to response of TACTI-002 to them is tricky because, like TACTI-002, both trials were also ongoing at the time the reports were prepared. The former was an open label, single arm, phase I trial, which contained two prescribed parts (initial and expansion) with a combined number of 192 HNSCC patients. This was the trial for which pembrolizumab received its approval for the second line treatment of recurrent metastatic HNSCC. It found a median time to response for patients of two months, with times to response ranging quite widely from two to 17 months. The latter was an open label, single arm, phase II trial of 171 HNSCC patients, who were treated regardless of PD-L1 expression levels. This trial also found a median time to response of two months, which ranged from two to five months. When KEYNOTE-012 was reported, patients had spent a median time of 98 days on the drug, which was similar to the 90 days for KEYNOTE-055. Both trials had some patients who had only been on the drug for one day when the data was reported. However, some patients had been on the drug for up to 749 days in KEYNOTE-012, compared to 401 days for KEYNOTE-055.

Thus, it seems safe to assume that the KEYNOTE-012 data was more mature than that for KEYNOTE-055. This, in turn, likely explains the differences between the two trials in terms of the range in time to response.

Finally, when you look carefully at the data from SITC and ASCO, you only need to see one or two of the patients who have been enrolled in TACTI-002 for less than 17 months to respond and the ASCO data will look equivalent to, or better than, that reported at SITC.

This is actually a very instructive point for investors who have not interpreted a lot of clinical trial data, much less data from cancer-specific trials. If you start to make buy/sell decisions based on small amounts of additional clinical data, you are trying to be overly precise in your investing activities. The only one who benefits from this type of behaviour is your broker, because your money becomes theirs in the form of brokerage. Moreover, for retail investors, across your portfolio, you will also be forgoing capital gains benefits you receive when you hold a particular stock for more than one year. It can become a costly exercise.

Back on the HNSCC trial, for reasons just explained, the data from SITC and ASCO are consistent with one another and the positive nature of our interpretation of them does not change from our CRR.

As previously announced, Immutep and Merck are formally collaborating on a 154-patient multi-centre, randomised, controlled trial dubbed TACTI-003 comparing efti + pembrolizumab to pembrolizumab alone in the first-line treatment of HNSCC. The study will have two cohorts. Cohort A will comprise patients with PD-L1 CPS ≥ 1 who will be randomised 1:1 to receive either efti + pembrolizumab or pembrolizumab alone. Cohort B will consist of patients with PD-L1 CPS < 1 and will be treated only with the combination of efti + pembrolizumab. The primary endpoint for the trial is ORR, while the key secondary endpoint is OS. On 6 July 2021, Immutep announced that it had received FDA and institutional review board approvals to commence the trial at sites within the US. The ClinicalTrial.gov entry for the trial can be found here: NCT04811027.

The details about cohort B are interesting. No biologic has been approved for HNSCC with PD-L1 CPS < 1%. It is likely that the FDA will take a close look at the efti + pembrolizumab, even if response rates are low.

The trial has not yet commenced recruitment, nor has Immutep announced regulatory approvals to commence the phase IIb trial in Europe or Australia. The start of clinical trials are often delayed. It is a fairly regular occurrence, particularly when you are trying to make a company the size of Merck move. Having said that, given the interesting situation that exists between Immutep and Merck, with Merck having no rights to efti, there is always the possibility that something is going on behind the scenes. If Merck believes, as we do, that results from TACTI-003 could lead to an accelerated approval for efti, it is possible that Merck is getting ready to make a move.

3) The INSIGHT Trial: Administration Method in Solid Tumours Including with the ICI Avelumab (004)

A discussion of the INSIGHT trial commences on page 16 of our May report.

Table 3. Final Clinical Data From Insight-004 Presented at ASCO on 4 June 2021.

Tumor response – according to RECIST 1.1	Total N (%) Total (N=12)
Complete Response (CR)	0 (0)
Partial Response (PR)	5 (41.7%)
Stable Disease (SD)	1 (8.3%)
Progressive Disease (PD)	6 (50.0%)
Objective Response Rate (ORR)	**5 (41.7%)**
Disease Control Rate (DCR)	**6 (50%)**

Sources: ASX announcement, 4 June 2021

This trial had four arms, of which three have previously been completed and reported. With strong, positive clinical signals that efti was adding benefit to pembrolizumab's performance when the drugs were used in combination with each other coming from TACTI-002 groups A (NSCLC) and B (HNSCC), the fourth arm (004) became the important one. The reason is that 004 was looking at the safety of combining efti with avelumab (Bavencio®, Pfizer Inc (NYSE: PFE) & Merck KGaA), which functions by binding PD-L1. This is opposite to the way PD-1 inhibitors work. PD-1 inhibitors bind PD-1 and prevent it from interacting with PD-L1, whereas PD-L1 inhibitors bind PD-L1 and prevent it from interacting with PD-1. Theoretically, there is no reason why the combination of efti with a PD-L1 inhibitor should not have the same effect that it appears to be having when combined with a PD-1 inhibitor. Nonetheless, that is not the way science works, particularly as it pertains to the development of a new pharmaceutical. Safety and, ultimately, efficacy need to be shown for efti in combination with any structurally different compound, as would be the case for any drug in efti's position. We discussed this issue earlier with respect to the data from TACTI-003 being used to support an NDA application to the FDA with nivolumab, rather than pembrolizumab.

The main commercial reason for Immutep to undertake arm 004, however, would be to demonstrate to those companies with a PD-L1 inhibitor on the market (of which there are three) or in development, that combining efti with its drug would be likely to have a similar effect that combining efti with pembrolizumab appeared to be having. By demonstrating that efti is likely to work in the same manner with avelumab as it appeared to be working with pembrolizumab, the risk associated with collaborating and/or, more importantly, looking to engage Immutep in a more meaningful way should be perceived as reduced by all PD-L1 inhibitor owners. **Immutep is simply increasing the potential for competition for efti by others**. That can only be a good thing.

The final clinical data from arm 4 of the INSIGHT trial is provided in table 3. The data is unchanged from the late interim analysis data we looked at in the May report. Moreover, our view of that data remains unchanged, as well. **That view is that combining efti with avelumab does not result in anything broadly unexpected.** The trial presenters, however, were more pointed in their conclusion, stating **"signals of efficacy with the CPI [checkpoint inhibitor] combination were seen (DCR [disease control rate] 50.0%)"**. While we would not dispute their conclusion about signals of efficacy, we would remind investors that efti is not a CPI, rather efti binds the same molecule on APCs, class II MHC (major histocompatibility complex) that LAG3 does, but, rather than suppressing APC activity, as LAG3 does when it binds those class II MHC molecules, it looks fairly clearly like efti acts to increase their activity. Ultimately, Immutep believes (and the data is supportive of this) that efti acts to increase the immune response against the tumours of patients, which its concomitant treatment with PD-1 or PD-L1 inhibitors are allowing to proceed.

What we have been referring to as arm 4 of the INSIGHT trial, Immutep refers to as INSIGHT-004 and sees as a trial in its own right. As it turns out, arm 4 of the INSIGHT trial was added after the INSIGHT trial began as a protocol amendment. This was done for the sake of simplicity, given the amount of paperwork involved in commencing a completely new trial. This is a relatively common practice and there is nothing inherently wrong with it, as long as nothing is misrepresented. We have examined the situation and are convinced that there has been no misrepresentation of the trial. Therefore, we see no problem with adopting Immutep's naming convention and from here on will refer to the study with avelumab as INSIGHT-004.

No adverse events, grade 3 to 5, were considered causally related to the use of efti (i.e., adverse events ranging from serious, such as those that would result in or prolong a stay, limit self-care activities of daily living, etc through to death). **While important, this is not surprising, and simply adds to what can only be described as efti's excellent safety profile**.

4) Recently Added Trials of Efti

In addition to the potential pivotal trial in hormone receptor positive, HER2 negative, metastatic breast cancer patients, continued recruitment for TACTI-002 Group A (NSCLC) and preparations for the commencement of TACTI-003, the phase IIb study in HNSCC, Immutep is supporting trials with efti with further combinations of cancer therapies.

INSIGHT-005: Efti in Combination with Bintrafusp Alpha in the Treatment of Solid Tumours

This is an investigator-led study being undertaken by the Institute of Clinical Cancer Research IKF at Krankenhaus Nordwest, a teaching hospital that is part of the Goethe University in Frankfurt am Main. **It is a small study that gives Immutep a significant amount of potential upside for a price that seems highly likely to be under the AUD1M mark**.

As for INSIGHT-004, INSIGHT-005 will be undertaken under the INSIGHT trial as a protocol amendment. The ClinicalTrials.gov entry for the INSIGHT trial can be found here: NCT03252938. At the time of writing, the INSIGHT trial entry had not yet been updated. Only the responsible party can make alterations to the ClinicalTrials.gov entry and academic investigators can often be a bit slower doing this, because they are not responsible to the FDA, as companies like Immutep are.

INSIGHT-005 will see efti given in combination with a drug called bintrafusp alfa, which is being developed jointly by Merck KGaA and GSK. Bintrafusp is a bifunctional fusion protein that targets transforming growth factor-ß (TGF-ß) and PD-L1. In fact, the portion of bintrafusp that targets PD-L1 is essentially the part of avelumab that binds PD-L1. A review taking a closer look at the compound can be found here: Lind et al (2020) J Immunother Cancer.

The reason for including domains targeting PD-L1 in bintrafusp is obvious. The reason for including those against TGF-ß are less so.

The specific role TGF-ß plays in normal and cancerous cells needs to be considered in a context-specific nature. TGF-ß is not a straight pro-inflammatory or non-inflammatory molecule. A review of its role in oncology can found here: Kim et al (2021) J Hematol Oncol. Particularly significant appears to be TGF-ß's role in maintaining an immunosuppressive tumour microenvironment (the area within and just around a particular tumour) and, almost certainly, why binding domains to it were included in bintrafusp. We are generally not talking about wildtype TGF-ß, as it seems that as tumours develop they will develop mutations within TGF-ß or, at least, in biochemical pathways affecting it. The net result is that its tumour-promoting activities (immunosuppression in the TME) are accentuated, while its tumour suppressive activities (e.g., control of cellular proliferation) are de-accentuated or lost altogether in tumour cells. Consequently, it, in itself, was seen as a viable drug target. However, the use of TGF-ß targeting monotherapies met with limited success, leading to the development of compounds, like bintrafusp, which target TGF- ß plus another anti-tumour target (Kim et al (2021) J Hematol Oncol, Lind et al (2020) J Immunother Cancer).

Early trial results with bintrafusp looked promising (Kim et al (2021) J Hematol Oncol, Lind et al (2020) J Immunother Cancer) and, although Pfizer is reported to have passed on the opportunity, GSK agreed to partner with Merck KGaA on the development of

bintrafusp in February 2019. For a 50% share in bintrafusp (comprising costs and revenues), GSK gave Merck KGaA an upfront payment of €300M (AUD484.1M; AUD=€0.62; 17/9/21) and promised €500M (AUD806.7M) in milestones related to the development of bintrafusp for lung cancer, as well as €2.9B (AUD4.7B) in commercial milestones (i.e., sales level triggered payments). **Unfortunately, two years later, negative results from the clinical trial of bintrafusp have been coming in**. In January 2021, Merck KGaA announced that the independent data monitoring committee, which was overseeing the company's phase III, 584-patient clinical trial, INTR@PID 037, comparing bintrafusp head-to-head with pembrolizumab in the first-line treatment of advanced NSCLC patients with high PD-L1 expression, told them that the trial was unlikely to meet its primary endpoint of progression-free survival and the trial was stopped for futility. In March, the results of a 159-patient trial, dubbed INTR@PID BTC 047, where bintrafusp was being used as a monotherapy in the second-line treatment of advanced or metastatic biliary tract cancer, returned an ORR for bintrafusp of 10.1%, which was below the hurdle rate for the study to be considered a success. Finally, in August, the independent data monitoring committee overseeing INTR@PID BTC 055, a 512-patient phase II/III clinical trial comparing bintrafusp, gemcitabine and cisplatin to gemcitabine and cisplatin alone in the first-line treatment of advanced or metastatic biliary tract cancer, reported to Merck KGaA that the trial was unlikely to meet its primary endpoint and it, too, was stopped for futility.

