RESEARCH REPORT

CORPORATE CONNECT

Kazia Therapeutics

A Laser-Like Focus on Adding Value

-5 Data Readouts in 9-Months

Share Price & Estimated Future Price

Price in 12-months*	$2.05
Current Price	$0.80
Implied Increase/Dec	156%

* Price at end FY21/beginning FY22

Since August 1st, Kazia Therapeutics has announced US Food & Drug Administration fast track status for one program & orphan drug and rare paediatric disease designation for another, while finishing the period by announcing a new trial for its cancer drug, paxalisib. Over the next nine months investors are likely to see six data readouts from five programs. How fast can a company go?

Introduction: A shake up of the board and senior management at drug-developer Novogen Ltd (formerly, ASX:NRT), brought the company a new CEO and several new board members, including a new chairman. Management wasted no time in trimming the dead wood from the development pipeline and licensing in a phase II ready, unique anti-cancer compound from storied cancer drug developer Genentech. The drug, that would later become known as paxalisib, had a very well understood mechanism of action and clinical data showing that the drug could do something other four marketed drugs of the same class could not do. It could cross the blood-brain-barrier and penetrate the tissues of the brain and the spine. Paxalisib and been purpose built to treat cancers of the central nervous system.

Clinical Trials: Kazia moved paxalisib into the clinic quicky and the trials in the table are underway. The best way for a drug developer to add value is by trialling their drug broadly, but also wisely, so as to inform future decisions they may have to make, while also protecting the drug from being studied in a no-win trial. The main program is in glioblastoma multiforme (GBM), an aggressive form of brain cancer. It is the one Kazia expects to take into a pivotal trial starting early next year and the one Kazia will be aiming to gain approval from regulators for, if and when the time comes. An added advantage of Kazia's strategy is that it will also build value in the eyes of those who might see paxalisib as valuable addition to their existing businesses. Any small pharma should be open to being acquired at the right price. Given the nature of pharmaceutical sales and marketing, good drugs developed by smaller companies invariably reach a point where they become worth substantially more to larger companies than to the existing owner. The reason is that the larger companies have the infrastructure, the human capital, and the financial capital to quickly and efficiently take advantage of all the opportunities a good drug provides.

Indication	Next Likely Readout	Study Completion
GBM[1]	Nov 19-20 CY20	1H CY21
DIPG[2]	Nov 19-20 CY20	Q4 CY20
PCNSL[3]	1H CY22	Q1 CY23
BMs[4]	1H CY21	2H CY21
BMs with Rad.[5]	1H CY21	End CY22
BMs Br Ca[6]	Q4 CY20	End CY21

[1] Glioblastoma Multiforme; [2] Diffuse Intrinsic Pontine Glioma; [3] Primary Central Nervous System Lymphoma; [4] Brain Metastases; [5] Brain Metastases with Concurrent Radiation; [6] Brain Metastases from a Primary Breast Cancer

Valuation Methodology: I have used a probability weight discounted cash flow approach to value Kazia. The biggest assumption I have made is that if Kazia is successful in moving paxalisib through trials for GBM, they will be acquired. The discount rate is also a big decision because of its large impact on the target price. Most large pharmaceutical companies use a rate of 11% or 12%. I have used 15% to keep my valuation on the conservative side. The third key assumption was that the US accounted for 55% of the world's cancer drug revenue. By doing this, I could go into the biggest market, by far, in some depth, rather spend time on much less lucrative geographies. Valuations can tell you whether an asset is mispriced, but it will not tell whether a mispriced asset will move to fair value over the coming year. The emphasis on the data readouts, above, provide a compelling argument that the target price target can be reached, if not exceeded.

Recommendation: Kazia's fate is in paxalisib's hands, and that is how it should be. We initiate coverage with a 12-month price target of **$2.05.**

Company Information

ASX Ticker	KZA
NASDAQ Ticker	KZIA
NASDAQ Price	USD6.04
Shares on Issue	126.1 million
Fully Diluted Shares on Issue	136.8 million
Market Capitalisation	$75.2 million
ASX Vol. (Shares/Day)*	0.9 million

* Shares per Day for the Last 20 Trading Days. **A** Includes 31.5 million Shares to be Issued through Recent Rights Announcement.

Cash Sufficiency

	$ Million
A) Last Appendix 4C	End June, 2020
B) Cash & Equivalents at 4C	8.8
C) Burn[1]	2.7
D) Quarters Cash Remaining[2]	3.2
E) Estimated Current Q Burn[3]	2.9
F) Estimated Cash Raised Post 4C[4]	23.8
G) Estimated Current Cash[5]	**29.9**
H) Significant Estimated New Commitment(s)[6]	27.4

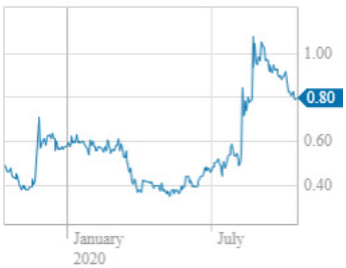
Description of Commitment(s): Estimated USD20m will be required to fund the GBM AGILE trial of paxalisib.

1 Burn = Net Cash from/used In Operating Activities; **2** Quarters Cash Remaining = B/C;
3 Equals C *(# Days Since previous Q end Q4 / # Days in Current Q);
4 Equals Capital Raising(s) – Estimated Costs; **5** Equals B – E + F
6 Equals estimated maximum new significant commitments that the company has or is likely to become contractually or ethically committed to.

Key Personnel

Mr. Iain Ross	Chairman
Dr. James Garner	MD & CEO
Mr. Bryce Carmine	NED
Mr. Steven Coffey	NED

Chart



Kazia Therapeutics

A Laser-Like Focus

Adding Value

One of the first companies I wanted to cover when I started at CCR was Kazia Therapeutics (ASX KZA). The reasons were a good board and management, as well as a very good drug candidate for a very serious brain cancer. It is that simple. Good people and a good program. If you stick with those types of companies in listed biopharma, you will be fine. In this report, I assess what good people can do with a good drug candidate, how they will continue to develop it and how investors should benefit. There is, really, only one way to add value to a drug. That is to put it into clinical trials, show that it works, what diseases it works for and move it through the regulatory system and on to the market. Ultimately, this is what will take the drug from clinical trials to a doctor who is injecting it into a patient during routine use. Each trial is a potential new market. Each positive trial increases the chances the drug will be used, as it was in the trial, but by paying governments/healthcare systems/insurers and/or patients. That is a progression that creates value. By the end of Q1 next CY (2021), Kazia will have its drug:

- In 5 different clinical trials for 4 different indications,
- Have completed 1 trial for its core indication,
- Completed 1 trial in an indication of high unmet clinical need,
- Started 1 trial in a new indication, and
- Started their drug in a pivotal trial that could lead to its approval.

That is a very full list of clinical activities.

In August, Kazia's share price nearly doubled when the company announced that, if their drug were approved for a certain childhood cancer, they would be eligible for a special voucher. They could sell the voucher for USD100 million, maybe more, if there was competition for it. I could understand why the market was interested in and talking about the voucher. I could not understand why the market was not more interested in and talking about the suite of clinical trials Kazia had gotten up and running. Each positive trial would be worth more than the voucher. Plus, the potential to value add with successive trials reporting interim and/or final results is tremendous. As the CEO of the company put it the other day, **we should be in a position to announce interim or final trial results at an average rate of one trial per quarter for the next few years**. I have never seen that from an Australian pharmaceutical development company before. But, this is a company focussed on adding value.

Introduction

Kazia Therapeutics has an extremely exciting drug named paxalisib on their hands.

After in-licencing the drug, Kazia set about determining its clinical strategy for it. This involves planning out the clinical trials that need to be done with the drug to affect a single outcome – ***maximising shareholder value***.

Clinical trials add value by de-risking a drug and moving it closer to and through marketing approvals, so that the drug may be prescribed and sold, and revenues derived from it. Usually, the company will focus its initial clinical trial efforts on the indication (disease state) for which the drug was developed since its initial inception. The reasoning is straightforward. If the drug has been developed with a particular indication in mind, the drug is most likely to find success in clinical trials for that indication. Paxalisib was specifically designed to treat a highly aggressive and deadly brain cancer called glioblastoma multiforme or GBM, as it is often abbreviated to.

Depending on how a drug works, formally termed its mechanism of action (MOA), there may be a theoretical basis to believe the drug will work in further indications. These additional indications will not share the precise same biology as the initial indication and are, generally, less likely to return positive results. As a result, studies in these indications generally do not begin until the company reaches a stage with the initial indication that gives them the confidence to start further trials. A lot of factors can go into a company's decision on when to start additional trials. Some preliminary signs of clinical activity in the initial indication can often be when they start to think about it. The result, though, is a staggered set of trials across different indications which move forward in that same staggered fashion.

Keytruda® (pembrolizumab, Merck & Co.) has worked its way to FDA approval for about 19 different cancer indications, from the time it was first approved by the US Food and Drug Administration (FDA) in 2014 to the end of 2019. Over that time, Keytruda®'s worldwide revenues grew to USD11.1 (AUD15.2) billion over 2019. Seven (7) of those indications were added in 2019 alone, indicating there is still a lot of growth to come. EvaluatePharma believes Keytruda®'s revenues will grow by 30% in 2020 to USD14.4 (AUD19.7) billion. Not too bad for a drug Merck was going to shelve in 2010 until it saw a competitor's results with a very similar drug at a conference.

Kazia Therapeutics

A Laser-Like Focus

There is evidence that what makes paxalisib useful in GBM patients, could well make it useful in many other brain cancer indications. As such, Kazia is laying the groundwork to develop paxalisib not only for GBM patients, but for many other types of brain cancer, as well. Paxalisib does have a pathway through several different brain cancer indications to make its own mark in medicine. If it can do that, it will make brain cancer patients very happy, as well as Kazia shareholders.

