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Bioshares

Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies

17 September 2018

Special Report: Amplia Therapeutics

Amplia Therapeutics (ATX)

Key Financials

Share price: $0.385
Shares on issue: 41.023 M
Options on issue: 4.2395 M
Market capitalisation: $15.8 M
12 month price range:
$0.25 - $0.47

Board and Management

Robert Peach – Director
Simon Wilkinson – CEO & MD
Christian Behrenbruch – Director
Warwick Tong – Chairman
Chris Burns – Director
Andrew Cooke – Director & Co Sec

Jeff Carter – CFO

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TAYLOR COLLISON

Investment Report: Amplia Therapeutics (ASX: ATX)

Bioshares recommendation: **Speculative Buy Class B**

The Preparation of this Report

The preparation of this report has been based on dialogue with company management, which provided corrections and clarifications through the drafting process.

Executive Summary

- In May 2018, Innate Immunotherapeutics acquired Amplia, to access two drug assets, AMP945 and AMP886. These two compounds inhibit FAK (Focal Adhesion Kinase), a kinase involved with cell adhesion processes and which has been found to have an immuno-suppressive role in fibrotic cancers, especially pancreatic cancer, as well as a role in fibrotic diseases.

- Amplia has been granted two families of compositions of matter patents in most major markets separately protecting AMP945 and AMP886 with patent terms extending to 2032.

- Pancreatic cancer has climbed in the ranks as a cause of death. According to the American Cancer Society's Cancer Facts and Figures 2017, pancreatic cancer is now estimated to be the third leading cause of cancer-related deaths in the USA, being responsible for an estimated 43,000 or 7.2% of cancer related deaths in 2017, with an estimated new number of cases of 53,700 in the same year.

- The American Cancer Society estimated the overall five-year survival rates for pancreatic cancer (all stages) stands at 7%. This figure when compared to those for prostate cancer (97%), breast cancer (80%), kidney and renal pelvis (73%), urinary bladder (64%), and colorectum cancer (58%), but also cancers of the liver and intra-hepatic bile duct (13%), lung and bronchus (15%), and esophagus (12%), shows that there is a major unmet need for finding better treatments for pancreatic cancer.

- Median overall survival gains for approved drugs for treating pancreatic cancer range from 5.6 months (gemcitabine), 6.2 months (erlotinib and gemcitabine), 6.7 months (gemcitabine and 5FU), 8.5 months (nab-paclitaxel), and 11.1 months (FOLFIRINOX). While FOLFIRINOX has achieved the greatest overall survival gain, its safety profile is less favourable and causes a significant deterioration in quality of life.

- Researchers (Jiang et al) have shown that samples of pancreatic tumours from 50 patients were found to have very high levels of FAK, being upregulated in over 80% of pancreatic tumours compared to normal pancreatic tissue. The tumours were also found to be highly fibrotic and had poor levels of T-cell infiltration into the tumours.

- FAK inhibitors as monotherapies have shown limited therapeutic effect. The Jiang paper in 2015 described a beneficial effect from combining checkpoint inhibitors with FAK inhibitors in preclinical work, making pancreatic tumours more responsive to treatment. Most studies now underway are combining FAK inhibitors with checkpoint inhibitors and is the approach Amplia will be following.

- The leading company with FAK inhibitors in development is Verastem (Nasdaq: VSTM), which has four clinical studies underway in pancreatic and ovarian cancer. Amplia's lead compound, AMP945, is a more potent inhibitor of FAK than Verastem's lead, based on preclinical data. Both AMP945 and Verastem's lead have high specificity for FAK, suggesting low off-target binding and therefore the prospect of a good side effect profile.

- Amplia has a highly experienced management team and board in place with which to commercialise its oncology drug development assets.

- The short-term value creation path for the company is to move one of these compounds, AMP945, into a Phase I study in healthy volunteers in 2H 2019. Preclinical drug developers listed on the ASX with programs in oncology and fibrosis have a market value of between $23 million - $40 million. Amplia's market capitalisation is $16 million.

Investment Summary

The Amplia investment proposition is built on five features. These are: first, the high level of unmet need in pancreatic cancer; second, the demand from large pharmaceutical companies for competitive, quality drug assets; third, compounds that are potentially superior to competing compounds; fourth, potential treatment gains that could be achieved from the combination of Amplia's compounds with checkpoint inhibitors; and finally, the potential for the company to leverage data from its Phase I safety study of AMP945 – planned for 2019 – into a commercial transaction (partnering deal).

1. Significant Unmet Need/Lack of Effective Therapeutics for Pancreatic Cancer

Pancreatic cancer has grown in significance as a cause of death, being responsible in the USA for 7.2% of cancer related deaths in 2017, with an estimated annual new number of cases of 53,700.

Current standard-of-care treatments have very poor outcomes especially for patients diagnosed with mid and late stage disease. While this highlights a difficult disease area, it also sets a low bar for new therapeutic options with potentially an accelerated path to market.

2. Demand for Competitive, Quality Drug Assets

Returns to investors in Amplia will depend on the demand for quality drug assets from larger pharmaceutical companies. Amplia's AMP945 has the hallmarks of a competitive, quality drug asset.