Obviously, there is a cloud over bintrafusp and that may be why we only have some of the information regarding INSIGHT-005 that we would normally get. The trial is a 12-patient study comprising three cohorts that will be conducted across two clinical trial sites. It also involves a formal collaboration between Immutep and Merck KGaA and that Immutep is financially supporting the study, while Merck KGaA is contributing to the biomarker-related work. However, the market has not yet been informed as to how each of the three cohorts will be treated or what the trial endpoints are. This is unusual for a collaborative clinical trial, but not unusual when the specifics regarding bintrafusp are considered.

Merck KGaA would not have known that the most recent result was coming for bintrafusp, when it agreed to the study with Immutep, although it may have expected it. It is also hard to figure out what the two companies will gain with only four patients in each cohort. Whatever they are hoping to see must be broad, given the limited number of patients in the study. Clinical outcomes with bintrafusp appear to correlate with various markers, such as increases in peripheral B and CD8+ cell counts, amongst others. It may well be that Merck KGaA believes there are a few markers that will move in a particular way in just about every patient and that they have developed a hypothesis as to why efti may do so. Given Merck KGaA is funding the biomarker analysis portion of the study, this view does have some merit. If so, a trial of such size may give them enough data to decide whether or not to pursue this line of enquiry. A design of n = 4 for cohorts of efti monotherapy, bintrafusp monotherapy and efti + bintrafusp could be a suitable design for such a study. Of course, if things start to look promising, an application to amend the protocol and expand the trial is easily made.

At this point, all we can do is speculate as to what exactly Immutep and Merck KGaA are looking/hoping to see in this study. **It looks as if the biomarker analysis will be important in determining whether this is the start of what could turn out to be a longer study of the two compounds in combination.**

As mentioned, this study could a produce a lot of upside for Immutep. If the trial's results pan out, Immutep finds itself with a drug that both Merck KGaA and GSK need to make bintrafusp a winner. Even if the results don't pan out as hoped, efti will still have interested onlookers in Merck KGaA, GSK and Pfizer (via the link between bintrafusp and avelumab INSIGHT-004). **At the very least, this trial is a cheap way for Immutep to market efti.**

This trial is a smart move.

5) INSIGHT-003 – A Study of Eftilagimod in Combination with an Anti-PD-1 Therapy and Chemotherapy

As with the previous study, this study is also being done as an amendment to the INSIGHT protocol but can be viewed as a study in its own right.

This study is similar to INSIGHT-004, except that efti will be paired with any PD-1 inhibitor. The main difference between this study and INSIGHT-004 is that the solid tumour patients will receive standard of care chemotherapy in addition to efti + PD-1 inhibitor (or, presumably, a PD-L1 inhibitor, where indicated). The principal investigator remains Dr Salah-Eddin Al-Batran and it is being undertaken at the Institute of Clinical Cancer Research IKF at Krankenhaus Nordwest. The study will recruit up to 20 patients and the first patient was recruited into the study in early August 2021.

As with the previous study, we need to theorize as to why it is being undertaken. This it isn't nearly as difficult to do as it was earlier.

One of the issues a company has with undertaking a combination clinical trial with a compound that is on patent and under a formal agreement with the owner of that compound is that the owner of the compound will have some rights to the data the trial produces. Essentially, this would limit Immutep from allowing another party full access to the data produced in the TACTI-002 trial, given it would not be in Merck's interest to allow other parties to have full access to the data.

This is probably the issue Immutep has run up against. Immutep needs the gravitas of a formal agreement with Merck to support the quality of the TACTI-002 trial and to help attract investment dollars. However, to truly market efti to other interested parties, it needs data that it can freely share to the other six companies with a PD-1/L1 inhibitor on the market, not to mention the companies that have one in development.

The solution to this issue is likely INSIGHT-003. Immutep will be able to use the data from this study as it sees fit and it is a capability that companies like Immutep preserve in all contracts with the clinical trial sites and investigators. As discussed in our May report, while Merck's pembrolizumab is the biggest game in town, it is not the only one. Another six companies have PD-1/L1 on the market, while others have them in development. The more data Immutep has to show these companies, the more interest Immutep can generate and, of course, the more pressure it can indirectly place on Merck.

We were curious when Immutep announced this trial why a particular PD-1 inhibitor wasn't named. Looking back, it did not need to name one. It is almost certainly better off collecting data with as many of the different PD-1 inhibitors as it can. The results Immutep has to date from TACTI-002 and INSIGHT-004 probably go far enough to show what the theory supports, which is that combining efti with any PD-1/L1 inhibitor is unlikely to lead to anything unexpected on the safety front and that efti will only enhance the performance of the PD-1/L1 on the positive front. **What would be of benefit to Immutep is data that potential partners can take a deep dive into to see exactly how efti would be likely to perform in combination with their compound.**

Events Beyond Efitlagimod Alpha

June Capital Raising

In the month after we released our CCR, Immutep undertook what is, for the Australian market, a large capital raise, which now has the EGM and all of the required ASX submissions behind it. In total, the company raised AUD67.1M before costs. When you consider that it had AUD60.6M on its balance as of its July Quarterly Activities Report & Appendix 4C, including AUD13.7M from the capital raise, Immutep is likely to have around AUD110M in cash when it next reports its 4C. This number includes the company's likely Q1 FY22 burn. In fact, a corporate presentation posted to the ASX on 27 September 2021 indicated it had a proforma cash balance of AUD114M, although that number does not include its cash burn for Q1 FY22.

This leaves Immutep well capitalised and, with over AUD100M in the bank, in a position few other Australian medtech companies find themselves. According to the presentation used during the capital raise, Immutep now has sufficient funding to see itself to Q4 CY23. As a reminder, activities that will be covered by the cash Immutep now has on hand include:

1) The expansion of the TACTI-002 first line NSCLC trial
2) A phase IIb trial in HNSCC
3) phase III registrational trial in breast cancer (final patient numbers and exact clinical design are subject to regulatory feedback).
4) A further phase II trial in NSCLC
5) An additional two Investigator Initiated trials of Immutep's choosing
6) Manufacturing of required quantities of efti and IMP761.

It is inevitable that some investors are disappointed by capital raisings, because of the perceived dilution it causes, and that the most vocal of these will complain to the company about it. We use the term 'perceived' not because in some reality dilution did not occur, but, rather, the company is charged with maximising shareholder value, not minimising dilution. Maximising return almost invariably means taking a compound as far down the development pathway toward market as possible, as well as conducting clinical studies that help to define how broad the market for a drug might be. We cannot see that Immutep could have avoided another capital raising, even if it ended up simply to bolster the company's balance ahead of corporate activity. The amount of cash Immutep has on its balance, post-raise, is at the lower end normally held by its US peers. **When you look at the comparables in the valuation section of this report, see how much cash it had in the bank. It will astound you**. Given the track record of American companies in the development of therapeutics, its lead is not a bad one to follow. In our view, any medically-focused technology development company that takes anything more than moderate steps to limit dilution, all else being equal, risks trying to be too specific in its decision making in that regard. The Australian economy has generally been pretty good and supportive of medtech capital raisings for a long time. It will definitely not stay this way forever. It is not if, but when the economy takes a downward turn that is open for debate. Immutep's chances of success are strong and the pay-off large. Gambling on the economy is not something small drug development companies should be doing. It is an activity well and truly outside their core competency.

The Activities of EOC Pharma - Immutep's Chinese Partner for Efti

EOC Pharma (EOC), Immutep's long-standing partner for efti in China, has already announced it will be commencing a trial of efti in breast cancer patients equivalent to Immutep's AIPAC trial. In late August 2021, EOC stated it would add an additional trial of efti in combination with a PD-1 inhibitor for an, as yet, undisclosed cancer. EOC expects this trial to commence in 1H CY22.

We believe EOC is in the final stages of establishing local manufacturing of efti, which will support the breast cancer and combination PD-1 inhibitor trials EOC is planning.

Development of a Small Molecule Anti-LAG3 Drug

Earlier this year, BMS announced that the anti-LAG3 antibody, relatlimab, had returned positive results in a phase III trial in combination with nivolumab in patients with previously untreated metastatic or unresectable melanoma. This event effectively

locked in LAG3, an undeniable checkpoint inhibitor. Additionally, Immutep previously licenced the anti-LAG3 antibody LAG525 to Novartis. Unfortunately, LAG525's development appears to be held back, because Novartis' anti-PD-1 candidate, spartalizumab, was not performing to expectations in clinical trials. It is yet to be seen whether Novartis will look to combine LAG525 with tislelizumab, the PD-1 inhibitor Novartis gained access to by partnering with BeiGene early this year.

Immutep revealed, however, that it began efforts in 2019 to "jump the field", looking to develop an oral anti-LAG3 small molecule in collaboration with Cardiff University. Oral small molecule drugs are often at a considerable cost-of-goods sold advantage compared to their biologic counterparts. Possibly more importantly, an oral LAG3 inhibitor would almost certainly be preferred by patients, physicians and payers compared to biologic LAG3 inhibitors, like relatlimab, which are given by intravenous infusion. Oral drugs can be taken at home and obviate the need for the patient to travel into a medical facility to receive treatment, giving them an advantage over biologics at many levels.

Given where the development of other anti-LAG3 compounds is at, investors should be pleased to hear about this program. It shows that Immutep has not just left it to LAG525 to be its only exposure to the area, but it also allows them to expand the application of its exceptionally advanced, likely world-leading, knowledge of LAG3 biology. It is also the sort of activity you like to see a company undertake, because it is right within its core competency, there is likely to be a clear market need if the program is successful, it represents a good opportunity to add value to the company and, of course, with efti where it is at, it shows that the company is still hungry and not resting on its laurels.

Progression of IMP761 for Autoimmune Disease

Although the development of efti has taken front and centre stage at Immutep, the company has a long-held interest in autoimmune diseases, as evidenced by the outlicencing of the depleting antibody IMP731 (GSK2831781). Under the shadow of efti, Immutep has been progressing the development of IMP761, which acts as an agonist of LAG3 or, rather, acts to increase LAG3's activity. The hope is that this will decrease the activity of the immune system, such that it no longer attacks self-antigens or, at least, reduces the severity of the attack.

The most recent news from this program (7/6/21) is that a particular line of Chinese hamster ovary cells that produces commercially-viable quantities of IMP761 has been chosen to take IMP761 forward into manufacturing. The company was last reported to be looking for a contract manufacturer to take the cell line on. Once up and running, Immutep will undertake the formal pre-clinical studies required to trial the antibody in humans and, although no definitive timeline has been set, the company will prepare an investigational new drug (IND) submission for the compound and submit it to the FDA upon successful IND-enabling studies. In fact, this activity was budgeted for in Immutep's most recent capital raising.

Other Events of Note

The other events of note that have occurred at Immutep since our May report are:

1) In early September, Immutep announced that the final patient in part B of the TACTI-002 trial had been recruited. The NSCLC patients in part B of the study were PD-1/L1 inhibitor refractory, such that their tumours had found a way around these inhibitors. This was always going to be a hard indication to tackle with the combination of efti and pembrolizumab. Still, the results were deemed positive enough relative to other available options for stage II of part B to be recruited. We expect the final results of part B of TACTI-002 to be presented at a conference later this year.
2) The EAT COVID Trial was mentioned in Immutep's last Quarterly Activities Report & Appendix 4C. It was simply stated that this investigator-led phase II trial in up to 110 hospitalised COVID-19 patients was proceeding.
3) The issuance of a patent in China entitled "antibody molecules to LAG3 and uses thereof", directed at providing IP protection for the Novartis licenced LAG525.