The history of a company and how it has evolved can tell you a lot about its prospects going forward and what you can expect from them. There are a bunch of dead giveaways that will signal to you, this one is not going anywhere. A classic in medical devices and biopharma is if they start to have an application of their technology for whatever disease is making the news at a given time. It takes focus and time to get a regulated healthcare product to market. If you are constantly changing focus, you are probably going backward. Kazia's focus has been consistent. There was no announcement about how about how the company had just learned paxalisib had anti-viral activity and could be developed to treat COVID-19. Just announcements about how the pandemic would affect the company's activities.

Box 1: Genentech Phase I trial

The phase I trial was carried out in 47 grade 3 and 4 glioma patients, each of whom had failed multiple lines of treatment. GBM is, essentially, grade 4 glioma.. Of the 45 patients with evaluable magnetic resonance imaging scans, 19 (40%) recorded a response of stable disease according to RANO (Response Assessment in Neuro-Oncology). 27 patients had evaluable positron emission tomography scans, of which 7 (26%) recorded a partial metabolic response. Since the MOA of paxalisib aligns more with slowing the growth of cancer cells, then killing them, this is largely the type of result Genentech should have expected to see.

The Genesis of Today's Kazia

Kazia Therapeutics was born in late 2015/16 after a board re-shuffle at Novogen Limited (formerly, ASX NRT). In fact, it is reasonable to see that re-shuffle as the birth of a distinct entity, unrelated to Novogen or its history. In late 2015, the well credentialed, Dr James Garner was appointed CEO. Dr Garner, a physician by training, also holds an MBA from the University of Queensland. He has small and large company pharmaceutical experience, that shows a strong focus research and development. Not long after the arrival of Dr Garner, a new, highly qualified, chairman was appointed. That chairman was Iain Ross. Mr Ross is an ex-multinational pharmaceutical executive, who now works as a professional biopharma director. He has an exceptional amount of experience with companies very similar to Kazia and is well-suited to the elder-statesman role he has taken on.

A solid board and management team are the core of any drug development company. Good drugs do not move themselves through commercialisation. Given the stringent requirements of regulatory agencies like the US Food and Drug Administration (FDA), the complexities of clinical trial design and execution, as well as manufacturing scale-up, little mistakes can be extremely harmful. Big ones can damage a drug beyond repair. Kazia has put together a small group of very talented individuals with the capacity to execute on their primary objective, maximising shareholder value through the development of paxalisib for the treatment several brain cancer indications. Those indications start with GBM.

A New Strategy

The new management at Kazia did not see much promise in the pipeline of drug candidates it was left by those previously in charge. All but one of the molecules in it were either sold or discontinued. The one that remained, Cantrixil, will complete a phase I study in Q4 of this year (CY20), but management has already said that they will spend no more money on it and will seek to out-licence it.

Large pharmaceutical companies mothball many clinical stage compounds (i.e. drug candidates), and this can happen for variety of reasons. For example, these large companies do change strategic direction and compounds that were once a strategic priority can fall out of favour overnight. Reasonably large acquisitions almost always see the acquirer gain compounds that are extraneous to the basis of the acquisition. There are also times when larger companies fail to see a pathway forward for a compound, because groupthink ties their focus to standard development strategies or dominant strategies of the time. If you are a Pfizer Inc. (NYSE: PFE; Market Capitalisation: USD198 billion) or a Roche Holdings (SWE: ROG; Market Capitalisation: USD306 billion) shelving development candidates simply creates rounding errors on the statement of income. Even shelving very good candidates can happen. The CEO of Roche does not want to develop a drug that decreases the companies return on equity. A drug that does that will be shelved.

Table 1 provides a series of examples where a small pharmaceutical company has licensed a compound from a major one. As can be seen some have gone on to derive revenues from the compound and continue to run more trials and expand the breadth of their drug's indications, while others have been bought by major pharmaceutical companies. In one of the cases, the major who licensed the drug out originally, ending up buying it back.

Paxalisib

In 2016, Kazia identified a shelved molecule at the storied cancer drug development company, Genentech. In fact, Genentech has been so successful at therapeutic development, when Roche Holdings took them over, it chose to leave it completely intact so as not to destroy Genentech's culture of success.

Kazia felt there was a lot to like about the drug, named GDC-0084 at the time, and we concurred. Specifically:

- The science behind paxalisib was outstanding,
- It inhibited a proven target, in that there were approved drugs on the market that inhibited the same enzyme,

Table 1. Examples of Successful In-licensing Deals Struck for Large Pharmaceutical Company Developmental Drugs.[1]

						Licensor
Licensor	**Licensee**	**Drug**	**Phase**	**Year**	**Paid**	**Received[1]**
Puma Biotechnology	Pfizer	neratinib	III	2011	Undisclosed future milestones and a royalty on sales.	2017 FDA Approval; FY19 neratinib revenues USD212m; New indication approved this year (2020), with further trials to expand indications ongoing.
CoLucid Pharmaceuticals	Eli Lilly & Co.	lasmiditan	Preclinical	2005	Undisclosed.	Acquired by Lilly for USD960m in 2017.
Tesaro	Merck Sharp & Dohme	niraparib	I	2012	USD7m upfront; USD57m in milestones on the first indication; USD29.5m for each successive indication; one-off sales milestone of USD87.5m; low teens royalty on sales.	Acquired by GlaxoSmithKline in 2018 for USD5.1B.
Clovis Oncology	Pfizer	rucaparib	II	2011	Undisclosed payment in Clovis equity; total milestone payments of USD255m; royalties on product sales.	2017 FDA approval; FY19 rucaparib revenues of USD143m; further indications being studied
Impact Bio-medicines	Sanofi	fedratinib	III	2016	Undisclosed equity.	Acquired by Celgene in 2018 for USD1.1b upfront; USD1.25b based on regulatory approvals; USD4.5b I sales milestones.

Source: M. Sinatra Research
1 Deals were accumulated as they were found and may are unlikely to be representative of all deals.
2 Only the latest amounts received are given. Income received from earlier regional licensing deals, sales revenues and royalty revenues are excluded.

- **But GDC-0084 was strongly differentiated from the approved drugs sharing its target**, in that it could cross the blood-brain barrier (BBB), whereas they could not, allowing it to be studied in brain cancer patients,
- GDC-0084 had, also, been shown by Genentech to have clear biological activity in patients with an aggressive form of brain cancer termed, glioblastoma multiforme (GBM; see box 1, top, page 3), and
- Finally, GDC-0084 was clinical stage and, essentially, phase II ready, meaning investors and analysts could easily see the value being added to it by clinical trial results, as opposed to the years of necessary, but low value add time, drugs spend in preclinical studies.

It is extremely rare to find a drug that shares the same target with four drugs that are already on the market and is also completely differentiated from them. The attributes of the market PI3K inhibitors are given in table 2 (top page 6). Normally a company worries about whether their drug is hitting the target, they hope it is and by hitting that target the company will have achieved the desired effect. The company will also have concerns about designing a trail that will maximise the benefit of the drug. The company will also have concerns about designing a trial that will maximise the benefit of the drug. If you remove the issues with the target and weather reaching it will do so you are left to focus on the trial. In other words, the job becomes a lot easier.

When a company is considering whether to in-license a drug, not only is it important to understand the drug, but it is imperative that you understand the reasons a company wishes to out-license it. It generally is not enough just to like the drug. As the saying goes, if a deal sounds too good to be true, it is too good to be true. However, there were clear reasons why a company like Genentech might have shelved GDC-0084, even though it appeared extremely promising to Kazia.

These reasons were:

1) Genentech had started GDC-0084's clinical development down a well-trodden path, when that did not pan out, even a storied drug developer such as Genentech can be blinkered and fail to see a way forward,
2) While the results were in-line with hind-sight expectations, given the strong theory behind GDC-0084, Genentech may have been hoping for an accelerated approval, which would have made commercialisation of the drug much easier,
3) Finally, as mentioned, Genentech is owned by Roche and Roche is a massive company. Anything, short of a near blockbuster is unlikely to move the revenue dial of the company enough to get senior managers excited.

Bring all of these points together, and it is understandable why the decision was made to shelve GDC-0084. Licensing it to a small drug development company would have also made sense to Genentech. It has become more popular with the larger pharmaceutical companies over recent years to out-licence potential difficult drug candidates to a dedicated team. These smaller teams have a history of doing better with drugs that require deeper thought and have been better at finding their way around developmental roadblocks, often, because the life of a small company can depend on it.

In the end, it came to pass that Kazia licenced GDC-0084 from Genentech in exchange for USD5 million upfront, unspecified regulatory and commercial milestones, and a royalty rate in-line with industry benchmarks. The drug named GDC-0084 by Genentech would, under Kazia's stewardship, go on to be given the formal name of paxalisib in 2019.

Box 2: The PI3K-AKT-mTOR Pathway

The following was summarised from Yang et al (2019) Mol Cancer. Paxalisib Inhibits PI3K, as well as the enzyme mTOR, in the PI3K-AKT-mTOR intracellular pathway. The pathway plays a key role be in the development of cancer. Under normal conditions, the pathway's level of activity simply leads to normal cellular growth and differentiation. If a mutation(s) leading to increased activity of the pathway occurs, it can affect many cellular activities, including the reduction of apoptosis (programmed cell death), increased cellular proliferation and to the over-differentiation of adult stem cells, specifically neural stem cells. The overall effect is to further contribute tumour growth. Paxalisib works by inhibiting the pathway, pushing the tumour cells towards normal levels of activity resulting in the inhibition of tumour growth, more so than tumour cell death.