These include: positive preclinical toxicology data so far (with further animal toxicology work to be completed); a mechanism of action which has novelty and which has been explored, albeit unsuccessfully as a monotherapy by only a few other companies; high affinity and selectivity for its target; an acceptable manufacturing profile, including scalability; and patents with at least 14 years of exclusivity with the potential for patent extension.

3. Improved Target Affinity Compared to Competition

In particular, one trial result expected in December this year that has the potential to positively influence the value of Amplia's assets, is Verastem's combination study of VS-6063 with the checkpoint inhibitor (PD-L1) drug avelumab.

Even though the trial is being conducted in ovarian cancer, any data suggestive of a synergistic performance has the potential to translate to an increase in the value of Amplia's assets, given both companies are working on the same (FAK) target.

It should be noted that to date VS-6063 has displayed a favourable side effect profile, being well tolerated, and delivered no serious adverse events or dose-limiting toxicity in multiple trials.

That AMP945 has shown to have a better target affinity and similar specificity to VS-6063 supports the outcome of a potentially improved efficacy and safety profile in clinical studies with AMP945, offering a 'best-in-class' not 'first-in-class' strategy.

4. Synergistic Outcome Expected from Combination with Checkpoint Inhibitors

There are 90 industry-sponsored pancreatic cancer trials underway at present. The world's top pharmaceutical companies which specialise in oncology are conducting studies (13) to explore how new immune modulating drugs might be used in combination with other drugs to make better therapies for pancreatic cancer. Immune modulating drugs seek to unlock immune-suppression mechanisms.

Amplia's lead FAK candidate has the potential to work synergistically with immune modulating therapies and chemotherapies, and therefore deliver superior treatment outcomes

(elimination of or reduction in tumours, elimination of metastases, increased survival, better quality of treatment, fewer and reduced side effects).

These studies are medical and commercial signals of the significance of the area for large pharmaceutical companies such as Novartis, Roche, AstraZeneca, Eli Lilly, Merck and Bristol-Myers Squibb. An implication is that these companies are obvious candidates for licensing AMP945, and/or acquiring the company's pipeline.

As data from these studies read out and if signals emerge in favour of immune-modulating therapies, then these data will directly benefit Amplia's oncology program because of the potential for Amplia's FAK inhibitors to make further gains in treatment outcomes.

5. Leveraging Positive Safety Data from Phase I Trial of AMP945 for a Drug Development Deal

The completion of a Phase I safety trial and the delivery of positive safety data for AMP945 would enable partnering discussions for the molecule, with a likely focus on companies with a portfolio interest in both oncology and fibrosis.

The benefit of the Phase I study is that in addition to generating essential safety data about AMP945, the study would also yield information on target engagement.

Tissue samples taken from healthy volunteers using a skin punch biopsy, could be tested to determine if AMP945 was modulating its intended target, the intracellular protein, Focal Adhesion Kinase (FAK), by using a phosphorylation assay. A phosphorylation assay measures the impact of a compound (or antibody) on intra-cellular signalling processes. The dose-related effects could potentially be explored using phosphorylation assays.

Background

Innate Immunotherapeutics (ASX: IIL), now Amplia Therapeutics (ASX:ATX), listed on the ASX in December 2013 to commercialise a novel therapy for the treatment of a severe form of multiple sclerosis (secondary progressive MS). The company conducted a 93 patient, Phase IIb study in Australia and New Zealand with its lead compound, MIS416.

While that compound had shown promising results in earlier studies and in a compassionate use program, the Phase IIb study failed to meet its primary endpoints. The therapy originated in New Zealand. The company has ended all MS programs with this therapy.

In March 2018, Innate announced it would access new drug development assets through the acquisition of a private Australian biotech, Amplia Therapeutics. In an all scrip deal, that transaction was completed in May 2018 and in late August it was agreed that the Company's name would change to Amplia Therapeutics.

The original Amplia shareholders included Christian Behrenbruch (CEO of Telix Pharmaceuticals, director of Factor Therapeutics), Christopher Burns (formerly research director at Cytopia Ltd), Mark Devlin, Mark Sullivan and Warwick Tong (former CEO of Cancer CRC in Victoria).

It also included the following research institutes and organisations that played a role in the development of the Amplia assets: Cancer Research Technology Limited in the UK (from where the technology was licensed), Cancer Therapeutics CRC Pty Ltd and CTxT Pty Ltd in Melbourne (where the technology was initially developed).

Prior to the acquisition by Innate, Amplia also made shares available to Edinburgh based Professors Margaret Frame and Neil Garragher, key thought leaders in FAK research and clinical development of FAK inhibitors.

Under the terms of the transaction, Innate shareholders were diluted to 55% with Amplia shareholders acquiring 45% of Innate stock in consideration for sale of the Amplia business and its assets to Innate.

10 for 1 Share Consolidation

In May 2018, Innate shares were consolidated on a 10 for 1 basis.

Board Changes

Around the time of the acquisition, Innate made significant changes to its board. Four of the company's directors resigned – Christopher Collins, Elizabeth Hopkins, Andrew Sneddon and Michael Quinn.

New directors added were Christian Behrenbruch, Chris Burns, Warwick Tong and Andrew Cooke (formerly Company Secretary of Innate).

The CEO of Innate, Simon Wilkinson, has remained as CEO and Managing Director. Existing board member Robert Peach, has also remained on the board.

New Business Plan for Amplia

The acquisition of Amplia comes with two core drug assets, AMP945 and AMP886.