To the best of our knowledge, there have been no other significant events known to the market than the above that would affect the content of our May report. Moreover, if anything, our view of Immutep's prospects have increased. This is because we have continued to see the company execute a high level of capability, produce clinical results that are in line with the solid results previously reported and, importantly, considerably strengthen its bottom line through the June capital raising.

Valuing Immutep by Comparables

As stated in the Introduction, using one-off risk-adjusted discounted cash flow (rDCF) analyses present considerable problems when valuing medtech companies. We see three key problems with valuing companies by rDCFs:

1) **Forecasting**: A typical rDCF requires forecasts for a full economic cycle. Generally, this has been taken to mean seven years. Many, however, do a 10-year forecast. A proper forecast requires the analyst to estimate every line in the Statement of Profit, Cash Flows and Balance Sheets. Further numbers sit behind those numbers, like individual trial costs, the start and finish of those trials, manufacturing and scale up costs (which have a whole range of estimates sitting behind them), clinical trial result probabilities, licencing or trade sales assumptions, regulatory approval probabilities, sales price

estimates and, of course, sales. You may ask, 'Why do you have to make sales price and sale price estimates if you choose a licencing or trade sale model?' The reason is because that is exactly what the group on the other side of the table will be doing and it will determine how much they are willing to part with. Over all of that, you need to consider management and other similar factors. Great CEOs, for example, do not generally hang around. It is a competitive market.

2) **Systematic Bias (Systematic Error)**: Systematic bias refers to unidirectional error that is introduced into activity or process, although the name for it may be different depending on the particular industry or area where this type of error is being discussed. Company research and, particularly, company valuations can be full of this type of error. Many studies have shown that there is positive bias in company research and, particularly company valuations. Unlike random error, which tends to cancel itself out, the unidirectional nature of systematic bias means that, rather than the error cancel itself out, it tends towards being additive and, in the case of company analysis, moves the valuation away from what the analyst is supposed to be trying to achieve, which is an accurate valuation. Take, for example, a medtech analyst who finds a particular technology to be very interesting or simply cool. Without even knowing it, the analyst may derive revenue forecasts that are higher than the data supports, or underestimate costs, as well, for the same reason. Here the valuation takes a double hit through inflated revenues and irrationally-reduced costs. Cognitive biases are a well understood phenomena in investment circles and represent a subset of systematic biases. Analysts are not immune to these either, despite knowing they exist. Analyst B respects analyst A and knowing analyst A's opinion is likely to bias analyst B's opinion whenever they cover the same company. In a DCF model, every estimate that must be made is a potential source of systematic error.
3) **Transparency**: Investors only ever receive a snapshot of any valuation done by an rDCF and some of the assumptions around which forecasts have been made. As an example, the average development time for a drug is about 12 years. Clearly, that is outside the analyst's forecast period. That program then falls into the terminal value. If a drug has not started selling in the forecast period or is only early in its sales cycle, that program, which may generate many 100s of millions dollars, has no effect on the valuation, except as an ongoing cost. Conversely, pharmaceutical companies only have a certain period of exclusivity over a drug. If that drug happens to be at peak sales during the last year of the forecast, those sales will be reflected in the company's perpetual terminal value, even though the patent may be about to expire.

Bringing Transparency and the Market Into it

The efficient-market hypothesis (EMH) is a hypothesis in financial economics that states the quoted prices of publicly-listed assets reflect all available information. By inference, this means the prevailing price of an asset, like a stock, should be the best estimate of the true value of the asset at any one time**. In the land of small capitalisation stocks, we know that isn't true, especially as we watch a $1.00 stock we own drop by 25% when somebody decides to sell 25,00 of them at the market price just before market close**. That doesn't mean the concept is totally useless, though. Highly watched, highly traded stocks are much more likely to feel the effects of the EMH, than the vast majority of the medtechs on the ASX.

The discount rate the analyst uses to value a stock also has a large impact on the final valuation. While you can calculate a discount rate using reliable numbers, some of the values used to calculate those rates are spot rates and don't necessarily reflect what the market thinks will happen over the forecast. Discount rates taken from data providers can be even more unreliable. They tend to group such that the discount rate for a small pharmaceutical company is the same as that for a large one, even healthcare companies, in general. Without revenue, though, the prices of small pharmaceutical development companies are often more linked to the finance sector or, more specifically, how much money is out in the community to invest. For this reason, many analysts use discount rates that are higher than those from data providers and, more often than not, higher than the ones they calculate themselves.

The beauty of valuing a company by looking at comparable companies is that it leaves it up to the market to make a lot of the decisions for you. For example, the appropriate discount rate to apply is built into the share prices of the companies in your comparables basket, as are the long assumptions for the therapeutics market, specifically.

The major downside of valuing a company by comparables is that it is almost a purely qualitative exercise. Qualitative exercises are not something the finance community is particularly keen on. However, that downside leads me to the major upside of valuing a company by comparables. It has an extremely high level of transparency, as the attributes of each company in the basket of comparables are easily provided and, if the investor needs more information, that information is generally easy to get.

Most importantly, though, if the investor disagrees with the conclusion the analyst has made, he/she has all of the information in front of them to derive their own valuation.

The Basket of Comparables

Table 4 provides a list of the six comparable companies we have chosen to value Immutep. It also includes Immutep and where it would fit into the list with its current enterprise value, as well as a company named Nektar Therapeutics. Nektar has a drug that, like Immutep's efti, is intended to "activate" the immune system, such that the immune system reaction, which takes advantage of the hole in the defences of the cancer created by a PD-1/L1 inhibitor, is heightened. After discussing Immutep relative to our comparable basket, we will compare it specifically to Nektar because it is a very similar company.

The basket was created after scanning approximately 50 immunotherapy companies. One website (www.immunofrontiers,com) lists a total of 143 NASDAQ-listed immunotherapy companies. To us, this number appeared high, mainly because the exposure of many companies to immunotherapy was relatively smally. Still, it was a large number of companies.

The major criterion we used to decide whether we would include a company in our list can broadly be described as "Do they operate in immuno-oncology and do they appear fairly valued?" Other factors went into our decision, as well. The factors included:

- Did they help us create a value ladder through which we could assess Immutep?
- Did we believe they were serious drug development companies?
- Did they introduce some level of variation into the basket, largely to help counter any hype around a particular technology?
- Were they not so complicated that we could not adequately get across their qualities in a reasonable amount of space?

When putting together our basket of comparables, we found a large number of companies with healthy cash balances. When you removed the cash to get an idea of the enterprise value (EV; i.e., the market value of the development compounds), we ended up with a large number of companies that had low or negative EVs. We also found a lot had EV's between USD500M and USD600M. If we had more time, we would have investigated this phenomena to see if it was real or perceived. Regardless, it resulted in a number of our preferred companies being left out of the comparables basket because it did not help us create that value ladder.

Why are no Australian Companies Included in the List?

The main reason no ASX-listed companies were included in our group of comparables is largely due to a lack of them and, in particular, a lack of ones that are at an advanced stage.

Prescient Pharmaceuticals Ltd (ASX:PTX) was one possibility, but its chimeric antigen receptor T-cell therapies are only at the early pre-clinical stage, which makes it hard to compare it to Immutep whose efti is about to start a phase IIb study in HNSCC.

The other one is Imugene Ltd (ASX: IMU). Imugene is an immunotherapy company and it came much closer to making it into our

Table 4. Comparable Companies used to Derive a Valuation for Immutep Ltd.

Table Number	Page Number	Company Name	Ticker	Company Headquarters	Market Capitalisation (MAUD)	Enterprise Value (MAUD)
5	16	Atreca Inc	BCEL	San Carlos, California, USA	337.7	62.0
6	17	Checkpoint Therapeutics Inc	CKPT	Waltham, Massachusetts, USA	369.0	278.9
N/A	**N/A**	**Immutep Ltd**	**IMM**	**Sydney, New South Wales, Australia**	**476.5**	**362.5**
7	18	Cue Biopharma Inc	CUE	Cambridge, Massachusetts, USA	627.7	528.3
8	19	Immatics NV	IMTX	Tuebingen, Germany	1,100	838.9
9	20	Zymeworks	ZYME	Vancouver, British Columbia, Canada	1,900	1,300
10	21	Trillium Therapeutics	TRIL	Mississauga, Ontario, Canada	2,600	2,200
11	***22***	***Nektar Therapeutics***	***NKTR***	***San Francisco, California USA***	***4,600***	***3,200***

Sources: Company press releases, presentations and website, and SEC and ASX filings.

basket of comparables. Its market capitalisation largely kept it out. With a cap of AUD2.3B, we simply felt it was overvalued to the point that it failed our fairly valued test and, while we really wanted an Australian company in the basket, it would have skewed the value ladder, making it harder to value Immutep. **At the end of the day, we may be proven wrong by excluding Imugene. There are summaries of seven companies at the end of this section, including their market capitalisations and EVs. You can examine them and make your own mind up about Imugene.**

What About the ASX Medtech Discount?

Some investors will believe we have not included any ASX-listed companies because of, what is commonly referred to, the ASX-medtech discount and a desire to give Immutep a higher valuation. The ASX-listed medtech discount is the belief that of two identical companies (except one is listed on the NASDAQ and the other on the ASX) the one listed on the NASDAQ would receive an appreciably higher valuation. **However, we cannot think of a single example where an ASX-listed medtech has gained an appreciable uplift in value by taking on a NSDAQ listing**. This includes companies like Opthea Ltd (ASX:OPT), Mesoblast Ltd (ASX: MSB) and Benitec Ltd (formerly, ASX:BLT), to name a few. There are also some very under-valued and over-valued medtech companies on the ASX. We do not, however, believe that just because a medtech is listed on the ASX it will trade at a large discount to its US peers. There are many reasons Australian companies appear to trade lower. Cash in the bank is one obvious difference you will see when you look through the companies we prepared summaries for. Only two of the seven have less than AUD100M cash and one of those has AUD99.5M

Please note that our group of comparables is not solely US-based. Of the six companies in it, one is from Germany, two from Canada and three from the US. Nektar is also US-based. This is probably a fair representation of the relative number of medtech companies in the US compared to those outside of it. All, however, are NASDAQ listed.

The ASX-medtech discount is, generally, small and largely driven by the fact that Australia is relatively out of the way and eye of some international investors. If anything, the interconnectedness of world markets should push solely distance-related discounts, leaving either national or quality issues to blame for any discount.

How we Valued Immutep

The way we valued Immutep is fairly straight forward.

We removed cash and cash equivalents from the balance sheets of all companies in table 4 to yield a simplified EV for each.

We then looked at each comparable, trying to ignore its EV, and decided whether Immutep deserves a higher or lower value than that company. This gave us a spot on our value ladder into which to insert Immutep.

We then discussed Immutep relative to Nektar Biotherapeutics, which is highly comparable to Immutep. We used the comparison with Nektar to help us see where decisions may be close, and refine our value of Immutep.

Once we settled on an EV for Immutep, we added the company's cash to the EV and divided by the number of issued shares in Immutep. The result was what we believe to be a fair value per Immutep share.

To follow along with the discussion, read the summaries prepared on each comparable, so you do not need to constantly refer to the tables. Also read the summary of Nektar Therapeutics before you read the discussion on the company. It is long and complex.

Valuation – Comparables Discussion

The valuation of Immutep should be higher than that of Atreca and Checkpoint Therapeutics.

Atreca's activities are too widely spread and its decision to focus on targets with little research behind them greatly increases the risk of each program. Their current clinical trial has an objective response rate of 10%, but since pembrolizumab refractory patients were not excluded from the study that single response could simply have been due to pembrolizumab alone. APN-122597 falls into the same category, with a poorly-researched target, which makes this program extremely high risk. In our view, Atreca is a demonstration that interesting approaches to drug development do not equate to good drug development.