Focus on Paxalisib

Mechanism of Action

Paxalisib Inhibits the enzyme PI3K (phosphoinositide 3-kinase), as well as the enzyme mTOR, in the PI3K-AKT-mTOR intracellular pathway (see box 2 for further information). Increased activity of this pathway in tumour cells, results in the cells living longer and dividing faster, leading to more rapid growth of the cancer. By inhibiting PI3K and mTOR, paxalisib slows the activity of the pathway down, in turn, slowing down the growth of the tumour (i.e. cancer). When Kazia licenced paxalisib from Genentech, the belief that it was slowing the PI3K pathway down was based on what was known about the four other PI3K inhibitors. This year, however, the researchers at Genentech published a paper based on the phase I trial they had conducted and tests they had carried out on patient samples (Ellingson et al (2020) Clin Cancer Res). The article quite clearly shows that paxalisib does cross the BBB and it ties the drugs mechanism of action with the clinical outcomes in the study. Having this information may seem trivial, but many drugs with fantastic theory behind them end up failing in clinical trials, because the theory did not pan out in real life. Ultimately, having this kind of data reduces a drug's risk profile.

Using Paxalisib as a Targeted Therapy

Targeted therapies have become all the rage over the last ten years, with the term personalised medicine now commonplace. A targeted therapy is one that takes advantage of a specific known genetic variation an individual has in their tumour (cancer). The drug is termed personalised because not all tumours have the same genetic variations. In the case of paxalisib, genetic changes can occur in the cells of the cancer which causes the PI3K-AKT-mTOR pathway to become more active than it should be. Paxalisib is, therefore, said to be personalised to patients who have cancers of that genetic type.

As you will see, it turns out that in some instances it is worthwhile targeting paxalisib at certain individuals and in some cases it is not.

Aberrant expression of PI3K appears to be found in about 80 - 90% of cases of GBM (The Cancer Genome Atlas Research Network (2008) Nature, Brennan et al (2013) Cell) and this percentage almost certainly increases with radiotherapy. Because the cells of nearly all GBMs aberrantly express PI3K, there is little added benefit from testing patients before given them the drug, because, when tested, nearly all patients will be shown to have aberrant expression of PI3K. The common-sense approach is to just give them all paxalisib.

Aberrant PIK3 expression, however, is not nearly so universal in cancers that have spread or metastasised to the brain from a solid tumour (i.e. as opposed to a blood or bone marrow tumour) elsewhere in the body. For example, 50% of breast tumour BMs have

dysregulated expression of PI3K (Adamo (2011) Breast Cancer Res). The toss of a coin. There are two implications which stem from this. The first one is reasonably obvious. In the clinical setting, it is the patients who do not have aberrant PI3K expression that benefit from all patients having their cancers tested. It means they can skip treatment with paxalisib and move on to something that has a better chance of prolonging their life. From a drug development point of view, a cancer drug will beat the control arm in a clinical trial much more often, if the tumours of all of the participants in the trial carry the genetic change that allows the drug to work. Including patients who do not carry the change and will not respond to the drug, dilutes the apparent response to it. The breast cancer example from above illustrates the point well. For every cancer that responds to paxalisib, there will be one that does not. Roughly speaking, to show what is termed a significant difference between the arm that gets paxalisib and the control arm, which does not, you will need to include twice as many people in a trial that takes all comers, compared to one that excludes patients that will not respond to paxalisib.

The key thing that Kazia will take home from these differences is that they need to understand the underlying genetic make-up of any target group of patients they may want to study paxalisib in before they start a trial or allow someone else to. Failing a clinical trial is fine. Even Keytruda® has failed several. However, if it can be avoided, it should.

Clinical Trial Strategy

While it is of academic interest to understand how a drug works and how it might be used in the clinic, it is how you apply that knowledge that creates commercial interest. Kazia clearly decided that to build value in paxalisib it needed to build out the clinical trial program of paxalisib beyond just GBM. If they did not do that paxalisib's value would be defined by GBM and only GBM. It is important to understand that a company does get some of the money they spent on a negative trial back, in a trade sale or partnership. The reason is that a negative trial result helps to create certainty around an assets value. Essentially, risk is reduced

Table 2. Details of the Four PI3K Inhibitors Approved by the FDA.

Company:	**Gilead**	**Bayer**	**Verastem**	**Novartis**
Drug:	idelalisib	copanlisib	duvelisib	alpelisib
Brand Name:	Zydelig®	Aliqopa®	Copiktra®	Piqray®
Date of FDA Approval:	2014	2017	2018	2019
Indication(s):	chronic lymphocytic leukemia, follicular lymphoma, small lymphocytic leukemia	follicular lymphoma	chronic lymphocytic leukemia, follicular lymphoma	HR+ HER2- breast cancer
PIK3 Isoform Inhibited:	δ	α, β, γ, δ	γ, δ	α
Side Effects:	**Black Box Warning** for fatal infections, hepatotoxicity, and GI complications.	Warnings for **fatal infections**, hyperglycaemia, and cytopenias.	**Black Box Warning** for fatal infections and fatal GI, skin, and lung complications.	Generally, more tolerable, but with high rates of diarrhea, rash, and hyperglycaemia.

Source: Kazia Therapeutics, M. Sinatra Research.

and value goes up. That is only part of the equation, though. It means there is a reason to tolerate a failed trial. It does not mean you should get reckless and go out looking for them.

The first clinical trials that Merck undertook with Keytruda® were in melanoma and lung cancer. They did this because they knew that Keytruda's mechanism of action was well suited to the genetic makeup of these tumours. Still while Merck was focussed on these two cancers, they began earlier stage trials in other cancers that they knew less about.

Kazia already knows its drug is suited to GBM and that is the indication the company is most invested in. However, Kazia has also gotten a study of paxalisib going in a very nasty childhood brain cancer, called diffuse intrinsic pontine glioma or DIPG for short. DIPG is another cancer primary brain cancer known to have a very high level of aberrant expression of PI3K. It is also a cancer that if paxalisib can do anything at all to slow it down, there is a fair chance of quick regulatory approval around the corner. Both valid reasons for undertaking the study.

Recently Kazia announced a new study that paxalisib would begin in early in the new year (2021) . In another primary brain cancer called, primary central nervous system (CNS) lymphoma (PCNSL). The rational for undertaking a study in PCNSL is straight forward. Three of four PI3K inhibitors on the market have proven efficacious against lymphomas and PCNSL is just a lymphoma that has occurred behind the BBB.

A further three trials are devoted to fleshing out paxalisib's ability to deal with cancer that has spread to the brain from a solid tumour somewhere else in the body. These are the BMs we mentioned earlier. BMs are becoming more prevalent. This appears to be a function of three things: 1) Improved treatments for the primary tumours from which BMs emanate are keeping patients alive longer, allowing for the disease to spread to the brain more often; 2) The aging population, since the incidence of cancer increases

with age and; 3) Improved detection of BMs, as imaging of the brain has improved (Ostrom et al (2018) Handb Clin Neurol). The point being that this is growing area where efficacious therapies are badly needed.

The trials that Kazia has underway or will start soon are given in table 3 (bottom page 8). The exception is the pivotal trial of paxalisib in GBM. That trial is discussed in great detail later.

What should be clear from the information discussed thus far and in the contents from the table is that, the GBM program is the leading edge of the wave driving value creation, with the other trials are adding value they are also about defining the breadth of that value. The similarity between the way Kazia is developing paxalisib and Merck developed Keytruda® should not be missed. One of the reasons Kazia has been able to do this is the lack of therapies for brain cancers, in general. For Keytruda® to achieve success, it has had to address numerous different solid tumours. To a certain extent, though, while the tumours have been different, there are underlying commonalities that are the same, that Keytruda® is exploiting.

To be clear, data adds value to paxalisib and Kazia is building this value out as well and as broadly as any company its size can.

FDA Designations

Paxalisib has been granted orphan drug designation (ODD) and Fast Track Designation (FTD) for GBM. For DIPG, it has been granted ODD and Rare Paediatric Disease Designation (RPDD).

All of these designations aim to do the same thing and that is to make it as easy as possible for a company to produce (A) the best quality clinical trial data to support its development candidates, (B) the right data to support FDA approval, (C) a high quality New Drug Application (NDA). Where possible and within the FDAs rules and requirements, the FDA will provide incentives, such as shortened review times, market exclusivity and the possibility of a Priority Review Voucher (PRV) for those with RPDD.

An approved orphan drug is automatically given 7 years of market exclusivity in the US and, if granted by the EMA, 10 years in the EU. With the various indications Kazia has for paxalisib, patents probably will not matter.

Should paxalisib be approved for DIPG, it will receive a PRV. These vouchers entitle the holder to an FDA review time of 6 months, rather than 10 months. Under normal circumstances a company needs to meet the FDA's criteria for priority review. With a voucher, though, any company can get a priority review for any drug they please. PRV's can be on-sold, the price for which has settled around the USD100 million mark.

Box 3 provides further details on the various FDA designations.

Box 3. FDA Designations

Orphan Drug Designation

- Granted for rare diseases/disorders that affect fewer than 200,000 people in the U.S.
  - Tax credits of 50% off the cost of clinical trials.
  - Waiver of new drug application fees (worth approximately, USD2.2 million)
  - Eligibility for market exclusivity for 7 years post approval

Fast Track Designation

- Granted to drugs for serious conditions & fill an unmet medical need.
  - More frequent meetings with FDA.
  - More frequent written communication from FDA.
  - Eligibility for Accelerated Approval and Priority Review.
  - Rolling Review, which means the FDA will work on sections of an application as they are completed, as opposed to when all are completed.

Breakthrough Therapy Designation

- Granted to drugs that may be significantly superior the standard of care in treating a serious disease.
  - All Fast Track designation features.
  - Intensive guidance on an efficient drug development program, beginning as early as Phase 1.
  - Organizational commitment involving senior managers.

Source: Adapted from FDA.gov.

A Quick Word About Trial Design

Under the normal circumstances, the FDA requires two large, multicentre, blind, randomised, controlled trials (RCTs) for an indication before it will approve a drug.