These two compounds inhibit FAK (Focal Adhesion Kinase), a kinase involved with cell adhesion processes and which has been found to have an immuno-suppressive role in certain cancers as well as an important role in fibrotic diseases.

Substantial work was conducted at the Cancer Therapeutics CRC in Melbourne over four years to select these optimal drug candidates with the properties required to both inhibit FAK in patients with cancer and fibrotic diseases.

The short term value creation path for the company is to move one of these compounds,

AMP945, into a Phase I study in 2H 2019. The company will need to raise funds to conduct this study.

This trial will provide important information around the safety profile of the drug, its ability to target FAK in vivo, and its suitability as a drug. Its drug suitability will be assessed from its pharmacokinetic profile in circulation (how long the drug remains in the body) while the pharmacodynamic profile will be assessed by looking at the downstream effect of FAK inhibition using simple skin punch biopsies.

If positive Phase I data can be achieved, then the company may raise additional funds to conduct a Phase II cancer study in 2020, as a combination therapy with immune-oncology drugs (such as checkpoint inhibitors) or seek to partner the program.

This would be the first study in which the clinical efficacy of AMP945 will be assessed.

Positive clinical data could deliver a substantial revaluation of Amplia's drug development assets.

However, should Amplia be successful in partnering AMP945 after the Phase I safety study, in a deal which covers both oncology and fibrosis indications, then the lead focus of the clinical development program would be at the option of the licensee. A licensee could place greater emphasis on oncology indications and less on fibrosis indications or vice versa. A licensee could also potentially fund Amplia to conduct studies in one or more indications.

Development of Technology

Amplia's FAK assets were developed by Cancer Therapeutics CRC (CTx) in Melbourne. Cancer Research UK, up until 2014, had options to license certain technologies from CTx and as part of that right, licensed the FAK program. Amplia then in-licensed the FAK program.

License Terms

Under the license terms, Cancer Research UK is entitled to a low-medium single digit royalty from any future product sales coming from this program. Amplia is also required to pay small development milestones to Cancer Research UK, which are not expected to exceed $200,000 over the next two years.

Board & Management

Amplia has an experienced board and management. A summary of key management, directors and advisers is provided below.

Board

Robert Peach PhD (Director)

Joined the board in 2015. Peach was a co-founder of US biotech Receptos, which was sold to Celgene in 2014 for US$7.8 billion. He is a highly experienced drug developer and undertook due diligence of the Amplia assets prior to the acquisition.

Warwick Tong MB ChB MPP GAICD (Chairman)

Formerly the CEO of the Cancer CRC in Victoria, has a high level of experience in cancer drug discovery.

Christian Behrenbruch B.Eng (Hons) D.Phil (Oxon) MBA JD FIEAust GAICD (Director)

Strong background as a biotech entrepreneur. Has been a change agent for Factor Therapeutics and last year raised $50 million with the listing of Telix Pharmaceuticals, which is commercialising molecular target radiotherapy and diagnosis in oncology.

Chris Burns B.Sc. (Hons) PhD FRACI FRSC (Director)

Formerly Head of Research at listed Melbourne oncology company Cytopia, which was sold to YM Biosciences in Canada (later acquired by Gilead Sciences). He is currently CEO of Melbourne-based oncology drug developer MetabloQ.

Simon Wilkinson (CEO & Director)

Gained considerable experience in trial recruitment, capital raising and management of a listed biotech as CEO of Innate Immunotherapeutics since listing in 2013.

Andrew Cooke LLB (Company Secretary)

Company Secretary since October 2013, joined the Board in May 2018. Has extensive experience in law, corporate finance, governance and compliance. As a Non-Executive Director and Company Secretary of a number of ASX listed companies, he has over 25 years of boardroom experience.

Advisers

Mark Devlin PhD

Chief Scientific Adviser to Amplia (two days per week). Devlin led the development work on the Amplia assets acquired from Amplia (AMP945 and AMP886). Devlin is currently the Chief Operating Officer of the Cancer CRC based at the Peter MacCallum Cancer Centre.

Mark Sullivan

Has considerable drug development expertise as the founder and Managing Director of Medicines Development for Global Health in Melbourne. MDGH recently gained FDA approval for a repurposed veterinary drug (Moxidectin) to treat river blindness in humans and in so doing received a Priority Review Voucher.

Research Scientists – FAK Experts

Together with the expertise of Mark Devlin in FAK research, the company has three scientific advisers with considerable expertise in the area of FAK research. These are Professor Margaret Frame from the University of Edinburgh, where she has investigated the benefit of combining FAK inhibitors with checkpoint inhibitor drugs, Professor Neil Carragher (Edinburgh Cancer Discovery Unit) and Alan Serrels (MRC Centre for Inflammation Research).

Scientific Rationale to Blocking FAK to Treat Fibrous Cancer Tumours

One of the most important breakthroughs in oncology in the last 30 years has been the arrival of checkpoint inhibitor drugs, such as Yervoy (approved in 2011 by FDA), Keytruda (approved in 2014) and Opdivo (approved 2014). Currently in the US, there are over 1,000 studies (1,053) enrolling patients in clinical studies in the US with Keytruda and Opdivo alone.

These drugs work by exposing cancer cells to the immune system, specifically T-cells in the body, allowing the body to recognise these cells as foreign and initiate an internal attack upon these cells.