Checkpoint is another high-risk investment. Its lead compound, cosibelimab, is late to the PD-1/l1 party and its point of differentiation, that cosibelimab is capable of inducing cell death when it binds a tumour cell, will need to have a major effect on tumours to get them into the race or garner interest from partners. It is also hard to believe Checkpoint is the only one to try this approach, given it is relatively obvious and so many PD-1/L1 inhibitors are on market, in development or have failed. **It is probably fair to say we are now in the post-PD-1/L1 period of drug development and drug developers and the market are asking "Where to next?" Drugs like Immutep's efti are an obvious answer.**

Cue Biopharma's technology is interesting and safety seems to be OK, so far, in the two trials of its lead and only clinical candidate, CUE-101. The compound is yet to provide any convincing signal of clinical activity. Certainly, if it does show convincing clinical activity, CUE's platform is expandable and there are plenty of cancer targets that it could be plugged into. CUE-100 series compounds also appear to be advanced cancer vaccines and only one of those was ever approved out of hundreds of attempts and it was a commercial failure. The infectious and autoimmune disease programs may hold more hope for them. It is certainly a positive that Merck is in a formal collaboration agreement with CUE regrading CUE-301, a putative therapy for type I diabetes. Certainly, if Merck was to take a licence or commit strongly in some other way that could be a real building block, but not for its cancer portfolio. **Without a signal of clinical activity, let alone a strong one, valuing CUE higher than Immutep simply on the basis of interesting science would simply not be logical. Immutep must have a higher value than CUE**.

Immatics is where things get interesting. It has shown, quite convincingly, that large pharma is willing to pay for its technology, to the tune of USD30M to USD50M for two or more of Immatics' targets or therapeutics or T-cell receptors, depending on how you want to classify them. While, to the average person on the street, this is a lot of money, to a larger pharmaceutical company it doesn't even qualify as a rounding error. The larger companies are regularly making much bigger deals, which turn billions into zero

very quickly. For example, Sanofi bought a company called Principia in August 2020 for USD3.7B to get its hands on a drug called rilzabrutinib, which was in a phase III study for immune thrombocytopenia. Rilzabrutinib flunked the study and with it went billions of dollars linked to the drug's valuation. Sanofi, like most companies who take large hits like that, usually does not give up immediately on a compound like rilzabrutinib, but more often than not, eventually does and, in doing so, says goodbye to more than a rounding error's worth of money. The point being, while the upfronts Immatics is getting may look good, it isn't a lot of money for a large pharmaceutical company who feels a technology may one day be important and they had better take a look at it.

The adoptive cell transfer products, including Immatics' version of CAR-T, look difficult. Even though they are in the clinic and a 10% ORR keeps them in the game, they look difficult not only because these phase I trials will take more than three years before they officially complete. **These products are hard to produce, logistically difficult to handle and are expensive (CAR-T therapies extremely so) ensuring a quality product is not easily done. For a good review covering the promises and limitations of the broad group of adoptive T-cell transfer type technologies, read this: (Moretti at al (2021) Br J Cancer).**

ACTallo and TCER® bispecifics seem like much easier technologies, at least, from post-commercialisation. Pre-commercialisation, the complexity of the technology indicates there are still many lessons to learn. Your average drug takes somewhere between 10 to 12 years to make it to market. It seems unlikely we will be seeing any approvals of ACTallo pr TCER® bispecifics any time in the near future.

Then you start to consider the competition in the space, as stated in the company summary: 111 CAR-T companies alone without even considering companies working in the technologies that are technically easier than CAR-T, like straight adoptive cell transfer, or will lead to products that should, theoretically, be much simpler, like ACTallo and TCER®.

Maybe if we had a stronger signal of clinical activity from Immatics' three clinical trials it might be easier to get behind the company. Knowing the company took IMA into a five-year phase III trial is particularly comforting, even if the technology is superior. Furthermore, it does not look like it preceded the renal cancer phase II and III studies with a satisfactory phase I study last time around. Clearly, it is not going to make that mistake this time around, but it makes for a long time in clinical trials. Granted, it probably could speed up future therapies, but the current ones seem likely to stay on a 'steady as she goes' course.

Again, Immutep and efti have shown a clear clinical signal in an area that does not face all of the extra challenges faced by technologies that fall under the adoptive cell transfer banner, including CAR-T, and the PD-1/L1 inhibitors have shown us what they can do for the treatment of cancer, to which drugs like efti can slide right into. That same broad-base or, really, even close to it doesn't exist for adoptive cell transfer, off-the-shelf genetically-altered T-cells from healthy donors or T-cell receptor bispecifics.

Zymeworks is a solid company, at least, from the drug development side of things, although it should have kept some of its earlier drugs, rather than licencing them for a relative pittance. The sorts of licences will never make Zymeworks a big company by pharmaceutical standards, although its more recent deals have been much better.

The company started its own internal efforts based on two drugs that have bispecific antibodies targeting two different and proven epitopes, both drugs retaining the Fc portion of the drug's ability to recruit other cellular components resulting in tumour cell death. The first of these drugs is zanidatamab. The second, which is a couple of years behind in development, is ZW49. ZW49 is essentially zanidatamab, but it is linked to a cytotoxic substance released by an enzyme once ZW49 has been internalised by the tumour cell HER2+. The perception you get from Zymeworks' corporate presentation is that it will climb the ladder to the largest market, the neoadjuvant setting. **The issue is that there are now a lot more drugs that target HER2+, and there are likely to be further ones on the market before either of Zymeworks' compounds. Climbing the treatment ladder might be akin to climbing Mount Everest.**

The issue is that the other available HER2+ indications are relatively small fry small. Zanidatamab has breakthrough designation therapy for biliary tract cancers, and of the 8,000 cases a year in the US, only 5% to 10% are HER2+. Similar statistics for other cancers are (cancer, US incidence HER2+ positivity rating): breast cancer, 281,000, 10.5%; gastric cancer, 26,000, 4.7%; bladder cancer, 87,340, 12.4%; cervical cancer, 14,480, 3.9%; uterine cancer, 65,570, 3%; testicular cancer, 9,470, 2.4%. The incidence figures are from the US National Institute of Cancer, while the rates of HER2 positivity come from Yan et al (2015) Cancer Metastasis Rev. Once you get past the 29,500 women with HER2+ breast cancer (a low estimate from others we have seen), the next largest group is bladder cancer patients at 10,800 and from there the market keeps getting smaller.

We do believe zanidatamab and ZW49 are likely to have a role in HER2+ cancer treatment. The question is how big that role will be. Initially, it is likely to be small, and it will have to conduct clinical trials carefully to ensure (a) it doesn't cannibalize its own drugs and (b) it does not get an unexpected trial result that keeps one or both of the drugs well down in the lines of therapy for the various cancers.

Zymeworks and Immutep are closer together than any of the other companies discussed. However, we reserve making a call before we discuss the last company in our group, Trillium Therapeutics.

Over the last 18 months, Trillium has started to fulfil its promise. It is doing this after it had a trial discontinued for safety concerns, several device failures and the realisation that TTI-621 was unlikely to be a hugely successful drug on the back of a poor safety record. As we said in the summary, good clinical results from TTI-621, followed by slid results from TTI-622, which did not have the same issues as TTI-621, caused Trillium's share price to quadruple over the last 21 months. **Then Pfizer stepped in with a**

USD2.3B bid to buy Trillium three weeks later. We kept Trillium in our basket of comparables even though it had accepted a takeover offer because in TTI-622, Trillium had a drug that a large pharmaceutical company wanted. Although Trillium had reached Pfizer's takeover offer price in November 2020, and the stock had drifted down since then to around ~USD6.00 to ~USD6.50. Officially, Pfizer paid a 170% premium for Trillium, paying USD18.50 share when Trillium was trading at USD6.85.

Had we used Trillium's pre-bid price, the company would have had a market capitalisation of AUD1.162B (USD852.0) and an EV of AUD788.1M (USD577.9M)

TTI-622 is a good drug but, at the moment, it is limited to blood cancers and it will also face competition from other CD47 antagonists. Efti looks to be in a class of its own, and is likely to be of use in a range of solid tumours, as well as giving a PD-1/L1 owner a competitive advantage, rivalling what will be a very competitive market. However, it is too early to be putting a takeover premium into Immutep's prices. Consequently, we are leaning toward an EV of that for Zymeworks for the, minute.

We will now we discuss Nektar Therapeutics before making our decision on Immutep's EV.

Valuation – Discussion of Nektar Therapeutics

Before reading this section, please refer to the summary of Nektar in table 11. Nektar is not a straight forward company and it will be a lot easier to understand after reading the table.

Nektar's market capitalisation is currently AUD3.2B. How much NKTR-255 is worth is debatable, given its early stage of development and the strange nature of the trial it is running with Janssen.

Given Eli Lilly paid USD150M upfront and has promised USD250M in milestones in exchange for a share of the rights to the NKTR-358 (which could change depending on Nektar's wishes, the compound is worth something and since the compound has definitely progressed since the 2017 deal into two fairly large phase II trials, giving it a fairly high value is probably reasonable. Overall, somewhere between USD700M (AUD954) and 900M (AUD1.2B).

Again, the vast majority of the value must sit with BPD, which is interesting, because we do not think Nektar is happy with BMS and BMS feels it has over-paid for BPD and that, under the current deal, BMS does not see much value in taking BPD forward.

In November 2018, there was scepticism at a presentation on BPD and nivolumab in melanoma that saw the ORR for the combo slide up just over the 50% ORR that was presented at the American Society of Clinical Oncology Conference in June 2018 (CARROLL J on NKTR-214/Opdivo - Endpoints 9 November 2018). Analysts had been looking for something in the 60%+ range.

It will be interesting to see how the Nektar-BMS relationship evolves. BMS may tell Nektar that BPD is not going into any new indications unless Nektar is willing to renegotiate the original licence agreement. Alternatively, BMS is targeting BPD at what it believes is appropriate and will go no further.

Coming to a Conclusion – The Valuation

With Zymeworks at an EV of AUD1.3B and Nektar sitting on AUD2.2B (Nektar's EV of AUD3.2B less AUD1B for NKTR-358), the valuation range is quite wide. Immutep and efti have certain advantages over Zymeworks' two compounds that value Immutep higher than Zymeworks. The competitive dynamics of the HER2 targeting drugs will make Zymeworks' life hard, as efti is in a class of its own.

If AIPAC comes up positive in November 2021 and efti is shown to have a monotherapy capability in breast cancer, the company's share price should skyrocket.

After our research, we do not have a very high opinion of BPD. Nonetheless, BPD is significantly more advanced and de-risked than efti, even if it may not have the same overall potential.

To arrive at our estimated EV for Immutep, we are going to use the mid of the two valuations, which means we are estimating Immutep's EV at AUD1.75B

To arrive at a per share value based on this estimate, we add the cash Immutep currently has (AUD114M) to this EV and divide that by the number of shares Immutep has on issue (850,992,801).

The result is an EV for Immutep per share of $2.20.