The term "controlled" means that the study has at least two arms, an arm where the drug is trialled and another arm that the results of the "test arm" can be compared against using appropriate statistical methods to determine if the drug lead to better clinical outcomes. The second arm is termed a control arm. The control arm can either be a placebo or another drug (termed an active control). Blind refers, in the first instance, to trial where the patient does not know which arm they are in. There can also be double-blind studies where neither the patient nor the doctor knows which arm the patient is in. For each additional person of significance involved in the trial (e.g. a patient's carer), a further level can be added. We have seen quadruple blind trials before. However, if the doctor and the

patient do not know which arm they are in, no one else should. Going beyond describing a study as double blind is superfluous, although it does help define key people in a study.

The reason clinical trials are designed like this is to eliminate each and every possible source that might bias the trial results. For example, one source of bias just about everyone has heard of is the "placebo effect". It is where the patient feels better just because they have been given something. This effect can readily be shown in sham clinical trials. Where the key or primary outcome(s) of a trial depends on a patient (or even a doctor) making a qualitative assessment of a clinical outcome, such as in the case of pain, it is never possible to completely get rid of the placebo effect. With cancer clinical, like Kazia's, though, the placebo effect is not an issue.

Clinical trials with a gold standard general design will be referred to as multicentre, double-blind, randomised, controlled trials (RCT). In the later stages of trialling, where a drug's efficacy or ability to improve a clinical outcome is the primary outcome of a study, is when control arms are truly required. Still, when Kazia gets to that stage in the trialling of paxalisib, they probably will not have many studies which are of the gold-standard multicentre double-blind RCT design. It simply has to do with the nature of the indications they are going after.

Gold standard is often used to describe one type of trial. However, the condition will determine how close you can get to tht design. l effect, the gold standard is defined by the condition being studied. GBM Agile, the pivotal in which paxalisib will be studied in and which will determine if paxalisib receives marketing approval by the FDA and other regulators, is a gold-standard RCT as far determining the effect of paxalisib on the overall survival of patients with GBM. It lacks blinding because it is not feasible in this setting. Nonetheless, it is still the gold stand, as far as GBM trials are concerned. They all lack blinding.

There are two reasons why later-stage studies will not have a control arm. The first is that, in cases of serious or life-threatening diseases where no alternative treatment exists, it is considered unethical to enrol patients in a trial where they are not given the drug being tested. The second is that running a controlled trial may not be feasible. This is especially true of rare and ultra-rare diseases. In some of these instances, you may not simply be able to enrol enough patients in a reasonable period of time to have a

Table 3. Ongoing Studies of Paxalisib and Select Details About Them.

Trial:	Glioblastoma Multiforme with Unmethylated MGMT Promoter Status	Diffuse Intrinsic Pontine Glioma	Primary Central Nervous System Lymphoma	Solid Tumour BMs with Genetic Testing	PI3K Over-Expressing Solid Tumour BMs in Combination with Radiotherapy	Breast Cancer BMs in Combination with Trastuzumab
Sponsor[1]:	Kazia Therapeutics	St Jude Children's Research Hospital	Dana-Farber Cancer Institute	Alliance for Clinical Trials in Oncology	Memorial Sloan Kettering Cancer Center	Dana-Farber Cancer Institute
Trial Identifier:	NCT03522298	NCT03696355	TBD	NCT03994796	NCT04192981	NCT03765983
Phase:	II	I	II	II	I	II
Trial Size:	n=30	n≤41[2]	n≤25	n≤150[3]	n≤36[2]	n≤47[2]
Start Date:	May 2018	Nov 2018	Jan 2021	Aug 2019	Dec 2019	Feb 2019
Est. Final Data[4]:	1H CY21	Q1 CY21	Q1 CY23	2H CY21	End CY22	End CY21
Potent. Interim Data:	Nov 19-20 CY21	Nov 19-20 CY21	Q1 CY22	1H CY21[5]	2H CY21	Q4 CY20

Source: ClinicalTrials.gov and M. Sinatra Estimates.

1 Trials where Kazia Therapeutics is not listed as the sponsor are investigator lead trials.

2 The studies have a dose escalation cohort, which may or may not lead to the maximum number of patients being recruited.

3 Paxalisib is one of three (3) drugs being used in this trial and the study will complete when combined total of 150 patients have been treated.

4 M. Sinatra estimate based on ClinicalTrials.gov estimated primary completion date.

control arm. There are also cases where alternative treatments may exist, but doctors still are not willing to enrol their patients in a trial for their own ethical reasons. This is particularly so when children are involved.

Trial design can be confusing, particularly in the rea Kazia is working, suffice to say:

1) Kazia is unlikely to be able to run many pivotal trials where a multicentre, double-blind, RCT will be possible. The regulators understand this and will simply be looking to make sure the company has done all that it can.
2) The further you move away from a rigid multicentre double blind RCT design, the easier it is to move a drug through clinical trials and, to a certain extent, the regulatory approval process and that is a good thing for Kazia,
3) Still, investors must be cautious about how they interpret studies with out a control arm. It can be easy to see differences that are not really there.

Studies without a control arm, generally, only have one arm and are, therefore, termed single arm studies. With studies of this nature, investors are always tempted to find earlier studies from which they can try and determine what the results of a control arm might looked like to satisfy themselves that the drug of the company they have invested in has produced good results. In the industry, such controls are referred to as historical controls. While there is nothing inherently wrong with doing this, the issue is the amount of weight they give to the comparison. Two studies never contain identical populations of patients who were treated exactly same and these differences can have a profound effect on the results. This only becomes apparent, though, when the same drug is put through a controlled trial. Generally, when a company studies its drug in single arm study, that is the most appropriate trial design to obtain the answers a company is looking for. Investors simply need to remember the limitations of this type of trial and factor that into their investment decisions.

Single arm trials, however, are the most appropriate type of trial to run in many situations and 2/3 of cancer trials are of a single arm nature. Moreover, we have never seen Kazia study or allow paxalisib to be studied in a trial that was not the most appropriately designed study for paxalisib's level of development for a particular indication.

Paxalisib: Defining a Development Path for GBM

An accepted practice in cancer drug development has been to study the drug in the last line of treatment for that cancer. There are a range of reasons for this but, suffice to say that with paxalisib, that strategy did not return the results that were hoped for. It is generally accepted that cancers become harder to treat as they progress and see more lines (different drugs) of therapy. Kazia presumed the reason Genentech obtained the results it did was because the patients' cancers were too resistant to treatment by the time, they studied them. From the literature, it appears any drug that comes after first-line treatment in GBM will be facing a near impossible task until we understand the disease a lot better.

In working out how they would study paxalisib to give it the best possible chance at success, Kazia hypothesized that taking the opposite strategy to Genentech and studying paxalisib earlier in the treatment of GBM patients may be the way to go. The reason for this that GBM is a very aggressive cancer and patients decline rapidly. By treating the GBM patients as early as they possibly could, they would also be treating the cancer when it was in its least resistant state. This would give paxalisib a better chance of having a clinically meaningful effect. Kazia also thought there might also another benefit to treating the cancer a patients earlier. Since they would be healthier, they may be able to tolerate a higher dose of paxalisib.

Box 4. Temozolomide and unmethylated MGMT promoters.

Temozolomide is a DNA damaging agent. It does so by alkylating the 0^6 position of the base guanine. Under normal circumstances, this would lead the cell to undergo apoptosis. The MGMT gene, however, encodes a DNA repair enzyme termed O^6-methylguanine–DNA methyltransferase. When the MGMT gene is methylated, it is inactive and temozolomide works. However, if the tumour cells have not developed a mutation resulting in the MGMT promoter remaining unmethylated, it will be expressed. As the name implies, the MGMT enzyme removes methyl groups from the O^6 position of guanine and effectively stops temozolomide from causing the desired result. Hence why an opening is left for paxalisib to exploit in the front-line treatment of GBM patients. Yu et al (2020) Front Oncol provide a review of the MGMT promoter and temozolomide.

As it turns, temozolomide, the only drug approved for treating GBM, has essentially no activity in approximately two-thirds of the GBM patients it is given to (Hegi (2005) N Engl J Med). Box 4 goes into this point further. The two-thirds of patients that do not respond to temozolomide have GBMs made up of tumour cells which have what is termed an unmethylated MGMT promoter. Moreover, MGMT tumour promoter status (unmethylated or methylated) can be identified prospectively (i.e. before treatment with temozolomide), allowing the course of treatment for those with unmethylated MGMT promoters to be changed. This can be done because it allows those patients to be treated as a distinct, separate, group. In this setting, it creates a group of newly diagnosed patients that represent a first-line unmet medical need. This was exactly what Kazia was looking for, in that this would be the healthiest group of patients they could have possibly hoped to have access to.

With that, paxalisib's pathway to the regulator (FDA, EMA) was now defined. Kazia would study paxalisib in the first-line treatment of patients with GBM who had unmethylated promoters. The patients would be at their healthiest if things were done this way and their tumours would be at their least resistant.

Ongoing Phase IIa Study of Paxalisib in the First-Line Treatment of GBM Patients

The design Kazia chose for its first study of paxalisib in GBM patients needed to answer at least four questions. They were:

1) Was it feasible to use paxalisib in the way they were intending,
2) What was the MTD of paxalisib when used in this manner,
3) What impact did paxalisib have on key clinical questions about how well the drug worked, and
4) What should they do to further develop paxalisib for GBM?

The results they have obtained for paxalisib from the phase II study are given in table 4. Kazia has access to this data because the study, like the others they are looking at paxalisib in, are single arm, open label studies. In short, this means taking a look at the results before the trial is complete is allowed, although it can be frowned on if done too much.

Kazia has or will get an answer to the four main questions they wanted answers to.

There was no trouble recruiting study participants and nothing has been made public that would suggest using paxalisib this way would present a problem. From my perspective, I cannot think of anything that could arise which has not already that would not have already reared its head. The point being that Kazia has shown that treating patients in this manner causes no unforseen problems.