However, with some cancers, particularly fibrous cancers such as pancreatic cancer and some subtypes of ovarian cancer, these immunotherapy approaches (such as checkpoint inhibitors) have had limited success in such tumours.

It is believed that the high stromal density of these tumours prevents the body's T-cells from penetrating the tumours, and these tumours have a higher number of immunosuppressive cells that also prevent effective T-cell destruction of the tumours. This same high stromal density may also lessen the effectiveness of chemotherapy treatments.

In 2016 in the journal *Nature Medicine*, it was reported that in preclinical studies in a human cell mouse model of pancreatic cancer in tumours that did not respond to checkpoint inhibitors (PD-1 drugs, the tumours became responsive when a combination of a checkpoint inhibitor with a FAK inhibitor was used. (The FAK inhibitor used was not Amplia's, but Verastem's VS-4718).

In that same paper, it was reported that samples of pancreatic tumours from 50 patients were found to have very high levels of the FAK, being upregulated in over 80% of pancreatic tumours compared to normal pancreatic tissue. The tumours were also found to be highly fibrotic and have poor levels of T-cell infiltration into the tumours.

In that study when the FAK inhibitor was used alone, it achieved a doubling in survival of the mice, substantially slower tumour progression, much lower tumour fibrosis and less immunosuppression within the tumours.

This study provides a strong argument that FAK inhibitors could be affective in fibrotic cancer tumours such as pancreatic cancer.

Preclinical Data on AMP945 & AMP886

Affinity for FAK

In biophysical studies, AMP945 has very high affinity for binding to the FAK protein with a KD value, (concentration required to bind to 50% of available binding sites) of 0.21 nM (1.3 nM for AMP886). This is an order of magnitude below the KD of many FAK inhibitors, meaning that AMP945 binds more tightly to FAK than these other kinase inhibitors.

In cellular assays, AMP945 showed potent inhibitory effects with an IC50 (concentration required to inhibit auto-phosphorylation of FAK by 50%) of **7 nM** (36 nM for AMP886). The cellular activity of AMP945 compares well with the leading FAK inhibitor in development, VS-6063 from Verastem. This compound reportedly requires a slightly higher concentration, of between 3**0 nM - 100 nM** to achieve the same inhibition. This indicates that AMP-945 is a slightly more potent inhibitor of FAK than VS-6063.

Specificity of AMP945 and AMP886

How specific is AMP945 to the FAK protein? Using a third-party vendor, the binding of AMP945 to 121 other kinases was assessed to determine compound specificity.

At a concentration of 100 nM, the only kinase inhibited greater than 90% by AMP945 was FAK. Even at a concentration of 1 µM (1000 nM), AMP945 only inhibited one other kinase at greater than 90% (AMP886 inhibited four other kinases at this concentration).

In a follow up assay, the IC50 for inhibition of this other kinase was 209 nM, compared to an IC50 of just 7 nM for FAK. This implies a 30-fold selectivity window for FAK over the next most inhibited kinase (of the 121 kinases screened). This high degree of selectivity suggests that AMP945 should be well-tolerated (without off-target effects). The published selectivity of Verastem's VS-6063 across a smaller panel of 42 kinases was similar to that of AMP945.

While AMP945 inhibits just the FAK cancer pathway, AMP886 inhibits three cancer pathways. These are FAK, FLT3 and VEGFR3. A low concentration of AMP886 of only 9 nM is required for IC50 inhibition of FLT3 and an equal concentration of 36 nM for IC50 inhibition of FAK and VEGFR3.

Pharmaceutical Properties of AMP945 and AMP886

AMP945 and AMP886 are small molecules currently exhibiting excellent drug like properties. They will most likely be provided to patients as a once daily or twice daily tablet or capsule.

The route of synthesis (manufacture) is straightforward and Amplia is working with third party vendors to make suitable quantities of lead candidate AMP945 to support preclinical and clinical studies.

The company has recently entered into a contract with a drug manufacturer to further refine the production process and deliver sufficient quantities of cGMP grade AMP945 to complete final preclinical toxicology studies and clinical trial material for the planned Phase I study.

Clinical Development Plan

Amplia's intention is to conduct a Phase I safety study in healthy volunteers with its lead candidate AMP945 in the second half of 2019, with funds needing to be raised to conduct this study. Further preclinical efficacy studies are currently being conducted with toxicology work to be completed this year.

In 2020, Amplia will aim to commence a Phase II study with AMP945 in a fibrotic cancer such as pancreatic or ovarian cancer, in combination with a checkpoint inhibitor. The company would also have the option of pursing a separate clinical development programme in a fibrotic disease such as Idiopathic Pulmonary Fibrosis (IPF).

In parallel to the AMP945 development plan, additional preclinical studies with AMP886 will be conducted to better define clinical opportunities and treatment combinations for this drug candidate. This work will be carried out at the Cancer Research UK facility at the University of Edinburgh.

Clinical Trial Considerations

Phase I studies of cancer drugs are routinely carried out in trial subjects who already have advanced cancers. The ability to recruit patients with the defined disease criteria in a timely manner can be a very common risk in clinical development as competition for patients can slow the rate of recruitment into a trial.

Amplia's plan to conduct a Phase I trial of AMP945 in healthy volunteers side steps this risk and also means that subsequent Phase II trials will not be limited to only cancer patient populations. Initial healthy volunteer safety studies are routinely carried out at Phase I clinical trial sites in Australia and can be expected to reliably recruit suitable subjects within predictable timeframes.