Table 5. Atreca Inc (NASDAQ: BCEL)

Enterprise Value:	AUD62.0M	USD45.5M	**Cash:**	AUD248.6M	USD182.3M	**Market Capitalisation:**	AUD337.7M	USD225.8M

Website: www.atreca.com **Location:** San Carlos, California, USA

Technology/Core Competency: Atreca's pipeline has been developed based on upon the company's deep understanding of the human immune response, using a proprietary discovery platform. Unlike other companies, Atreca focuses on active B-cell responses, interrogates them and then turns the antigen they target into therapeutic candidates more suited to treating cancer

Development Programs:

1) ATRC-101: This compound is based on an antibody, which targets a novel ribonucleoprotein complex found primarily in tumour cells and is induced by chemotherapy. Tumour antigens picked up in this way by ATRC-101 are then thought to be delivered to the cells of the innate immune system which, in turn, involve other components of the innate and adaptive immune systems. ATRC-101's activating Fc region also appears to give it single agent activity, at least, in mice (i.e., The Fc region of an antibody is capable of killing living organisms it is bound to, potentially, in several ways). The company believes ATRC-101 remodels the tumour microenvironment making it more susceptible to attacks from other immune system components. Atreca is currently studying ATRC-101 in a 160 patient, open label, sequentially assigned phase Ib, three cohort study, in patients with advanced solid tumours. ARTC-101 is given at one of two dosing frequencies in cohorts 1 and 2, while it is given in combination with pembrolizumab in cohort 3 (NCT04244552). The trial started in February 2020, with data collection expected to be complete in December 2024 and the trial to close in March 2025. Twenty-six patients have so far been enrolled into the study. The results of an interim analysis were consistent with disease control and associated with target expression, according to the company. The company has various plans for further study of ATRC-101, including developing a diagnostic, as monotherapy, in combination with pembrolizumab, as well as a combination study with chemotherapy.
2) APN-122597 is being developed to target EphA2 (ephrin type-A receptor 2), a receptor that is highly produced by tumour cells. In normal cells, though, the family of 14 receptors is not highly expressed and seems to be involved in cell-cell adhesion or revulsion. This is a very early program, with the company as yet to decide the format it will use to target EphA2.
3) The company also claims to have four programs aimed at multiple targets, one involving T-cell engagement in a collaboration with Xencor (NASDAQ: XNCR), another based on antibody dependent cytotoxicity (a function of the Fc region of an antibody) and another based on immunostimulation and is a collaboration with an undisclosed partner. The company also appears to claim multiple other programs based on undisclosed methods of action.
4) COVID-19: Atreca is also involved with, at least, three companies with the aim of discovering, developing and manufacturing therapeutic antibodies to the disease. Little reference is made to this program in the company's most recent presentation.

Analyst Comments: Atreca appears to be involved in programs that employ just about every way an antibody could be used to address cancer, which isn't the tight focus you would expect to see from a company whose real expertise lies in analysing IgG antibodies from B-cells. The rationale for combining ARTC-101 with pembrolizumab does not seem to be overly strong, unless ARTC-101's activity would normally be inhibited by PD-1/L1 interaction. The way it plans to address EphA2 is still up in the air with multiple approaches still under consideration. Frankly, we are not sure why it has chosen EphA2 to target. This is not inspiring. Neither is the lack of transparency concerning its other programs given they are a publicly-listed company. There could be some method to all of this, but we cannot see it.

Sources: Company Press releases, presentations, website and SEC filings.

Table 6. Checkpoint Therapeutics Inc (NASDAQ: CKPT)

Enterprise Value:	AUD278.9M	USD204.5M	**Cash:**	AUD90.2M	USD66.1M	**Market Capitalisation:**	AUD369.0M	USD270.6M

Website: www.checkpointtx.com **Location:** Waltham, Massachusetts, USA

Technology/Core Competency: Checkpoint is interesting in that it doesn't seem to focus on a technology or technologies, but rather is actively seeking product purchases, in-licencing opportunities and co-development opportunities. Certainly, over the last decade we have seen great changes in the way therapeutics are developed, with the larger pharmaceutical companies leaving much more of the early-stage development to other companies and, effectively, using those companies as its new early-stage pipeline. To speed development, the company is choosing indications that represent unmet medical needs. Often, this allows a company to seek regulatory approvals with less data than it might otherwise need.

Development Programs:

Checkpoint has the following three compounds in development for seven different indications:

1) **Cosibelimab**: This is an anti-PD-L1 antibody that the company is developing as a monotherapy for (1) metastatic cutaneous squamous cell carcinoma (CSCC) and (2) as a monotherapy for locally-advanced CSCC. Checkpoint claims that cosibelimab is differentiated from other anti-PD-1/L1 drugs on the market because it contains a functional Fc region. A functional Fc region should mean that not only will the drug open up the tumour to attack by the immune system, but that any tumour cells the antibody binds may set off a process, such as antibody-dependent cellular cytotoxicity or ADCC, which can cause the death of the cell the antibody is attached, as can other methods using the Fc region. The company has stated that pivotal trial results for the metastatic HSCC indication are due in December 2021, while those for locally-advanced disease are due exactly one year later. The trial that is expected to produce these pivotal quality results for both indications appears to be one in the same, as no other trials containing cosibelimab and CSCC are listed in the ClinicalTrials.gov database, except this one NCT03212404. Obviously, Checkpoint may expect the metastatic group of patients to readout first, particularly given their life expectancy should be much shorter than those with locally-advanced disease. Nonetheless, most major regulators require a therapeutic to show substantial evidence of both safety and efficacy before they will provide it with marketing approval. In an ideal world this would mean a positive, large, randomly assigned, multi-centred, blinded, randomised, control trial, which was supported by existing adequate and well-controlled clinical investigation(s) that demonstrated the effectiveness of the drug for its other, closely-related approved indication(s). Trial NCT03212404 will not even come close to providing that. While the target enrolment for the trial is 500 patients, at least 12 cancer types may be enrolled in it. There is also no method for determining who will be offered a spot in the trial, which could bias the results in several ways (e.g., healthy patients will be more likely to attend the hospital and to receive their infusion, their doctors may advise the same of other healthy individuals, while the sicker individuals do not attend). The single arm, open label, nature of the study may further introduce biases into the results. Other treatments for CSCC do exist, such as imiquimod, reducing the requirement for a new drug that has not been fully tested to be allowed on to the market. Before it was granted its INN, cosibelimab was known as CK-301. We have been able to find no additional work that was done with CK-301 that would not have been attributed to cosibelimab. If cosibelimab were to produce some absolutely stellar results in CSCC patients, it is possible that an accelerated approval may be on the cards. Nothing appears to have happened that would portend that possibility. Even if cosibelimab hit the jackpot and gained an accelerated approval, Checkpoint would still need to undertake the additional studies required for normal therapeutics while they are on the market. Should the trials fail after an accelerated approval, they would quickly find themselves off the market.
2) **Cosibelimab**: Checkpoint is also studying cosibelimab in combination with the chemotherapy pemetrexed and a platinum-based chemotherapy. While platinum-based chemotherapy has been a mainstay of NSCLC treatment, pemetrexed is also often prescribed. Provided a safe dose can be found for all three therapies, the worst cosibelimab could do in a lot of ways is nothing. This, of course, leaves room for Checkpoint to point to other things about the trial that went wrong, rather being forced to say, "our drug added no benefit". This appears to be a fairly large study (n = 500; NCT04786964) so how much room it will have to argue is questionable. Going into a trial of this size and complexity seems to be a poorly thought-out exercise. It seems highly likely it could get the result it is after (or maybe not after) in a much shorter period of time at a lot lower cost, using a different approach. Having said that, a solid win could turn it into a player in the anti-PD-1/L1 field. (B) Checkpoint is taking a slower, but still aggressive, approach in pursuit of marketing approval for cosibelimab to treat epidermal growth factor mutation-positive NSCLC patients (i.e., NSCLC patients in whom treatment with the usual first-line standard-of-care dugs will not work due to mutations their malignancies carry). The study Checkpoint plans to conduct is a 560-patient, phase III trial, which is much better designed trial than the one it is looking at for CSCC. Patients to be enrolled in this study will be confined to NSCLC with a demonstrated mutation(s) rendering them ineligible for the standard first-line therapy given to metastatic NSCLC patients. This type of study will remove many of the potentially confounding observations that can plague studies that simply recruit general solid tumour patients. The primary endpoint for the trial is median overall survival (mOS). Median OS is considered to be the gold standard endpoint in cancer clinical trials because it is a hard endpoint that shows patients have benefited from a clinical intervention by living longer than patients who did not receive the intervention. This trial (NCT04786964) is expected to start any day now and has an expected primary completion date of May 2024 and an estimated study completion date of May 2025.
3) **Olfertinib**: This drug candidate is now being referred to as a third-generation epidermal growth factor receptor (EGFR) inhibitor. As the use and success of EGFR inhibitors in treating about 20% of NSCLC patients is leading to mutations in the EGFR genes of tumours cells, resistance to existing EGFR drugs is becoming a problem. It is very much the story of evolution in a microcosm. Olfertinib is being developed to treat the growing group of NSCLC patients this resistance is creating. The drug is currently in an ongoing phase III trial as a single agent with an Asian partner. No ClinicalTrials.gov entry exists for this phase III study. A phase 1b study is planned, which uses a combination of cosibelimab and Olfertinib also in NSCLC patients with an EGFR mutation. It is not clear when this study will start.
4) **CK-103, CK-102 and CK-103:** These three compounds are all in preclinical development for cancer, each having a different target. A timeline does not yet appear to have been set for when they will begin formal clinical trials.

Analyst Comments: A strategy of targeting unmet medical needs in an effort to get a compound on to the market quicker than standard development usually allows is not a new one and was all the rage about 10 years ago. The storied cancer drug developer Genentech was the company that made this strategy popular. Of course, in that period of time the routes to do this, though, have shrunk. Checkpoint seems to be making some progress with cosibelimab, although not terribly well. Olfertinib appears to be stuck, having yet to begin any clinical trials in the US. Cosibelimab appears to be the company's best bet, however, interim data presented at two conferences last year did little to excite investors. Given the number of PD-1/L1 inhibitors on the market and in development it is also hard to believe that the tumour cell death the antibody may cause is significant in the scheme of things. Otherwise, one of the larger players would already be there. When this is combined with the appearance that the FDA is tightening its rules regarding companies that take drugs to market using this shortened development path, cosibelimab appears to be facing an upfill battle. Cash is also likely to become a major issue for Checkpoint given the size of the trials it wants to run and is running.

Sources: Company Press releases, presentations, website and SEC filings.

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Table 7. Cue Biopharma Inc (NASDAQ: CUE)

Enterprise Value:	AUD523.8M	USD387.4M	**Cash:**	AUD99.5M	USD72.9M	**Market Capitalisation:**	AUD627.7M	USD460.3M

Website: https://www.cuebiopharma.com **Location:** Cambridge, Massachusetts, USA

Technology/Core Competency: Cue is focused on engineering novel injectable biologics that target T-cells in the hopes of developing treatments to cancer, infectious diseases and autoimmune diseases. The compounds it is developing are based on the company's proprietary platform, Immuno-STAT™ (Selective Targeting and Alteration of T cells), which is designed to enhance the body's ability to fight disease without the need for the external manipulation of the T-cells. The aim is to restore the balance that exists within the immune system that allows it to detect aberrant pre-cancerous cells, while not over-reacting and attacking normal tissue. The core of Cue's compounds are rationally designed drugs that focus both on the need for T-cell specificity, as well as their need for activating or inhibiting signals to refine their responses to the molecules they encounter.