The study commenced at 60mg paxalisib daily. The patients tolerated that dose and the study progressed to 75mg/day. Unfortunately, dose related toxicities were seen in two patients at 75mg/day and the dose was deemed too toxic. Consequently, the MTD was determined to be 60mg/day. A major aim of the trial was achieved, though. **The MTD of 60mg was 33% higher than the dose used in the Genentech study and Kazia would be able to use this dose for the remainder of the current study and in future trials.** A higher dose of a drug does not always mean better efficacy, but without evidence to say this would be the case, you would have to go with the higher dose, just on the balance of probabilities that you would get a better response.

Table 4. Interim Results from the Ongoing Phase II Trial of Paxalisib in the Treatment of GBM Patients with Tumours with an Unmethylated MGMT Promoter.

	Median PFS (Months)[1] n=30	Median OS (Months)[2] n=9
Paxalisib	8.5	17.7
Historical Control[3]	5.3	12.7

Source: Kazia Therapeutics

1 Progression Free Survival. Final data from MTD cohort and expansion cohort.

2 Overall Survival. Preliminary data from the MTD cohort only

3 Derived from Hegi et al (2005) N Engl J Med

Moreover, the safety profile of paxalisib was similar to that seen in the phase I Genentech study. This is important because, as can be seen in table 2, two of the other four PI3K inhibitors on the market have boxed warnings, another warns of fatal infections, while the fourth, alpelisib, doesn't carry any warnings about an increased risk of death, it does state that patients on the drug exhibit high rates of diarrhea, rash, and high blood sugar (hyperglycaemia).

A boxed warning is the most stringent warning the FDA provides to doctors and it is done via the way of a black box on a drug's packaging. The FDA describes boxed warnings this way, "black box warnings, or boxed warnings, alert the public and health care providers to serious side effects, such as injury or death". So far, Kazia and Genentech have described a safety profile for paxalisib, that is milder than alpelisib, the approved drug with the most benign side-effect profile (table 2). Given the overall safety profile of drugs in this class (i.e. PI3K inhibitors), investors should still watch for signs that paxalisib might have rare, but very significant side-effects. **Still, the side-effect profile seen so far is more than fine, particularly in the light of the high mortality rate of patients with GBM**.

PFS is defined by the US National Cancer Institute as the length of time during and after the treatment of a cancer that a patient lives with the disease but it does not get worse. PFS is considered to be a reliable surrogate marker of OS. A final median PFS of 8.5-months was recorded in the combined (n=30) dose escalation cohort and expansion cohort. This is 3.2-months longer than the 5.2-months recorded by the historical control from Hegi (2005) N Engl J Med. **While a 3.2-month extension of PFS does not sound like much, when you consider it is 61.5% greater than that seen in the historical control arm, it does put things into context**. Overall, this is a solid result.

The median OS estimate from the trial so far is 17.7-months and is 5.0-months greater than that seen in the historical control of 12.7-months from the Hegi study. This observation, however, is based only on the nine (9) patients from the dose escalation cohort. As such, this number is not very solid and could still change appreciably when the 21 patients (2.3 times the number of patients in the dose escalation cohort) from the expansion cohort of the study are added to the data pool to finalise the results.

The dose expansion phase of the trial also looked at whether it was better for the patients to have paxalisib with food or while fasting. No data on that subject appears to have been released, yet.

These results speak for themselves when answering the third question Kazia needed an answer to from this trial, what impact did paxalisib have on key clinical questions about how well the drug worked? At the moment, a question of how good the final data will be, rather than whether paxalisib has a clinical effect or not.

While there is still a significant amount of OS data to come, the fourth question has really already been answered, as well. That answer is that Kazia has decided to move paxalisib into a pivotal trial in newly diagnosed GBM patients with unmethylated MGMT promoters. A pivotal trial will give Kazia more safety data to support the use of paxalisib, but, much more importantly, it will also be definitive assessment of paxalisib's ability to extend life.

We will see an update to the data from the phase II GBM trial on either the 19th or 20th of November (US time) this year (2020), when the data is presented at the Society for Neuro-Oncology Annual meeting. The final trial results are likely to be released in the first half of next year (2021). Having said that, it is possible we could see a final OS or possible a minimum OS figure in November, if enough patients have died.

GBM AGILE: Paxalisib's the Door to Regulators

Kazia had been planning to run its own phase III trial up until they agreed with Global Coalition for Adaptive Research™ (GCAR) to join an ongoing study GCAR had established. This trial has been named GBM AGILE (AGILE = Glioblastoma Adaptive Global Innovative Learning Environment). AGILE came about as a result of the actions of neuroscience focussed academics frustrated with the lack of progress in developing new therapeutics for GBM. While the coalition is GBM focussed, it seems likely that it will look to broaden its activities to other disease states where therapeutic development has been slow. GCAR's website can be found here. In fact, this is already starting to happen with GCAR's involvement in a COVID-19 study.

Kazia undertook its own due diligence (DD) on the GBM AGILE trial, as any company normally would, with the main question being whether the results would pass muster with the FDA. The DD confirmed what GCAR had promised. It showed that the results from AGILE would be of regulatory quality, with the FDA having been consulted extensively in the trial's design. A global contract clinical research company, IQVIA, has been engaged to conduct the study. IQIVIA's involvement is important since it is IQIVIA and companies like them who run trials for the major biopharma companies. In short, they know how to run a trial to the standards required by the FDA and the EMA. Another factor in Kazia's decision to join the AGILE would have been that GCAR, who are responsible for administrating AGILE, have been recruiting senior managers from industry and academia, with most appearing to have worked in both. Once it was decided AGILE would deliver a regulatory body quality trial, it was simply a matter of determining, on a cost-benefit basis, whether Kazia could design and fund a better study on their own. The company has been quite clear, that AGILE will provide them a more robust data set and at a lower cost than anything they could do on their own.

GCAR has set-up a master protocol for GBM AGILE which can be found be found here: NCT03970447. Kazia will have its own clinical trial protocol, which will fit in with the master protocol.

GBM AGILE is an ongoing randomised, open label trial, control trial. Where GBM AGILE departs from a normal clinical trial, is that it is designed to run continuously, such that new, promising, drugs can be cycled into it and then out when sufficient data has been gathered to determine if a drug is efficacious. The control arm of the study is shared between whatever drugs are being studied in AGILE at the time. Looking at AGILE from a cost point view, many of the expensive things that a company has to do to conduct a pivotal trial have already been done. Things like contacting and reaching agreement with trial sites, training staff members in the trial's conduct, logistics, etc take an inordinate amount of time and money, as does shutting the trial down when it is over. All of this has been pretty much been done by GCAR.

To illustrate what this means from a financial point of view, a clinical trial of 400 patients, is likely to set a company back in the range of about USD100k per patient, although it can vary widely between studies, according to a study undertaken by Eastern Research on behalf of the US Department Health and Human Services (here). If GCAR simply covers the cost of the control patients, the cost of the study is, at least, halved, from USD40m to USD20, in my opinion. It could be cut further given Kazia is likely to be the only second company to put its drug into the study. To stay on the conservative side, however, I will stick with an estimate of USD20 million. That estimate looks pretty good since management said Kazia will end up raising a little over AUD25 million in a recent rights issue, before fees.

The AGILE trial incorporates further fairly unique trial design features, than simply its continuous nature and shared control arm. Agile is in fact two clinical trials rather than one. When a new drug is put into AGILE, it is first studied in a phase IIb study. This is to ensure that that the drug is as promising as the study coordinators believed it was when they offered to incorporate it into AGILE in the first place. Normally, a drug would undergo a phase IIb study to ensure that the efficacy signals seen in earlier trials were, at least, broadly accurate. With orphan indications, though, smaller companies often theorise that they are saving money by attempting to skip a phase IIb assessment. This logic is flawed to a certain extent though, because by doing so, the company is just taking a much bigger bet with higher risk. The design of AGILE makes conducting such a phase IIb study relatively painless for the company, because, if their drug is successful, it simply transitions into the phase III or pivotal study without missing a beat.

To ensure AGILE is efficient at assessing drugs, both the IIb trial and the phase III or pivotal trials are adaptive in nature. Adaptive means that each patient's trial results are fed into a database as soon as they are available. The computer housing the database is programmed to assess the trials results after each patient's data is entered. The computer then reworks the study parameters and adjusts how many patients will be required to show that the drug is efficacious. It also examines the study for futility. A clinical trial may be abandoned for futility, if the trial results reach a point where it becomes highly unlikely that the study drug will demonstrate a statistically significant improvement over the control arm. In this way, each drug that enters AGILE will see only enough patients

to determine whether it is efficacious or not. There is an opportunity cost when a drug is not studied in enough patients and a real cost when it is studied in too many.

AGILE is an open label, randomised trial, which means patients are randomised by a computer to the test or control arm and the patients and doctors **will know** which arm they are in and what drugs they are receiving. With open label trials selection bias can work against the drug being studied, because, although well intentioned, doctors often want to see their sicker patients given the study drug. This sort of behaviour, though, is not really seen in Western trials, because all of the patients end up being taken care. In some trials in Eastern, if the patient is not randomised to the study drug arm, they can struggle to pay for treatment. That is the point at which the doctor may try and get slide them into the treatment arm, without being noticed.

This results in the study drug being placed at a disadvantage. It could also keep drugs off the market that should have been approved. In AGILE, the control arm patients are treated with the current standard of care (radiation followed by temozolomide), while the test arm patients are given radiation followed by paxalisib. Other than not giving control arm patients' paxalisib, doctor's will, as always, treat control-arm patients to the best of their ability, as they will those receiving paxalisib.

The statistics used to assess a drug's performance as it moves through the AGILE study are fairly complex and describing them here is not a prudent use of your time. Suffice to say that paxalisib the study will finish at the point sufficient data has been collected for the computer to make that call. The highest number of patients any one drug will see is 200 and that test arm is likely to be compared against 200 and 250 control patients. If a drug does see the full 200 test arm subjects, it is likely to mean that the drug has registered a strong trend, but not significance and accordingly has failed the trial.