Phase II Recruitment – Access to Patients

With respect to a possible Phase II trial in pancreatic cancer, the number of newly diagnosed patients each year in the USA is greater than the number which enter clinical trials. The nature of the disease is that even for the 10-20% who undergo surgery, inevitably, the vast majority of patients are likely to become enrolled in a trial of at least one investigational therapy or regime.

The poor performance of the standard frontline regimes and the absence of better approaches means that the accessibility of patient subjects for clinical trials is generally favourable for drug development firms, which on average need to enrol 40 patients for a Phase I study and 60 patients for a proof-of-concept Phase II study.

According to Clinicaltrials.gov, there are currently 43,800 patients enrolled or being enrolled in Phase I, II and III trials of interventions for pancreatic cancer. This figure also includes patients with other types of cancers and patients recruited from trial sites outside of the USA.

The estimated annual number of new pancreatic cancer cases in the USA for 2017 is 53,700. The global annual estimate of new cases of pancreatic cancer was estimated for 2012 to be 338,000.

There are 7,000 patients being recruited in 105 Phase I studies, 7,150 in 85 Phase I/II studies, 18,700 in 140 Phase II studies, 1,500 in 8 Phase II/III studies and 9,400 in 28 Phase III studies.

The median number of patients in each of these study phases was: Phase I, 42; Phase I/II 60; Phase II, 60; Phase II/III, 123 and Phase III, 300.

Industry-sponsored trials account for 30% (13,300) of patients being recruited, across 89 Phase I, II and III and other phase 'not stated' trials. There are another 22 industry sponsored trials registered with Clinicaltrials.gov which intend to enrol 2,700 patients.

Analysis of industry sponsored trials in the Phase I, II and III stages is a reliable means to directly assess commercial thinking on new therapeutic approaches.

Combination Therapy Considerations

Jiang et al* showed that the targeting of FAK made pancreatic tumours more responsive to checkpoint inhibitor drugs (PD-1 receptor antagonists). Higher levels of FAK sustain the immune-suppressive environment of the pancreatic tumour stroma. Jiang et al showed that inhibition of FAK led to temporary tumour stasis and extended survival in KPC mice.

More importantly, in studies of KPC mice with both a FAK inhibitor (VS-4718) and high dose gemcitabine (an approved chemotherapy for pancreatic cancer), median survival was more than doubled. In a study of a FAK inhibitor with low dose gemcitabine, a PD-1 antagonist and a CTLA4 inhibitor, a greater than 2.5-fold increase in median survival time was observed.

The authors noted that monotherapy trials of FAK inhibitors so far had failed to achieve tumour regression in advanced cancer patients.

An implication of the Jiang paper is that for a FAK inhibitor such as Amplia's AMP886 and AMP945, an evaluation in patients with fibrotic tumours may be best explored in various combinations which include checkpoint inhibitors along with low dose chemotherapy.

Of the 89 industry-sponsored pancreatic cancer trials currently underway, 13 include an immune modulator, such as the anti-PD1 antibodies, (e.g. pembrolizumab, nivolumab, cemiplimab, spartalizumab), the anti- PDL-1antibodies (durvalumab, atezolizumab, avelumab, MEDI4736 and LY3300054) and CTLA4 inhibitor (tremelimumab).

The progress of these trials will be of benefit to Amplia as it designs its human clinical proof-of-concept studies. These trials will yield information about safety and tolerability, and potentially reveal general trends towards multiplicative benefits, whether clear differences exist between checkpoint inhibitors which target PD1 (the receptor) versus PD-L1 (the ligand), and what role a CTL4A inhibitor might play.

Worth monitoring will be Roche's trial of atezolizumab with nab-paclitaxel, gemcitabine, oxaliplatin, leucovorin, cobimetinib, PEGPH20 and BL-8040. BL-8040 inhibits CXCR4, a chemokine receptor implicated in fibrosis. Incyte's trial of pembrolizumab, itacitinib and INCB050465, may also be worth monitoring because itacitinib, a JAK1 inhibitor is believed to play a role in fibrosis.

**Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy - Hong Jian et al, July 2016, Nature Medicine*

Intellectual Property

Amplia has two core patent families over its FAK assets arising from the two PCT applications detailed below.

PCT/GB2012/000175

This application, titled "FAK Inhibitors" claims the compound AMP886. A compound patent, also known as a composition of matter patent, provides the strongest patent protection. The application also claims the use of AMP886 to prevent and/or treat proliferative diseases such as cancer.

Patents arising out of this PCT application have been granted in the major markets such as the US (US9012461), Europe (EP12705383.3), and Japan (JP5937111), as well as in Australia (AU 2012216893), and China (ZL201280018969). Corresponding patent applications are pending in a number of other markets.

The PCT application was filed in February 2012 and the patent term for each patent in the family will extend to 2032 in each jurisdiction (plus the extensions potentially available in each jurisdiction).

PCT/GB2012/000176

This application, titled "Selective FAK Inhibitors" claims the compound AMP945. The application also claims the use of AMP945 to prevent and/or treat proliferative diseases such as cancer.