Development Programs:

1) **CUE-101: This compound has been designed to selectively and specifically modulate disease-relevant T-cells only.** CUE-101 combines a pair of tumour peptides bound MHC molecules (pMHC) flanked by interleukin-2 (IL-2) variants. The pMHC molecules display antigens to the immune system, which a cell or cells determine the immune system should see. The major role of IL-2 in the body is to help the immune system determine between 'self' and 'non-self-antigens". The IL-2 has been modified, the idea being to achieve the optimal level of response the immune system should mount to the peptide bound to the MHC molecules. The peptide CUE-101 has been loaded with is derived from the human papilloma virus (HPV), which is prevalent in a number of cancers, like HNSCC and cervical cancer. CUE-101 is currently in a phase II trial as a second-line therapy for oropharyngeal squamous cell carcinoma, where it is being used with the standard of care. The study is expected to complete in 2H QY22 (NCT04852328). Cue claims it has seen one objective response in 10 patients, so far, but the patients are also treated with surgery, chemotherapy and radiation therapy, which compounds any attribution of the result to CUE-101. Cue also claimed to have seen partial responses in the dose escalation phase of the study, but why they would not provide hard numbers suggests the responses did not correlate with the CUE-101 dose, but were a result of the other treatments patients received. CUE-101 is also in a first-line phase I trial in combination with pembrolizumab (NCT03978689), where the combination is being looked at in head and neck cancer, HPV-positive oropharyngeal squamous cell carcinoma and HPV-related carcinoma. This phase I study consists of a standard a dose escalation part, followed by an expansion phase. Asian rights to CUE-1010 have been licenced to LG Chem.
2) **CUE-102, CUE-103 & CUE100 series:** These are both preclinical compounds that leverage the same platform as CUE-101. CUE-102 uses peptides from the Wilms tumour protein, which is over-expressed in many cancers. CUE-103 uses proteins from KRAS G12V. KRAS G12V predicts susceptibility to certain targeted drugs and, itself, represents a therapeutic target. CUE also has a number of putative early-stage therapeutics being developed under the banner of the CUE-100 series.
3) **Infectious Diseases – CUE-200 series:** The intention with the CUE-200 series is to leverage the co-stimulatory cell surface receptors CD80 (B7-1) and/or CD137 (4-1BBL). CD80 is expressed on a number of immune cells, but primarily antigen presenting cells (APCs). APCs display proteins to the rest of the immune system and play a central role in coordinating an immune response, if any occurs. CD80 helps the APC determine what it should do based on other signals it is receiving (i.e., co-stimulatory signals). CD137 is a member of the tumour necrosis receptor family, which some immunologists believe to be an immune checkpoint. Putative drug candidates in this series of compound are very early in development (lead selection).
4) **Autoimmune Diseases – CUE-300 series** – Other than candidates that are currently in lead selection, the CUE 300 series consists primarily of CUE-301, which is about half-way into preclinical studies. This compound is aimed at type 1 diabetes and the cells believed to cause the death of the pancreatic cells leading to the disease. The compound consists of two copies of PD-L1 (which, if you will remember, signals T-cells to stand down) and two copies of pMHC loaded with a peptide derived from pro-insulin. The theory here is relatively straightforward. Proinsulin has been recognised as an important target antigen in type I diabetes. Should a T-cell that would normally attack a pancreatic cell come across CUE-301, that T-cell should, in theory, standdown. At the right dose, CUE-301 could prevent the development of type I diabetes. This program is a collaboration with Merck and is, in fact, quite interesting.
5) **Autoimmune Diseases – CUE-401 & CUE-400 series** – Regulatory T-cells are thought to hold particular promise in the treatment of autoimmune diseases, where the body's immune system attacks normal tissues. CUE-401, which is in early preclinical development according to the company, is likely to be a combination of IL-2, mentioned before, and transforming growth factor beta (TGF-β). The theory here is that a combination of IL-2 + TGF-β would increase the maturation rate regulatory T-cells (Tregs). It is hoped that these Tregs would, in turn, dampen the immune system enough to prevent or, at least, have a significant effect on certain autoimmune disease.

Analyst Comments: It is hard to know where to start with Cue Biopharma. There is no question that it is an interesting company and that its science is fairly leading edge. Cue-101 and the other compounds in that series sound like advanced cancer vaccines and we know how the story ends for those. A further issue is that cancers tend to have numerous unique antigens and targeting just one appears to be limiting. CUE-101, the only one in clinical trials, has an interesting design that does seem quite intelligent. However, the sole example it offered up to support a signal of efficacy with CUE-101 was thoroughly unconvincing, coming from one of 10 patients in the expansion phase of a phase I trial. There is also no question that the programs it makes sound so easy are going to be very difficult, and the complexity involved in executing them, enormous. It is hard enough to develop a drug that does one thing. The complexity involved in developing a drug that does two is huge. It shouldn't be forgotten that the programs it is undertaking not only bring two different molecules together, but two different chemical pathways, as well. Of course, these pathways will also involve other pathways and, at the end of the day, the question of whether the science has advanced far enough for these programs to be anything other than very high-risk is open to debate and their stage of development tells us they are high risk, in that respect. Cue may have its day in the sun, but the number of days with cloudy skies that precede it may seem like an eternal blackout. Our view is that it is more likely to be a predecessor of CUE, which has that day in the sun, unfortunately.

Sources: Company Press releases, presentations, website and SEC filings.

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A Truly Undervalued Company

Table 8. Immatics NV (IMTX)

Enterprise Value:	AUD838.9M	USD615.2M	**Cash:**	AUD295.4M	USD216.5M	**Market Capitalisation:**	AUD1.1B	USD831.7M

Website: https://immatics.com/ **Location:** Tuebingen, Germany

Technology/Core Competency: The company is based on developing immunotherapies using two distinct modalities. 1) Adoptive cell transfer (ACT) and 2) antibody-like TCR Bispecifics (TCER®). Neither technology is unique to the company, although aspects may well be. Both technologies focus on solid tumours. ACT involves taking a patient's blood or tumour tissue and amplifying it in a laboratory, after which the greatly increased number of cells are infused back into the patient (sometimes the patient's T-cells are genetically altered, in which case they are referred to as chimeric antigen receptors T-cell (CAR-T) therapy). Immatics does ACT products in phase I trials. The rest of the pipeline is preclinical or earlier, as best we can tell. TCER® is similar to the next logical step many individualised cell therapy companies are endeavouring to take, given the process of making individualised therapies is expensive, even without the manipulation of the T-cells and is generally not easy. That step is to create an off-the-shelf product that is used more like a pharmaceutical than a cell therapy. TCER® combines an antibody specific for T-cells pHLA targeting T-cell receptor, where the p stands for a particular peptide unique to, at least, some cancers. TCER® (which stands for T-cell engaging receptor). When the TCER® links a T-cell to a tumour cell, the tumour cell is destroyed. According to Immatics, laboratory studies have shown that TCER®'s potency and stability is superior to six alterative TCER bispecific formats.

Development Programs:

Immatics keeps its product candidates undisclosed and, while this is unusual for a listed company, it would be helpful when negotiating licences, etc, given the secrecy the larger pharmaceutical companies prefer. It is common knowledge that if a large pharmaceutical company doesn't need to release information for statutory or contractual reasons, it won't. The reason is that the focus of investors is more on the financial performance of such companies, than the development of individual products. Obviously, if the intellectual protection of a large revenue-generating therapeutic for a particular company is about to expire, then investors' focus has a remarkably fast ability to shift to what is in the company's pipeline. Immatics' development programs can be broken down into three groups:

(1) Autologous Adoptive Cell Transfer: Refer to products where the patient's own cells are used. ACTengine refers to a personalised approach in which the patient's own T-cells are genetically modified to express a TCR to one of Immatics' cancer targets and then reinfused back into the patient. ACTengine® IMAO201 (MAGEA4/8) (NCT03247309); ACTengine® IMAO202 (MAGEA1; NCT03441100); and ACTengine® IMAO203 (PRAME; NCT03686124) are in long-running phase I trials that started between December 2018 and May 2019 and have 22, 15 and 42 patients, respectively. So far, the company has reported data on just 10 patients, with nine having stable disease and one having a partial response, leading to an ORR of 10. Like most studies of this nature, patients have been heavily pre-treated, usually making them harder to treat. Some of the data looking at tumour size does look interesting, but that is all you can say. The ACT programs (Target Undisclosed) are in the early stage of preclinical development and are licenced to BMS, while further ACT programs (Target Undisclosed) are in the early stages of preclinical development and licenced to GSK.

(2) Allogeneic ACTallo IMA301 (Target Undisclosed): is another proprietary therapy in the early stages of preclinical development. It involves TCR-engineered gamma delta T-cells from healthy donors, which Immatics intends to produce as an off-the-shelf product.

(3) TCER® Bispecifics: TCER® IMA401 (MAGE4/8) and TCER® IMA402 (PRAME) are both proprietary cell therapies in the early stages of preclinical development. Bispecific programs (Undisclosed) are early preclinical stage programs licenced to Amgen, while the same is true is of another set of bispecific programs licenced to GenMab.

Notes: Where the antigen is disclosed: MAGEA = melanoma-associated antigen; PRAME = Preferentially-expressed Antigen in Melanoma. Where further information is given: MAGEA refers to the MAGEA gene, which is found at chromosomal position Xq28. The numbers thereafter refer to particular variations, some which may be disease causing, found at the position designated by the number after the term MAGEA numbers / (e.g., /8) refer to a specific abnormality, if known. While the MAGEA gene was discovered in a melanoma patient, its expression is also well documented in cutaneous and ocular carcinomas and it represents a therapeutic target. Certainly, having partners like BMS, GSK, Amgen and GenMab serves to underscore the nature of its technology, but, just as importantly, how crucial many companies think it could be to be in on the ground floor if cell technology does become a dominant force, particularly in cancer treatment.

Analyst Comments:

Immatics is heading into various areas of cell therapy, which it probably needs to do. One list (Hildreth C - BioInformant - 30 August, 2021) noted 111 CAR-T companies worldwide, without even touching on companies focusing on the technically easier general adoptive cell transfer techniques or the numerous companies looking for off-the-shelf solutions. While CAR-T is certainly the high-profile game in town, there are plenty of others that recognise the limitations of CAR-T and are playing games easier than CAR-T or looking for solutions that are better than CAR-T. Many of the CAR-T players are looking for better solutions. Competition is a major challenge for all of the players in all of the T-cell therapy spaces. We only have a small amount of data with which to judge Immatics ACT IMAO201, 0202 and 0203. Collectively, 10 patients have been reported, nine with stable disease and one with a partial response, giving an ORR of 10%. Strictly speaking, patients with stable disease are not supposed to be taken as an indication of a therapy's activity because cancer doesn't progress in a straight line and can often stay static for quite a while. One thing that did become clear is that these three therapies really are Immatics second go at things, having had five ACT therapies in the clinic before that all failed, from 2009 to 2019. IMA901 progressed to a 339-patient trial in renal cell carcinoma that failed in July 2015. The new therapies are intended to be an advance on the original ones. In a deal that now rests with BMS after BMS acquired Celgene, Immatics received USD75million upfront, but other than that all we know is that Immatics may be eligible for future opt-in rights, milestones and a royalty in a deal done in August 2019. BMS obtained the rights to three of Immatics' ACT programs in that deal. In the February 2020 GSK deal, Immatics received USD50 million upfront for two of its ACT programs. If the deal follows historical Immatics deals, potential milestones of USD550m are linked to each therapeutic, as well as a tiered royalty on sales up to double digits. In July 2018, Immatics received USD54 million upfront from Genmab A/S. The number of bispecific programs was not released, but it is more than one and the following applies to each: USD550M in potential development, regulatory and commercial milestones. The royalty rate we have hypothesized for GSK would apply here, too. Finally, in January 2017, Immatics received USD30M upfront from Amgen Inc in exchange for bispecific immunotherapies targeting multiple cancers. Each bispecific is eligible for over USD500M in development, regulatory and commercial milestones and tiered royalties up to a double-digit percentage of net sales. Of course, there are lots of unknowns with these deals in respect of specific milestones and how the royalties actually tier. There are many ways to make licencing deals look better than they actually are. The upfronts, however, are real money, easy to add up and while they are not huge, we are talking about very speculative early-stage programs. In certain cases, we don't know how many programs were actually licenced. Most importantly, though, all of these programs were early pre-clinical when they were licensed. If you take generally accepted industry figures, at best you are probably talking about a 5% chance of making it to market, while, at best, 10% would probably apply to programs that make it into the clinic. The point being all of those milestones and royalties need to be very heavily discounted. After the GSK deal, Immatics has stated that it will be concentrating on its internal programs and will not be doing any more deals of this nature. One of the issues we have with technology of this nature, with the exception of the autologous adoptive cell transfer products, is that at most, they can target two epitopes (particular spots) on one antigen, largely for safety reasons. CAR-T studies have shown that while responses may be durable, follow-up indicates a common mechanism leading to resistance, which is a change in the antigen the therapy targets (Sterner & Sterner (2021) Blood Cancer J). This would be expected to occur with therapies that are limited in the breadth of epitopes and antigens they recognise.