Currently, GBM AGILE is up and running at 28 different hospitals around the world, with plans to add more. Regorafenib, an approved colorectal cancer drug in the US and EU, from Bayer is the first drug to have entered GBM AGILE. Paxalisib is likely to start the trial at the end of this year or beginning of next (2021). VAL-083, a drug from Kintara Therapeutics (NASDAQ: KTRA), looks like it will be the third drug in the trial, perhaps in mid-to-late Q1 CY21.

We believe 24 to 30 months is a reasonable estimate of the amount of time the study is likely to take. However, due to the study's adaptive nature it is hard to make solid estimates, when you cannot be sure what the final number of patients will be.

In general, when a study such as GBM AGILE takes longer to conduct than expected, it is generally taken as a positive signal. The logic from interested parties is usually, "well, it is taking longer, because the drug is working and patients are living longer, increasing the time it takes to get a result". The logic does hold water, but it could also be that all patients are living longer. There is no need to go over this type of stuff just yet in terms of paxalisib, but I would suggest investors always temper the weight they give to positive signals such as this. There are almost always alternate explanations that can explain events that are as logical as the factored explanation.

As you would expect for later stage studies, the primary endpoint for AGILE is OS. OS is the gold standard endpoint not just for cancer, but any disease that can limit life severely. PFS will be a secondary endpoint, as well as a number of other parameters. The primary endpoint is the primary endpoint, though, and secondary endpoints mean little if you do not have a significantly improved primary endpoint.

The Market - Unmethylated GBM

The United States National Cancer Institute has estimated the country will see 23,890 new cases of brain and central nervous system cancers in 2020 and that there will be 18,202 deaths from the same (NCI). According to the Central Brain Tumour Registry of the United States, the average number of incident cases of GBM was 11,883 (Ostrom et al (2019) Neuro Oncol) per year.

In terms of MGMT promoter status, it has been estimated that between 35% and 45% of GBMs have methylated promoters (Hegi (2005) N Engl J Med). Put in terms of paxalisib's target market, between 55% and 65% of GBMs have unmethylated MGMT promoters, which translates to a target market of between 6,508 and 7,691 GBM patients per year in the US. Since paxalisib would be the first line of therapy, using the full target market as the addressable market (i.e. the maximum number of patients that paxalisib could be used to treat in year) is a reasonable assumption.

Paxalisib Pricing

Drug pricing, particularly in the US, is an art, rather than a science, with the prices commanded by new cancer drugs especially high. A study of cancer drugs approved in the US between 2009-2017 and in Europe up until September 1st, 2019 found the median cancer drug price in the US was 2.31 times (interquartile range: 1.7 to 3.17) higher than the median price in Europe (Vokinger et al (2020) Lancet Oncol).

A further study compared the cost of drugs, as adjusted to 2018 prices, which had received breakthrough therapy designation (BTD) to those that did not. The study was done on cancer drugs approved in the US, between July 2012 to December 2017. Over that period, the FDA approved 52 drugs for 96 solid tumour indications, with 40% (n=38) indications approved following granting of

BTD (Molto et al (2020) Cancer). Those drugs that had received BTD had a median price of USD12,592.5 per month compared to those that did not of USD10,062 per month. The costs, on annual basis, for the two groups of drugs were USD163,702 and USD130,800, respectively, assuming thirteen 4-week periods per year.

The intention of the BTD program is to obtain drugs for patients who cannot wait on to the market as soon as possible. One would certainly like to have thought that drugs which the regulatory authorities think will have major impacts on patient health ultimately do, and that companies are rewarded for making that impact possible. The result should not really be surprising. That is how capitalism is supposed to work in the healthcare system.

Finally, launch prices for new cancer drugs averaged USD143,574 between 2012 and 2018. The average price in 2017 was USD209,406 and in 2018 it fell to USD175,578 (Global Oncology Trends (2019) IQVIA Inst). Median prices were considerably lower, though. The median price for new brand drugs in 2017 was USD162,150 and in 2018 it was 148,800. This suggests it is a smaller number of high-priced cancer drugs that are lifting the average up.

How much investors should really take home regarding the drug pricing numbers that make it into the market is debatable. The reason is the numbers really are a sham, so much so that the biopharma industry invented an accounting term called, “net revenue”, to explain the lack of a clear link between the list prices they have for drugs and the money that they earn through the sales of therm. While it is not clear that anybody has a great handle on how drug pricing actually works in the US on a granular level, but broadly the reason they seem to have ended up with the sort of system they have is because drug companies don’t like to reveal more than they need to about that side of the business for competitive reasons, most likely with a liberal sprinkling of shareholder management on the side. Essentially, a number of groups sit between the biopharmas and their customers, the patient. Since each of these groups can influence how much of a biopharma’s product will actually make it through to the patients, they are in a position to claim some of the revenue stream that they allow through. Money that many people would think just goes back to the biopharma companies and stays there, instead ends up in somebody else’s pocket through a variety of mechanisms, like discounts and coupons, just to mention a couple.

A study was undertaken in 2017 which, among other things, aimed at estimating the actual size of the gross to net margin (Reports (2018) IQIVIA) They calculated that it was about 28%. There are others who argue it is bigger and we tend to fall on the side of those who think it is bigger.

Building Out Paxalisib’s Value: Follow-On Indications

The five trials we look at next, reflect Kazia’s effort to build out the data on paxalisib beyond Kazia’s core focus of GMB. Paxalisib’s unique ability of being able to cross the BBB has given Kazia a fairly straight forward path to follow. Test paxalisib in as many forms of brain cancer as can be feasibly done. The lack of new drugs to treat brain cancers testifies to the fact that this will not be the easiest of roads to walk. The reality, though, is that paxalisib is not expected to cure these patients. It just has to demonstrate small, but clinically significant improvements in OS.

Off the top of my head, I cannot think of another ASX listed biopharma who has ever had as many trials going at the same time as Kazia has now. To do this, Kazia has had to lean heavily on public/government/charity funding, such as through government research grants and the like. Kazia is also making the most of the relationships it has built with clinicians and researchers in brain cancer at many off the highly regarded US cancer hospitals and institutes over the last five or so years. Certainly, having a drug that was born in Genentech would have helped to open a few doors and there is no question the science behind paxalisib would have impressed them. Nothing tops data, though, and, while I am sure the researchers would have been saying, “well, the patient numbers in the trial are only small at this stage”, **I am also certain they would have been wondering on their way home on the night, whether they would be using paxalisib with their brain cancer patients in three to four years.**

The studies are referred as investigator lead studies (ILS) by industry, because it really is the investigator who is in charge of the study. In the past, commercial drug development companies have viewed ILS’ with a certain degree of scepticism. The main reason being that there was a tendency for investigators to go their own way with these studies, without thinking, like the company who owns the drug would, about the drug as an investment that should have its return maximised.

In ILS’, the investigator, basically, assumes the role of the company and takes on ultimate responsibility for everything to do with the trial, including hypothesis generation, developing the study protocol, including the study design, organising for the appropriate submissions to gain their institution’s ethical approval to run the study, implementing the trial, recruiting the patients, collecting the data and, of course, analysing it, too. On top of those “internal” duties, the investigator needs to organise for abstracts to be submitted to conferences, often presenting the study results themselves, and, once the study is completed, they need to draft a paper and find a journal willing to publish it. Essentially, they are responsible for getting word about the study out to other clinicians and piquing their interest. When a larger pharmaceutical company takes on a trial, they pretty much have experts to cover each particular area off and, where they don’t have the in-house skills for things, they will have consultants they regularly use that can be brought in at a moment’s notice to apply their own unique talents.

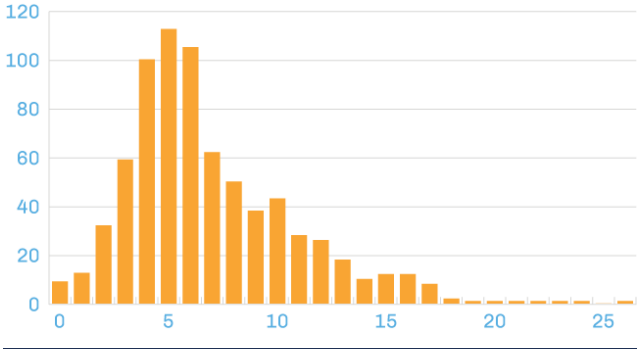
The central question is whether these trials will fulfil Kazia's aim of defining paxalisib's value? I am certain the answer is yes. While there are differences in approach between academics and biopharma companies, the groups have been working side by side for decades now. With that, has come an appreciation for what each side brings to the table, which has worked to bring them closer together. In our view, the key thing that Kazia must do is to maintain as close a relationship as possible with the investigators and to provide them with as much support as possible. For investors, it is important to remember that these are not pivotal clinical trials. The results and details will never be parsed by the regulators to near the same level of detail as pivotal trial data will be. This means, from a commercial point of view, the question of whether the trial informs Kazia's decision making is more important than the regulatory quality of the actual data. This difference may be subtle, but it is important and reduces the risk in handing the running of these trials over to investigators.

It is expected Kazia will take sole carriage of any pivotal trials that come about as a result of these earlier stage trials. GBM AGILE is simply an exception to that rule, because pivotal trials of its academic/commercial nature are rare. The data is the most important output of a pivotal trial and the process around the trial must reflect that. This is something that is beyond the workload and skill set of almost all academic investigators.

Clinical Trial: Diffuse Intrinsic Pontine Glioma

DIPG is a rare highly aggressive brain cancer that means certain death. To make it that much worse, it primarily occurs in children aged between 5 and 10 . At the time of diagnosis, life expectancy is 8 to 11 months and between 150 to 300 cases of DIPG occur per year in the US, as per DIPG.org. Figure 1 provides the distribution of cases by age in the United States. Surgery generally is not an option, because these cancers arise in a largely in-accessible part of the brain called the pons. The pons performs many important regulatory roles, but, probably, none more important than breathing, which, along with the aggressiveness of DIPG, probably explain its high mortality.