Patents arising out of this PCT application have been granted in the major markets such as the US (US 9120761) and Japan (JP5937112) with the corresponding European patent application expected to be approved for grant in the coming months. Patents have also been granted in Australia (AU 2012216894) and China (ZL201280018816.6). Corresponding patent applications are pending in a number of other markets.

The application was filed in February 2012 and the patent term for each patent in the family will extend to 2032 in each jurisdiction (plus the extensions potentially available in each jurisdiction).

Amplia plans to file additional patents directed to innovations identified in the development of the AMP945 and AMP886. These additional patents will expand the patent portfolio protecting the AMP compounds and potentially further extend the term for which patent protection is available.

The Unmet Need in Pancreatic Cancer

The Pancreas

The pancreas is a gland which has multiple functions, including the production of a number of key hormones. The exocrine pancreas (95% of the pancreas) produces enzymes which breakdown proteins, carbohydrates and fats, which are released into the intestine via the pancreatic duct. The endocrine pancreas (5%) contains Islet cells which release glucagon, for increasing blood sugar levels, and insulin, which controls the metabolism of proteins, carbohydrates and fats. The inability to produce sufficient insulin is a defining characteristic of diabetes.

Pancreatic Cancer

Pancreatic cancer has climbed in the ranks as a cause of death. According to the American Cancer Society's 'Cancer Facts and Figures 2017', pancreatic cancer is now estimated to be the third leading cause of cancer-related deaths in the USA, being responsible for an estimated 43,000 or 7.2% of cancer related deaths in 2017, with an estimated new number of cases of 53,700 in the same year.

Survival Rates

The American Cancer Society estimated the overall five-year survival rates for pancreatic cancer (all stages) stands at 7%. This figure – when compared to those for prostate cancer (97%), breast cancer (80%), kidney and renal pelvis (73%), urinary bladder (64%), colorectum cancer (58%), but also liver and intra-hepatic bile duct (13%), lung and bronchus (15%), esophagus (12%) – shows that there is a major unmet need for finding better treatments for pancreatic cancer.

Symptoms

Pancreatic cancer is challenging relative to some other cancers because its symptoms are often non-specific, with fatigue, malaise, weight loss, middle abdomen and back pain serving as examples.

Diagnosis

Some tests that aid the diagnosis of pancreatic cancer include tests for levels of bilirubin, ALP and GGT; serum amylase (which is elevated in 50% of patients with resectable pancreatic cancers but only in 25% of patients with non-resectable cancers); and cancer biomarkers such as CA 19-9 (75-85%) and CEA (40-45%). Various imaging modalities are also used to aid diagnosis.

Staging

Pancreatic cancer is defined in the AJCC Cancer Staging Manual by the following stages:

TX - Primary tumor cannot be assessed
T0 - No evidence of primary tumor
Tis - Carcinoma in situ
T1 - Tumor limited to the pancreas, ?2 cm in greatest dimension
T2 -Tumor limited to the pancreas, >2 cm in greatest dimension
T3 - Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4 - Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Less than 20% of patients are diagnosed with localised small tumours (?2 cm), and no lymph node metastases. Complete resection leads to five-year survival rates of 18%-20%.

Treatment Options

Surgical treatment options include the complete removal of the pancreas, a distal pancreatectomy and the pancreaticoduodenectomy, otherwise known as the Whipple Procedure.

Drugs approved to pancreatic cancer include gemcitabine, nab-paclitaxel, FOLFIRINOX and erlotinib. There are 90 Phase I, II and III currently recruiting trials of new investigative

monotherapies, combinations of chemotherapeutics with new agents, including a number of emerging immunotherapies, in addition to several CAR T, vaccine and radiation therapeutic interventions in development.

Median overall survival gain for approved drugs range from 5.6 months (gemcitabine), 6.7 months (gemcitabine and 5FU), 11.1 months (FOLFIRINOX), 8.5 months (nab-paclitaxel), and 6.2 months (erlotinib and gemcitabine).

While FOLFIRINOX has achieved the greatest Overall Survival rate, its safety profile is less favourable and causes a significant deterioration in quality of life.

The poor prognosis for treatment with these regimes is because of barriers created by pancreatic tumour stroma, which is the connective tissue and resident cells that develop into fibrotic mass, creating an immune-suppressive environment.

ASX-listed Oncosil Medical is developing an implantable radioactive phosporus32 device. Early trial data shows that its device is having success in reducing tumour volume, sufficient to enable surgical resection with potential for remission.

The Unmet Need in Ovarian Cancer

The estimated number of new cases of ovarian cancer in the US for 2017 was 22,400, with 14,000 deaths due to that cause. Deaths due to ovarian cancer accounted for 2.3% of overall cancer related deaths.

Deaths have been declining over the longer term due to the use of oral contraception medications. In 28 European countries, ovarian cancer death rates decreased 10% from 2002 to 2012, with the USA reporting a 16% decrease over the same period.

For the US, up to 2014, the five-year survival rates by stages were as follows : All stages, 46%; localised 92%; regional,73%; distant, 29%; and unstaged, 25%.

Treatment protocols often begin with surgery for stage I-IVa of epithelial ovarian cancer but only a small percentage receive surgery.