Sources: Company Press releases, presentations, website and SEC filings

Table 9. Zymeworks (NYSE: ZYME)

Enterprise Value:	AUD1.3B	USD928.0M	**Cash:**	AUD643.9M	USD472.0M	**Market Capitalisation:**	AUD1.9B	USD1.4B

Website: https://www.zymeworks.com/ **Location:** Vancouver, British Columbia, Canada

Technology/Core Competency: Zymeworks is not all that different to Cue Biopharma, with the exception that some of its programs are more advanced. It is focused on drugs that have multiple mechanisms of action. The company uses a range of therapeutic platforms to develop compounds, many being outlicenced, while others remain in house. The platforms it uses are:

1) **AZYMETRIC™**: More of a slogan than a technology, it refers to creating multifunctional therapeutics that enable enhanced efficacy and new biological approaches for treating diseases.
2) **ZYMELINK™**: A proprietary library of cytotoxins (cell-killing compounds), stable linkers (which enable two molecules to be easily bound together) and conjugation technologies (methods of linking proteins to non-protein substances).
3) **EFFECT™**: A deep understanding of the Fc region of antibodies (the tail) and ways to alter them to tailor their biological effects.
4) **PROTECT™**: A single, transferable, conditionally-active design, making it possible to develop new compounds quickly.

Development Programs:

The company has a past of outlicencing drugs, zanidatamab and ZW49 appear to be its first compounds kept for real in-house development.

(1) Zanidatamab (ZW25): This compound is a HER2 x HER2 bispecific antibody that binds HER2 on two different sites of the molecule. Herceptin® (trastuzumab, Roche) was a blockbuster drug for breast cancer that also bound HER2, but only on one site. By creating a drug that binds HER2 on two different sites, the chances of resistance developing to the drug are dramatically reduced. The occurrence of resistance-causing mutations is fairly rare, but, because there are a large number of cells in a cancer, they appear to occur quite frequently, because you only need one cell to develop the mutations. With zanidatamab you need two of these rare mutations to occur in the one cell, because even if one resistance-causing mutation occurs, zanidatamab should address the tumour cell through the site that has not mutated. This drug is being developed for biliary tract cancer for which it has FDA Breakthrough Therapy Designation, HER+ gastroesophageal adenocarcinoma, HER2+ breast cancer and solid tumours expressing HER2. There drug provides a clear signal of efficacy, as would be expected of a breakthrough therapy designation drug. Zanidatamab is currently in a pivotal trial for biliary tract cancer (NCT04466891), phase II trials for gastroesophageal adenocarcinoma (NCT03929666) and HER2+ breast cancer (NCT04224272) and a phase I trial for solid tumours (NCT02892123). BeiGene Ltd (NASDAQ: BGNE) has commercial rights to zanidatamab in Asia, ex-Japan. The company is also due to start a phase II trial in colorectal cancer sometime during Q4 CY21, although a ClinicalTrials.gov entry has not yet been made.

(2) ZW49: This is another HER2 x HER2 bispecific antibody, but it is also linked to cytotoxin (auristatin) attached to ZW49 by a cleavable linker. The cytotoxin is freed from ZW49 within the tumour cell by an internal cellular enzyme. ZW49 is currently in your typical phase I (n = 174; NCT03821233) dose escalation and expansion study, the general design of which we have described many times before. This study began in April 2019 and the estimated primary completion date for the study is August 2023, while the estimated study completion date is August 2025. This program is also partnered with BeiGene.

(3) Preclinical and Advanced Discovery Programs: Zymeworks has bispecific antibody drug conjugates, T-cell engaging bispecific antibodies and tumour microenvironment modulators at these stages of development for solid tumours.

(4) Current Partnerships: Zymeworks has excelled in inking partnerships with a number of larger pharmaceutical companies, including Merck, Eli Lilly, BMS, GSK, Daichi Sankyo and Johnson & Johnson.

Analyst Comments: Zymeworks is a poster child for the classic mistake many small drug development companies make: licencing their compounds too early. In doing so, they often relinquish significant stakes in compounds that may have huge risk-adjusted upsides. These huge upsides can be hard to see through a haze of clinical trials, manufacturing issues and regulatory applications and regulatory decisions, particularly for a company that has traditionally operated some distance from those types of events. Zymeworks has many licensing deals, which can be difficult to assess because large portions of them are commercial-in-confidence, making valuing them difficult. But, consider this: for two thirds of its deals, it will receive a royalty of less than 10%. In almost half of them, that royalty is in the low single digits. The lesson here should be clear. The real question for Zymeworks going forward is, “How well will zanidatamab and ZW49 do?” Both appear to have clear clinical activity. If this were 1998, the answer is they would likely fly through to an approval since they target the same molecule as trastuzumab (Herceptin®, Genentech, Inc), but in a superior fashion. The issue is, it is 2021 and there are now, at least, 10 drugs approved for Her2+ breast cancer, which is by far the biggest of the HER2+ tumours. There are also close to another 20 HER2+ targeting drugs in clinical trials, including three checkpoint inhibitors. Zanidatamab and ZW49 stand a good chance of making it to market. The real question is, “For which HER2+ cancers and where in the treatment regimen they land?”

Sources: Company Press releases, presentations, website and SEC filings.

Table 10. Trillium Therapeutics (NYSE: TRIL)

Enterprise Value:	AUD2.2B	USD1.6B	**Cash:**	AUD436.0M	USD273.7M	**Market Capitalisation:**	AUD2.6B	USD1.9B

Website: https://trilliumtherapeutics.com/ **Location:** Mississauga, Ontario, Canada

Technology/Core Competency: Trillium's focus is on addressing the treatment of cancer using both arms of the immune system, the innate arm and the adaptive arm. Most companies focus on the adaptive arm of the immune system, which, as its name implies, adapts to the threats it believes the body faces. The innate arm of the immune system is more of a first-line of defence. It doesn't really adapt. It has simply evolved through natural selection to be ready to meet challenges, as and when they arise. The company focuses on a transmembrane protein (i.e., it has parts outside of the cell and parts within it) called CD47, which is also known as an integrin associated protein. In layman's terms, CD47 is signal to the immune system from the cell that APCs, in particular, should not attack it. In reality, however, it is involved in a lot more cellular processes than that. One key interaction that CD47 is involved in is with another transmembrane protein called SIRPα (signal regulatory protein alpha), which is found on other cells of the immune system. Interaction of these two proteins on different cells can stop one cell from eating the other, causing the two cells two fuse and/or T-cell activation.

Development Programs:

Trillium has the following two main developmental candidates (although they are all aimed at a number of diseases):

1) **TTI-622:** This compound consists of two main parts. The first is the section of SIRPα that binds to CD47. The second is the Fc region of IgG4. This is notable because most compounds constructed in this way use the Fc region of IgG1. Trillium has decided to use the Fc region of IgG4, because the Fc regions of bound antibodies give off an 'eat me' signal to cells of the immune system, which is believed to be lower with the Fc region IgG4. Consequently, Trillium believes that using the region it has chosen will lead to higher and more TT-622 remaining in the patient and blockade of CD47 for longer. It should be noted that red blood cells have CD47 on their surfaces, but TTI-622 has been shown not to bind to it appreciably. This is a significant advantage over many other CD47-targeting drugs. TTI-622 is currently in a 150 patient, non-randomised, sequentially assigned, open label phase I study in certain haematological malignancies. Like just about all phase I studies, it has two parts, a dose escalation part to find the recommended phase II dose, which is then followed by an expansion phase at that dose. The study is being undertaken in lymphoma, multiple myeloma and acute myeloid leukaemia patients. Each of these diseases will be treated separately, such that there will be three dose escalation "sub-studies", followed by three expansions studies. The ClinicalTrials.gov entry for the study can be found here: NCT03530683. Not all of the subjects in the trial will be given the same drugs. In addition to TTI-662, patients will be treated with drugs that are considered to be the standard of care for the particular disease they have. The ORR in this study is a healthy 33%, including some sub-optimally treated patients. Trillium also plans on conducting one or more phase Ib/II studies in solid tumours. It is possible that these trials may be combined. One of these trials will be in ovarian cancer patients. The second will be in a solid tumour, which has yet to be chosen. The ovarian cancer trial is slated to start in Q4 CY21, while the second trial is slated to start in 2H CY22. Additionally, the Mayo Clinic intends to commence a Phase Ib/II, combining study TTI-622 with a PD-1 inhibitor sometime before the middle of 2022.
2) **TTI-621**: TTI-622 appears to have overtaken TTI-621 as a Trillium lead compound. The only difference between the two compounds is that the Fc region of IgG1 that was used in this compound was swapped out for the Fc region of IgG4 in TT-622. TTI-622 is currently in two clinical trials. The ClinicalTrials.gov entry first and oldest of these trials (it began in 2016) can be found here: NCT02663518. This is a n=260 patient phase I trial with the usual trial design and is being undertaken in solid tumour patients. In this study, TTI-621 is being tested as a monotherapy, in combination with Rituxan, a drug used to treat certain types of cancer as well as certain types of autoimmune diseases, and nivolumab. This trial is due for completion in December 2021. So far, it has recorded an ORR of 18-29% across indications. A second trial of TTI-621 commenced in leiomyosarcoma, a rare cancer that grows in smooth muscle, in June 2021. This n = 80 phase I study, again, consists of the usual two parts. The estimated primary completion date for the study is June 2023, while the estimated study completion date is July 2024. Interestingly enough, it was a study of TT-621 in which the compound was injected directly into solid tumours that started the company's share price moving northwards, moving from the USD3.50 to USD4.00 level up to its current level of ~USD17.50.

Analyst Comments: It has taken Trillium a long time to hit is straps. The company has seen the failure of several device studies, although its biggest failure was the discontinuation of a clinical trial of a compound known as TTI-1612 on 13 June 2013. Trillium's share price hit a high of USD28.73 on 16 April 2015 before it began its first clinical trial with TTI-621. As noted, TTI-621 had some problems given off by the Fc portion of the antibody it was anchored to. This caused the company to develop TTI-622 using the Fc portion of a different antibody. While some of the results with TTI-621 have been impressive and the company has said it will move both candidates forward, it looks like TTI-622 will be its main focus. **Some of the results with TTI-621 got the share price rolling northwards, but it has been TTI-622 that has maintained the gains and, ultimately, led Pfizer to bid USD23b, which the company has accepted.**

Sources: Company Press releases, presentations, website and SEC filings.

Table 11. Nektar Therapeutics (NYSE: NKTR)

Enterprise Value:	AUD3.2B	USD2.3B	**Cash:**	AUD1.4B	USD1.1B	**Market Capitalisation:**	AUD4.6B	USD3.4B

Website: https://www.nektar.com/ **Location:** San Francisco, California, USA

Technology/Core Competency: Nektar believes its core competency lies in its understanding of the immune system and the pathways with in it. We do not disagree. It must also have some knowledge of chemistry or be able to access it, although some of its developmental compounds tend toward the relatively simplistic, based on available information. It may be more advanced than we know, since we haven't seen the actual structure of some of their compounds.