Figure 1. Age Distribution of DIPG cases in the United States



Source: www.DIPG.org

Treatment of DIPG is largely limited to radiotherapy, followed by experimental chemotherapy, because the tumours cannot be accessed for surgery. As such, DIPG is a classic unmet medical, which could be important, if and when, the regulator takes a look at the data from Kazia's current phase I trial.

It would be fair for the reader to ask why the ongoing GBM trial is called a phase II trial and this DIPG study is called a phase I, given the studies are virtually identical in design, with both having a dose escalation/finding cohort followed by an expansion phase at the MTD. The DIPG study does not look at the effect of food in the stomach of the patient, but it is looking at two different ways the children could ingest it. Despite the latter wrinkle, the answer to the question is that clinical trial phases are not a formal classification. Rather, it is simply a qualitative way of describing a clinical trial in terms of how far down the development path for a particular indication and drug is.

The first trials with a drug look primarily at safety and are often referred to as phase I studies. Phase II is when efficacy hits the scene, with greater emphasis being placed on efficacy the more advanced a drug is in phase II. Phase III or pivotal trials are those that are destined to be given to the regulator as part of a marketing approval or authorisation application, such as a New Drug Application (NDA) for the FDA. I would have called the study a phase I/II study, but that is just my personal opinion.

Although it is difficult to find data to reference it, expert opinion is that DIPG is similar to GBM in that 80%-90% of patients present with disordered PI3K expression, with the percentage only becoming greater as a result of radiation therapy.

The aims of this trial are to examine paxalisib's safety in children, determine a MTD and to take an initial look at the clinical activity of the drug.

The study has already successfully determined the MTD and it is 27mg/m^2 in children, which is comparable to the dose found for adults. Since children are growing rapidly dosage is based on weight, rather than using a one-size fits all doing approach. The study will also look to determine the rate and duration of radiographic response of the tumour to paxalisib (i.e. what happens to tumour size as a result of paxalisib treatment, as well as to collect data on PFS and OS.

The market will get its first look at data from this study in November (Table 3). A positive result would be momentous, given the lack of available treatments. This is a hard, aggressive, cancer to treat. On the back of positive results, I would expect Kazia to apply to the regulators for BTD. If it is granted, almost anything could happen from there, including a very quick marketing approval for

DIPG. That approval would almost certainly be conditional on Kazia conducting a pivotal trial in DIPG while paxalisib is on the market. Such an event may push other companies to start seriously running the ruler over Kazia. Small to mid-tier, established, biopharmas would be the ones expected to move first. These smaller established biopharmas usually have to bid for assets earlier than the big ones. A combination of further asset de-risking and the entrance of the big biopharmas on the scene, can push asset prices beyond the ability to pay of the smaller ones.

DIPG is a high hurdle for paxalisib to get over, given how fast the cancer progresses. Even a glimpse of efficacy from the results of the DIPG trial, could bode well for paxalisib's chances in GBM and some other less aggressive brain cancers.

Paxalisib has been granted rare paediatric disease designation (RPDD) for DIPG. The designation and the potential awarding of a priority review voucher (PRV) upon approval of the drug for the disease for which it received the designation were signed into law in an effort to provide an incentive to companies that would result in the increased development of drugs for rare paediatric diseases. **Kazia only becomes eligible for the voucher if they gain approval for paxalisib for DIPG from the FDA**. Should Kazia gain approval for paxalisib to treat DIPG, they will be given a PRV. Kazia is then free to do whatever they want with the voucher, including selling it to the highest bidder. A company holding a PRV can give the voucher back to the FDA and have the New Drug Application (NDA) of its choice receive a priority review rather than a standard review. The FDA is required to complete a priority review within 6 months, as opposed to 10 months for standard review. Since patent lives are finite, the use of a priority review voucher will gain the company using it an extra four months of sales. Moreover, since drugs are usually at or near peak sales when their intellectual property does expire, an extra four months of sales can generate significant revenue. For example, an extra four months of sales for a drug generating $3 billion a year in sales would be worth one billion dollars to the company. Typically, smaller companies sell their vouchers to bigger companies, while large companies tend to hang to any PRV's they receive to use later. If a company has a drug in development that they think will make more money in an extra four months of sales than the voucher will cost them, it makes sense for them to bid for a voucher. Vouchers are fetching around USD100m to USD125m. This would be a nice present for Kazia's shareholders. Having said that, USD100m is small change in the world of cancer drugs. Moreover, if Kazia is in a position to take paxalisib to the regulator for DIPG, it probably means that paxalisib is on course to make the kind of money that would make the proceeds from selling the PRV look like a waiter's tip.

Another benefit that could flow to Kazia from the DIPG is one regarding pricing. Drugs for ultra-rare diseases affecting children tend not to run into too much pricing pressure from insurers for a variety of reasons. This would give Kazia a chance to peg paxalisib's price at the higher end of the pricing scale before the drug is approved for higher incidence cancers. This should make it possible for paxalisib to maintain a higher price for the drug than it otherwise would.

Primary Central Nervous System Lymphoma

Just a few weeks ago, Kazia announced that paxalisib would be studied in a new trial for primary central nervous system lymphoma (PCNSL) to be undertaken with the Dana-Farber Cancer Institute. This is the second study, in addition to one in combination with trastuzumab for brain cancer metastases arising from a primary breast cancer, that Kazia is undertaking with the institute. The study is likely to begin early next year.

Lymphomas normally arise in the lymphatic system. The lymphatic system is part of the circulatory system and, to a certain extent, in can be visualised in the same manner as the circulatory system. Rather than carrying primarily red blood cells around the body, the lymphatic system carries white blood cells throughout the body. White blood are the cells that represent your immune system. There are several different types of lymphomas, but they all arise from white blood cells. PCNSL is the result of the malignant transformation of a white blood cell when it is within and confined to the brain, the spinal column, or the eye.

PCNSL becomes more frequent as people age and it also has a higher frequency in acquired immunodeficiency syndrome (AIDS) and organ transplant patients. The latter two indicate that a compromised or weakened immune system contribute to the development of the disease. PCNSL normally manifests itself due to symptoms caused by increased fluid pressure or its own physical pressure within the relevant area of the CNS. Mean OS from diagnosis is poor and thought to be 2 to 4 years (Nelson et al (1992) Radiat Oncol Biol Phys). PCNSL is a rare disease, but not as rare as GBM, with the number of diagnoses a year likely to be around 23,000 (Shiels et al (2013) Br J Haematol).

Surgery is of no benefit in PCNSL. Radiotherapy and chemotherapy are used to treat it initially. Radiation and a few drugs may be used to treat PCNSL. Nivolumab (Opdivo®, Bristol Myers Squibb) and rituximab (Rituxan, Genentech & Biogen) are two targeted therapies that are used where appropriate. A tyrosine kinase inhibitor known as Ibrutinib (Imbruvica, Pharmacyclics & Janssen) is also used.

The planned study will look at how well paxalisib performs when given to patients who have relapsed or become refractory (resistant) to existing therapies. This is a more standard indication to study a new cancer indication in, rather than putting it up against drugs that have been on the market and used for a long time. The primary endpoint of the trial is objective response rate. The study will be a single arm, open-label study and take approximately two years to complete.

This is a fairly obvious indication for Kazia to want to pursue with paxalisib. The reason is that three of the four PI3K inhibitors already on the market have been approved for lymphomas (table 2), which would suggest that paxalisib has a good chance of

producing a clinically meaningful result in this trial. The other PI3k's do target different sub-types of PI3K, but since paxalisib is a pan-PI3K inhibitor this should not matter too much.

Brain Cancer Metastases – A Growing Problem

Brain cancer metastases (BMs) represent the most common brain tumours, and are thought to occur in 25-50% of all cancer patients at some point (Posner (1996) Neuroocol; Johnson et al (1967) Clin N Am). Newly diagnosed BMs occur at 3X–10X times the incidence of newly diagnosed primary malignant brain tumours (Davis et al (2012) Neuro Oncol). As a general rule, Melanoma is the cancer most likely to metastasize to the brain, followed by lung cancer, breast cancer, kidney cancer and colorectal cancer. Importantly, the frequency of BMs in increasing. The is thought to be the result of three different factors (Hatiboglu et al (2020) Neurosurg Rev) that were mentioned earlier.

Clinical Trial: Paxalisib for Brain Metastases

This is a relatively straight forward study which looks at the use of genetic testing to guide the treatment of patients with BMs based on the mutational changes that have occurred in the cancer. The drugs being studied are paxalisib, abemaciclib (Verzenio®, Eli Lilly and Co.) and entrectinib (Rozlytek®; Genentech, Inc.). Each drug targets a different enzyme associated with cancer progression.

The trial plans to recruit 150 patients with BMs arising from a solid primary cancer. The total number of patients who end up being treated with each drug will depend on the frequency with which mutations the drugs can exploit occur. No effort will be made to balance the numbers between the different drugs.

From this trial, Kazia will begin to understand which solid tumours produce BMs that are amenable to treatment with paxalisib. Ultimately, data from this trial could support the undertaking of a pivotal trial using paxalisib to treat BMs that arise from a particular type of tumour, such as lung cancer. On the other hand, they may decide to do what is called a basket study. The primary endpoint of this trial is objective response rate. There is a whole raft of secondary endpoints, but one that will be interesting to see relates to the effect of the study drugs on tumours outside the brain. This will be our first look at whether paxalisib can generate a response on the other side of the BBB.