First-line chemotherapy regimens include paclitaxel and carboplatin, docetaxel and carboplatin, pegylated liposomal doxorubicin and carboplatin. For patients with recurrent disease, docetaxel and paclitaxel, gemcitabine, bevacizumab with carboplatin and paclitaxel, or with gemcitabine may also be used. For platinum resistant patients, the drugs just listed but excluding carboplatin are used, as well as etoposide and nab-paclitaxel. Advanced cancer patients can be treated with one of the PARP inhibitors: olaparib, rucaparib or niraparib.

Combination platinum and taxane therapies have been shown to increase overall rates of survival. The Katsumata study of conventional dose carboplatin and paclitaxel versus dose-dense carboplatin and paclitaxel treatment of stage II-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer, showed a 100-month median Overall Survival benefit for the dense form versus 62 months for the conventional form.

Due to the fibrotic nature of ovarian tumours, that act as a shell and can prevent immune cell entry, the use of FAK inhibitors that interfere with the fibrotic process are believed to offer a new approach to treating ovarian cancer, particularly with immunotherapy options such as checkpoint inhibitors. Verastem is currently conducting two clinical studies in ovarian cancer with its FAK inhibitor (see table, p 16), both with and without a checkpoint inhibitor.

The Opportunities in Fibrosis

Fibrosis is a condition which can take place in many organs and tissues. Fibrosis is often caused by chronic inflammation and chronic injury. Fibrosis can occur naturally in the context of wound healing, when scarring results. When changes to collagen and other tissue structures become irreversible and cause loss of function, then fibrosis can precipitate a shift to a fatal condition.

In addition to the pancreas, fibrosis can occur in the heart, lungs, kidneys, liver, eyes and in the skin. Some fibrotic diseases, such as cystic fibrosis, are caused by genetic mutations.

While there are no drugs approved for the specific management of cardio-fibrosis, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists have been associated with decreased cardiac fibrosis. These same drug classes are suggested to be able to slow diabetic nephropathy and by extension mitigate fibrotic trends.

Two drugs, nintedanib and pirfenidone, were the first drugs approved to treat Idiopathic Pulmonary Fibrosis (IPF), which have been able to have an impact on mortality but at the expense of tolerability. Pirfenidone, which was approved by the FDA in 2014, reduced deaths at 52 weeks by 68%, at the expense of high rates of nausea, headaches, fatigue, rash, upper respiratory infections and diarrhea. Nintedanib was similarly shown to reduce mortality and improved lung function

These two drugs generate sales of more than US$1 billion per annum, for a patient population of more than 135,000 in the US and 5,000-10,000 in Australia. IPF has a 50%-70% mortality rate and accounts for 50% of all lung fibrotic conditions.

There are no disease-modifying drugs approved to treat liver fibrosis. NASH (non-alcoholic steatohepatitis) is the chronic inflammation of the fatty liver, and which is a precursor to fibrosis and cirrhosis. An estimated 3-5% of US adults have NASH, indicating that a large market opportunity exists. Drug development efforts to treat NASH have been unsuccessful, and look to remain that way, which means that new mechanisms and candidates are worth pursuing.

Competition with other FAK Programs

How do Amplia's FAK inhibitors compare with other FAK inhibitors in development?

Analysis of Clinical Studies with FAK Inhibitors – Underway, Completed and Terminated

According to Clinicaltrials.gov, there are five clinical studies underway with FAK inhibitors. Four are being sponsored by Verastem with the same compound, VS-6063 (also known as defactinib), and one is being sponsored by Centaurus Biopharma.

Three of these studies are being run in combination with a checkpoint inhibitor drug (U1, U2 and U3), two with Keytruda and one with an experimental PD-L1 inhibitor avelumab (under development by Pfizer and Merck KGgA).

We found 10 studies that have been completed with FAK inhibitors, five studies had been terminated, and two studies are ongoing but not recruiting. None of these 18 studies are with checkpoint inhibitors.

This indicates that FAK inhibitors alone have limited clinical development success as monotherapies for cancer. However, and based on preclinical data, combination with checkpoint inhibitor drugs may have an opportunity to deliver a clinically valuable therapy.

Competing FAK Inhibitor Clinical Programs

	Company	Phase	Drug	Combination therapy	Indication	Nº patients	Completion date
Trials underway							
U1	Verastem	1b	VS-6063	Keytruda & gemcitabine	Pancreatic cancer	50	Jul-20
U2	Verastem	1	VS-6063	PD-L1 Inhibitor (avelumab)	Ovarian cancer	98	Dec-18
U3	Verastem	1/2	VS-6063	Keytruda & gemcitabine	NSCLC, pancreatic cancer, mesothelioma	59	Dec-21
U4	Verastem	1/2	VS-6063	Carboplatin & cisplatin	Ovarian cancer	90	Oct-23
U5	Centaurus Biopharma	1	CT707	-	NSCLC	40	Mar-18
Active but not recruiting							
ANR1	Verastem	2	VS-6063	-	Mesothelioma	38	Sep-18
ANR2	GlaxoSmithKline	2	GSK2256098	MEK inhibitor	Pancreatic cancer	16	Dec-18
Completed studies							
C1	Verastem	2	VS-6063	-	NSCLC, lung cancer	55	Jun-16
C2	GlaxoSmithKline	1	GSK2256098	MEK inhibitor	Solid tumours	34	Jun-16
C3	GlaxoSmithKline	1	GSK2256098	-	Solid tumours	74	Dec-15
C4	Boehringer Ingelheim	1	BI 853520	-	Non-hematalogic tumours	96	Dec-15
C5	Verastem	1/1b	VS-6063	Paclitaxel	Ovarian cancer	22	Feb-15
C6	Boehringer Ingelheim	1	BI 853520	-	Metastatic solid tumours	21	Aug-14
C7	Verastem	1	VS-6063	-	Non-hematalogic, Japan	9	Jun-14
C8	Verastem	1	PF04554878	-	Non-hematalogic cancers	46	Feb-12
C9	ArQule	1	ARQ197	-	Solid tumours	51	Feb-10
C10	Verastem	1	PF00562271	-	Head & Neck, prostate, pancreatic cancer	99	Apr-09
Terminated studies							
T1	Verastem	1	VS-4718	Paclitaxel & Gemcitabine	Pancreatic cancer	13	
T2	Verastem	1	VS-4718	-	Non-hematalogic	48	
T3	GlaxoSmithKline	2	GSK2256098	Vismodegib	Meningioma	69	
T4	Verastem	1	VS-6063	VS-5584	Mesothelioma	21	
T5	Verastem	1	VS-4718		AML & ALL (Leukemia)	0	