Development Programs:

Nektar has a few programs, but the main one is a compound called bempegaldesleukin, which we covered in our CCR:

1) **Bempegaldesleukin (BPD)**: BPD (formerly, NKTR-214) has been returning some good trial results in combination with PD-1 inhibitors. BPD targets CD122, which is the Interleukin-2 receptor (IL-2R) subunit beta. Interleukin-2 (IL-2) on its own was approved for renal cancer in 1992 but proved to have a (1) poor blood half-life and (2) systemic toxicity issues, which limited its use. Nektar got around those issues by using pegylation, where releasable polyethylene glycol chains are conjugated to the BPD core. When this is done, the BPD is released more slowly into the blood stream. Nektar claims that BPD stimulates and expands cytotoxic T-cells and natural killer cells, without having the normal effect of IL-2 on expanding regulatory T-cells, particularly in the tumour microenvironment, where regulatory T-cells work to thwart the immune system's attack on a tumour. A review has stated that BPD increases tumour-infiltrating lymphocytes, T-cell clonality and PD-1 expression (Gellrich et al (2020) J Clin Med). BPD was granted FDA Breakthrough Therapy Designation after it combined with nivolumab to produce a 53% ORR and a 34%CR in a phase I/II trial of melanoma (Gellrich et al (2020) J Clin Med). BPD is in a strong list of clinical trials, tabled below. The list should be taken lightly, as there have been some controversies regarding BPD and, while solid, the list of trials is not what you would expect. Both of the issues will be tackled in the analyst comment section and main section of the report.

Combining Agent	Partner	Indication	Phase	ClinicalTrials.gov Identifier	Estimated Primary Completion Date
1. Nivolumab	BMS	First-Line Metastatic Melanoma	III	NCT03635983	April, 2022
2. Nivolumab	BMS	First-Line Renal Cell Carcinoma	III	NCT03729245	December, 2021
3. Nivolumab	BMS	Muscle Invasive Bladder Cancer – Ineligible Cisplatin	III	NCT04209114	August, 2023
4. Nivolumab	BMS	Adjuvant Melanoma	III	NCT04410445	July, 2027
5. Nivolumab	BMS	First-Line Cisplatin Ineligible Locally Advanced or Metastatic Urothelial Cancer	II	NCT03785925	April, 2022
6. Nivolumab + TKI	BMS	First-Line Advanced Renal Cell Carcinoma	I/II	NCT04540705	October 2024
7. Pembrolizumab	Merck	First-Line Metastatic or Recurrent Head and Neck Carcinoma	II/III	NCT04969861	August, 2025
8. Pembrolizumab	None	First-Line Metastatic Lung Cancer	I/II	NCT03138889	September, 2023
9. VB10.NEO	Vaccibody AS	Locally Advanced or Metastatic Solid Tumours	I/II	NCT03548467	March, 2024
10. NKTR-262	None	Range of Solid Tumours	I/II	NCT03435640	September, 2021

In trial 6, the TKI is a tyrosine kinase inhibitor (either axitinib (Inlyta®, Pfizer Inc) or cabozantinib (generic)). TKI expression is often disordered in tumour cells. In trial 9, VB10.NEO is a cancer vaccine being developed by Vaccibody A/S based on a patient's neoepitopes (parts of an antigen unique to a particular patient). In trial 10, NKTR-262 is a toll-like receptor (TLR) agonist active towards TLRs7&8. The activation of TLR's generally increases an immune response.

2) **NKTR-255**: This molecule is claimed to be an agonist of the IL-15 (interleukin-15) receptor. Its main function is to induce the proliferation of natural killer cells, which can have an anti-tumour effect. It may also increase the proliferation and survival of memory cytotoxic T-cells. Nektar says that NKTR-255 has been designed to overcome the fast clearance associated with natural IL-15. It is currently being studied in two clinical trials. One (NCT04136756) is a 118-patient dose escalation and expansion trial, where NKTR-255 is being looked at in multiple myeloma, non-Hodgkin lymphoma and indolent non-Hodgkin lymphoma. The dose escalation portion of the study will involve NKTR-255 only. Patients in the expansion cohorts will receive NKTR-255 plus either daratumumab (DARZALEX FASPRO®, Janssen Biotech) or rituximab (Rituxan®, Genentech, Inc). The former targets CD38 (cyclic ADP ribose hydrolase), which is thought to kill cells expressing CD38 by multiple mechanisms, including ADCC and antibody-dependent cellular phagocytosis. Rituximab also acts via the same mechanisms to cause cell death but, as noted, through a different receptor. In the second trial, NKTR-255 is being combined with cetuximab (ERBITUX®, Eli Lilly). The estimated primary completion date for this study is June 2022 The ClinicalTrials.gov entry for that trial is NCT04616196. This study is a 78-patient phase I/II dose escalation and expansion study. Patients will receive both NKTR-255 and cetuximab during both the dose escalation and expansion parts of the study. Cetuximab is a cytostatic drug that acts by inhibiting the epidermal growth factor receptor, which some cancers rely on the stimulation of to grow. The hope here is that NKTR-255 will decrease the tumour burden, killing off the colorectal cancer cells or HNSCC tumour cells of the patients. The estimated primary completion date is April 2022.

3) **NKTR-358**: Like many companies operating in the immunotherapy space, Nektar also has an interest in autoimmune diseases and that is why NKTR-358 exists. In fact, NKTR-358 is essentially the opposite of BPD. Like BPD, NKTR-358 also uses pegylation and it also targets the IL-2 receptor (interleukin-2). NKTR-358, however, is structured in such a way that when it interacts with the IL-2R, rather than stimulating cytotoxic T-cells and natural killer cells, it stimulates the production of regulatory T-cells, whose role is to suppress immune responses largely to prevent autoimmune reactions. It is, however, unclear exactly how NKTR-358 achieves this, nor have we been able to easily find a hypothesis behind the way it works. NKTR-358 is partnered with Eli Lilly and is currently in four monotherapy trials. NCT04433585 is a 280-patient, phase II, randomised, double blind, placebo-controlled trial of NKTR-358 in

patients with systemic lupus erythematosus, which is an autoimmune condition where the immune system attacks healthy tissues in many parts of the body. NCT04677179 is a 200-patient, adaptive design, phase II, randomised, double blind trial in patients with ulcerative colitis. Ulcerative colitis is a disease that causes severe ulcers in the colon and rectum. A large number of patients with the disease will ultimately have their bowel removed. The estimated primary completion date is November 2023. NCT04119557 is a 30-patient, phase Ib, randomised, placebo-controlled, multidose trial in patients with psoriasis. The main purpose of this study is to learn more about the safety and side-effects of NKTR-358 when given by injection just under the skin. NCT04081350 is a phase Ib, randomised, double-blind, placebo-controlled, multidose trial in patients with atopic dermatitis. Its aims are largely the same as those of the psoriasis study, mainly to gain multidose safety and side effect data.

4) **Bempegaldesleukin (BPD)**: Many companies have compounds that may be of some help in COVID-19 and Nektar is no different. BPD is in one study for the condition and that is NCT04646044. The trial is a 30-patient, randomised, double-blind study in patients with mild COVID-19. The study is comparing BPD + standard of care, to standard of care alone. While the study concluded in May 2021, no results have been released.

Analyst Comments: Nektar is doing a fair bit of trialling and that is what you would expect of a company with more USD1B in cash (Nektar has sold the rights to the revenue-producing drugs it owns for USD150M). **Clearly BPD is the big one and BMS paid a lot to get a share of it in November 2018**. It paid USD850B upfront, USB1.78B in milestones (USD1.4 developmental, 0.25 on sales), with a global profit split going 65% Nektar's way to 35% BMS. In return, BMS obtained exclusive rights in 20 indications across nine tumours included in the joint clinical development plan for a specified time period. Where things are at in terms of the tumours and indications is unknown. Ten trials have been, or are being, undertaken with BPD + nivolumab, which is not even close to what you would expect to see if BMS has used all of its options. When you scan Nektar's BPD pipeline, you see more interesting things. Nektar has no partner for its phase I/II trial in NSCLC. Nektar and BMS are at the end of a 557-patient phase I/II trial, which started in 2016 and included NSCLC and five other cancers (NCT02983045). Melanoma, renal cell carcinoma and urothelial cancer made the cut. NSCLC, metastatic breast cancer and colorectal did not. The study that includes NSCLC patients Nektar has listed in its pipeline and combines BPD with pembrolizumab, began in 2017 before Nektar's agreement with BMS and, while BMS may not have been allowed a deep dive into the study data, it would have had the chance to see the topline results, at least, and they did not change BMS' mind (NCT03138889) As far the phase II/III in HNSCC is concerned, Merck is a partner of sorts. It is supplying drug product for the trial, as Merck and many other companies often do to learn more about their drugs at a limited cost. Moreover, Nektar is not standing like steel behind this trial. It has laid off some of the risk to SFJ Pharmaceuticals, who will run the trial and have sole responsibility for regulatory interactions and filings. SFJ will also pay up to USD150M of the trial's cost. Similarly, a phase I/II trial, including HNSCC patients using BPD + nivolumab is close to complete (NCT03435640). There are seven cancers in that study and BMS has already moved on strongly with melanoma and renal cell carcinoma. Considering the open-label nature of the trial that began in 2018, it seems time has run out for the other five cancers in the study. It appears obvious that BMS is not interested in BPD for either HNSCC or NSCLC. The following information regarding market sizes comes from Trefis, 20 March 2020 . The issue for Nektar and BMS is that NSCLC is the #1 indication in the PD-1/L1 inhibitor market and HNSCC equal #6. Moreover, BMS appears to have passed on BPD for breast cancer, which is #3. BMS doesn't appear to even be considering BPD for bladder cancer which is #2, prostate cancer which is #4, nor cervical and gastric cancers, which are equal #5. The bright spot for BPD is that renal cancer is the #2 indication. There have also been a couple of issues regarding Nektar's behaviour, discussed in our valuation section. Whatever the case, it looks unlikely that BMS will use BPD in the nine tumours and 20 indications it has a right to, particularly given renal cell carcinoma + TKI is the only study earlier than phase II that Nektar and BMS are collaborating on. **NKTR-255** is a little hard to get a read on. Nektar **does not** appear to have a formal licensing agreement with Janssen as its pipeline table would indicate. Instead, this appears to be a pure preclinical and clinical collaboration. This does not appear to be a straight case of Janssen hoping to establish an advantage over rituximab with daratumumab, given it is studying both drugs in combination with NKTR-255. The trial with cetuximab in colorectal cancer and HNSCC is set to finish a couple of months before the trial with daratumumab. Biosimilar (generic biologic) versions of rituximab have been developed, which would give Janssen the green light to pair rituximab with NKTR-255. Either way, the study looks to be aimed at finding a treatment that can improve on daratumumab, which already has FDA approvals for the three indications the study is looking at. Clinical data is required here to get a solid handle on what NKTR-255 might be worth. **NKTR-358** is partnered with Eli Lilly, who paid USD150M upfront, and promised USD250 million in development and regulatory milestones in 2017. Phase II development costs are split 75%:25%, with Eli Lilly paying most and Nektar has the right to participate in phase III development on an indication-by-indication basis. Nektar will receive a royalty rate that could be double digit (read teens) and commensurate with its participation in any phase II trials and to what level it participates. It is also interesting to note that, where it can, Nektar will hedge its bets or lay off risk, which does not necessarily say a lot for a commitment to a compound. Much of the following has come from Satyanarayana M (2021) c&en. IL-2 is hot, both in terms of cancer and in autoimmune diseases. While Eli Lilly may have paid a bit to get a good slice of NKTR-358, Merck shelled out USD1.85B to buy Pandion Therapeutics in February 2021, primarily to secure PT101, an IL-2 mutein (protein with an altered amino acid sequence) fused to a protein backbone. It was apparently designed to selectively activate and expand regulatory T-cells. Looking at that USD1.85B figure, it must be recognised that PT101 was not even half way through its first full phase I trial, yet it seems to have completed a significant part of it, according to a Merck announcement regarding the acquisition (Merck Buys Pandion, 25 February 2021). There have also been, at least, six IL-2-focused IPOs since 2018, although not all of these are autoimmune focused. Neither the list of IPOs, development deals or acquisitions is intended to be exhaustive. While these deals have values, interpreting those values may be difficult. With the number of compounds being trialled in COVID-19, most of them must be long shots and, given Nektar does not talk about its program much, that is where you would have to place the BPD COVID-19 effort.

Sources: Company Press releases, presentations, website and SEC filings.

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