Results from Verastem Studies with VS-6063 Lead FAK Inhibitor

U1: Phase Ib study in patients with pancreatic cancer, in combination with Keytruda
Initial data from Verastem's Phase Ib pancreatic cancer study (see table - U1) was reported in June this year. That trial is seeking to recruit 50 patients with pancreatic cancer (PDAC) and other solid tumours, and started in January 2016. The completion date is July 2020. The trial is combining VS-6063 with the checkpoint inhibitor Keytruda and the chemo-therapy drug gemcitabine.

Twenty patients have completed the dose escalation phase, with data available from 15 patients. Of the eight patients with pancreatic cancer, at least stable disease was achieved in 50% of patients (three with stable disease and one with a partial response). This is an encouraging result given that pancreatic cancer has the highest mortality of all major diseases.

Across all 15 patients, 60% (nine patients) achieved at least stable disease (including one partial response).

C5: Phase I/Ib study with VS-6063 with paclitaxel in ovarian cancer
This study involved 22 women with ovarian cancer who were treated with VS-6063 and paclitaxel. In 60% of the women (14 patients), at least a stable disease was achieved, which included two partial responses and two complete responses. (Reported June 2014).

At the start of 2017, Verastem commenced a Phase I study with the same drug candidate, but this time in combination with the checkpoint inhibitor (PD-L1) drug avelumab (being developed by Pfizer and Merck KGgA). Results are expected in December this year.

ASX Listed Cancer and Fibrosis Drug and Product Companies

The table below provides the capitalisations of biotechs listed on the ASX with oncology and fibrosis drug and product development programs. There are three companies at a preclinical stage of development with these capitalisations varying between $23 million and $40 million.

A transaction relevant in the fibrosis sector is the acquisition of Melbourne-based Fibrotech Therapeutics in 2014, which was bought by Shire Pharmaceuticals for US$75 million upfront payments. At the time of the deal, Fibrotech had completed Phase Ia testing with its lead compound in healthy volunteers. Fibrotech was developing an anti-fibrotic drug candidate.

ASX Listed Cancer & Fibrosis Drug & Product Companies (14 August 2018)

Company	Stage of development	Market Cap. $M
Sirtex Medical	On market	$1,756
Telix Pharmaceuticals	Phase II	$157
Pharmaxis	Phase I fibrosis program plus other assets	$115
Oncosil Medical	Phase II	$112
Immutep	Phase IIb	$106
Noxopharm	Phase I/II	$79
Imugene	Phase IIa	$73
Kazia Therapeutics	Phase II	$23
Prescient Therapeutics	Phase Ib/II	$19
Patrys	Preclinical	$40
Adalta	Preclinical	$34
Vectus Biosystems	Preclinical	$23
Amplia Therapeutics	Preclinical	$16

Investment Risks

Two of the most significant risks in drug development are with drug safety and efficacy. The risk of off-target effects can result in severe adverse events that can stop drug development. Inadequate efficacy can result in failure to gain regulatory approval, failure to partner and fund the program, failure to recruit patients into studies, and failure on the market to be adopted for use by prescribing doctors. Drug profile risk may also arise, whereby a compound may not present with suitable drug properties, such as sufficient half-life in the body to achieve a sustained effect.

Recruitment risk exists with all drug development companies. A highly competitive disease indication can make it difficult to attract patients into clinical studies, which can slow or halt commercialisation of a drug. This can be reflective of the market demand for a particular therapy in development.

Funding is a risk for most smaller drug development companies. An inability to attract funds will impact the financial execution capacity of a drug developer.

All drug developers face regulatory risk, which can occur early in the process, in gaining ethics and regulatory approval to commence trials, as well as final regulatory clearance to gain marketing authorisation.

Drug development, as with all commercial pursuits, is open to competition. Given the dynamic nature of drug development, the competitive landscape will continue to change and thereby impact the value and appeal of drug compound as new therapeutics progress through clinical studies and gain market clearance.

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Some Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A

These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B

These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C

These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Cogstate, Bionomics, LBT Innovations, Opthea, ResApp, Pharmaxis, Dimerix, Cyclopharm, Adalta, Medibio, Pharmaust, Actinogen Medical, Patrys

Blake Industry and Market Analysis Pty Ltd will be paid a fee for this report.