The trial is sponsored by the Alliance for Clinical Trials in Oncology, which, in turn, is sponsored by the US National Cancer Institute. It comprises approximately 10,000 cancer physicians and scientists from hospitals, medical centers, and community clinics, across the United States and Canada. It is designed to be a network through which new therapies for cancer patients can be assessed.

This study is set to conclude in the 2H CY21, but investors are likely to get a look at interim data sometime in 1H of next year (2021).

Clinical Trial: Paxalisib for Brain Metastases in Combination with Radiotherapy

This study will also use genetic testing to determine whether a patient is suitable for treatment. Qualifying mutations, however, are restricted to the particular subunit of PI3K which is responsible for an enzymes overall activity and only paxalisib will be used in the study.

This study really serves two functions for paxalisib. The first is that it will determine whether or not paxalisib can be given while a patient is receiving radiotherapy. While there is no reason to think that it cannot be given at the same time, medicine has become very science-based. I fit has not been shown to be so in a study, then it probably should not be done. The obvious benefit is that this will get the patient on drug sooner. It is also possible that the two therapies together could have a synergistic effect. Likewise, the opposite could be true, but, if that were the case, in general, the study would have been stopped by now and investors would have heard about it. The second is that this trial will serve to beef up Kazia's knowledge of how well paxalisib performs as a treatment for solid tumour derived BMs, which ones it performs best in and, importantly, it will allow Kazia to make more certain decisions about the direction it wants to take paxalisib in the future as far as BMs are concerned.

This trial is very similar in design to the GBM and the DIPG trials, in that it starts with a dose escalation cohort to determine an MTD and then moves into an expansion phase in which another 12 patients will be recruited at the MTD. The primary endpoint is safety and determination of an MTD. The main secondary endpoint is tumour response. This study is sponsored by the Memorial Sloan Kettering Cancer Center, which is probably one of, if not the, most recognised hospital around the world in terms of cancer care and research.

This study commenced in December 2019 and is due to complete in December 2022. Like all of the studies paxalisib is involved in, this one, too, is an open label trial, so the barrier to interim analyses is lower. Kazia expects the principal investigator to present at a conference in the first half of next year and that is when investors should get to see and interim analysis of how things are going.

Clinical Trial: Paxalisib for Brain Metastases Arising from Primary Breast Cancer

Of the three trials using paxalisib to treat BMs, this one is probably the most interesting. It also sees paxalisib being studied in combination with another drug, trastuzumab (Herceptin®, Roche (EBS: ROG)), that was developed by Genentech. This is also a rather obvious study for Kazia to undertake, given Novartis' PIK3 inhibitor, Piqray® (alpelisib) was approved for use in primary breast cancer last year (May 2019) but it does not cross the blood brain barrier.

Trastuzumab targets a molecule on the surface of breast cancer cells termed HER2 (human epidermal growth factor receptor 2). According to the NCI about 20% to 30% of primary breast cancers express HER2. Trastuzumab is also used to treat breast cancer BMs. However, trastuzumab's efficacy against HER2 BMs has been lower than expected. HER2 is thought to act through the PI3K-AKT-mTOR pathway. The current consensus of opinion on the topic appears to be that trastuzumab is working as it should, but that there are other pathways which feed into and upregulate the PI3K-AKT-mTOR pathway downstream of HER2. These downstream pathways work to reverse the effect of trastuzumab, giving the impression that trastuzumab is not doing as in is intended in BMs. The hypothesis being tested in this study is that the combination of trastuzumab and paxalisib will have a greater clinical effect on BMs then trastuzumab alone. The combination will achieve this by shutting down HER2, PI3K, and mTOR, such that any additional pathways intersecting the main pathway between HER2 and PI3K and between PI3K - mTOR will be limited in their ability to increase the activity of the pathway. A review on the topic can be seen by clicking on the following reference: Hosonaga et al (2020) Cancer Metastasis Rev.

The study has two cohorts. Cohort A will be treated with the combination of trastuzumab and paxalisib after surgery. The second cohort will be treated prior to surgery, in an effort to shrink the tumours, so that they be excised more easily and with the least amount of damage to the surrounding tissue as possible. This study is being sponsored by the Dana Farber Cancer Institute located in Boston. This is another renowned US cancer institute. A presentation introducing the study by the principal investigator, Jose P Leone, MD, can be seen here.

The trial will recruit a total of 47 participants and is scheduled to complete in November of next year (2021). The primary endpoint is objective response rate. There are a range of secondary endpoints that will also be examined. The response of the tumour outside of the central nervous system is one of them. An interim presentation of the data from this study will be made at a suitable conference in 1H CY21 seems likely.

Cantrixil for Ovarian Cancer– a Legacy Asset

Cantrixil is the only surviving development program from the old Novogen. The compound is currently in a phase I study of persistent or recurrent platinum resistant ovarian cancer. Platinum resistance refers to a type of chemotherapy that ovarian cancer patients are treated with initially, but, eventually, fail to respond to.

The study design follows the familiar path of a dose escalation cohort followed by an expansion cohort. The study has defined a dose of 5mg/kg as the MTD based on 9 patients. A further 11 patients were recruited into the expansion cohort and the last patient had their last visit in April of this year (2020). On a preliminary basis, there has been one complete response and two partial responses. This gives the study an objective response rate of 15%, this actually compares well to that of 10% for a historical control group from a published phase III study, Pujade-Lauraine et al (2014) J Clin Oncol. Median PFS also trended Cantrixil's way at 5.5 months, with the historical control rate coming in at 3.4 months.

The final results from this study will be released in Q4.

Cantrixil is an unusual drug, with the old Novogen determining that intraperitoneal delivery was the best way to use it. While this drug might be helpful for women who develop ascites as a result of their ovarian cancer, its commercial prospects are unclear in our eyes. Kazia's existing management feels the drug is better off in a partner's hands. A partner that really knows the ins and outs of the ovarian cancer market. Our assessment is exactly the same.

The Competitive Landscape - GBM

The only widely accepted treatment for GBM is temozolomide.

Bevacizumab (Avastin®, Roche), another Genentech drug, was given accelerated approval for the second-line treatment of GBM by the US FDA in 2009. Finally, in early December of 2017, the FDA gave Avastin full approval in the recurrent GBM setting. However, it seems to see little use for the indication, most likely because bevacizumab failed all three of its pivotal trials in GBM. Two studies used the drug in the first-line setting, while the third looked at it in the second-line setting. The EMA last rejected it in 2014. It may well have been the case that the FDA wanted to approve something for the second setting in GBM and, while the data was not really supportive of that, it was less supportive of any of the other possibilities.

In terms of development of the next drug for GBM, it is a race of three, really, with paxalisib being one of them. The other two are marizomib, a pan proteasome inhibitor, from Bristol Myers Squibb (BMS) and VAL-083 (dianhydrogalactitol) from Kintara Therapeutics (NASDAQ: KTRA).

Marizomib – Bristol Myers Squibb NASDAQ: BMY

BMS acquired marizomib in 2019, when it acquired Celgene Corporation. The drug is thought to be a pan-proteasome inhibitor (it inhibits cells from producing proteins). This inhibition then pushes the cancers cells into a programmed cell death cycle or, at least, sensitizes them to entering the process. There are currently three approved proteasome inhibitors. They bortezomib (Velcade®, Takeda Pharmaceuticals), carfilzomib (Kyprolis®, Amgen) and ixazomib (Ninlaro®, Takeda Pharmaceuticals). All three drugs can be used in the treatment of the blood cancer multiple myeloma. Proteasome inhibitors are reviewed in Kambhampati et al (2020) Adv Exp Med Biol.

Celgene already had three trials of marizomib underway when BMS bought it. A phase I study of marizomib in combination with temozolomide in the first-line treatment of GBM has determined an MTD and an expansion cohort is expected to read out this month (October 2020; ClinicalTrials.gov Identifier: NCT02903069). This study is very similar to Kazia's ongoing phase II trial of paxalisib in treating GBM. The second study is a phase I/II in the second and third-line treatment of relapsed GBM in combination with bevacizumab and on its own (NCT02330562). This study is also due to read out this month, as well. The main study is a phase III study of marizomib in combination with temozolomide in the first-line treatment of newly diagnosed GBM (NCT03345095). This study, known as the Mirage study, is an open labelled controlled trial in 750 patients (i.e. 375 are in the test or marizomib arm and 375 are in the control arm).

An abstract at the American Society of Clinical Oncology conference in 2019 suggested that the combination of marizomib and temozolomide resulted in a 14.8-month median overall survival (n=66) in a population where **just over half of the patients had unmethylated MGMT promoter status** (Mason et al (2019) J Clin Oncol). In the Hegi study we have been drawing a lot information from, two cohorts of patients were treated with radiation therapy and temozolomide. Those patients with methylated promoters (n=46) were found to have an OS of 21.7, while those with unmethylated promoters (n=60) had an OS of only 12.7 months. If patients had responded in the Mason study only to the radiation therapy and temozolomide, as they did in the Hegi study, the Mason study should have produced an overall survival of 18.3 months. The 14.8 months OS the Mason study found would, if it were not for the historical nature of the comparison, almost suggest marizomib was having a deleterious effect on patient OS. As it stands, you would have to conclude that it had no effect, at best.

BMS is not footing the bill for the large phase III trial (n=750) of marizomib in GBM, that is being done by the European Organisation for Research and Treatment of Cancer (EORTC). Given the results I have just spelled out above, the fact that BMS is not funding the trial sends a pretty strong signal. You may also notice that the study is being carried out in 750 patients, almost twice the number of patients you normally find in a pivotal GBM trial. This suggests that EORTC believes the clinical effect of marizomib is likely to be considerably smaller than most companies have attributed to their drugs in the past when designing their own pivotal trials. This provides another signal consistent with our negative interpretation of the results.

The trial is not supposed to complete until July of 2022, but that would put it ahead of paxalisib. However, We think marizomib is quite unlikely to demonstrate any improvement on top of the standard of care. While investors should still keep an eye on marizomib and its pivotal trial, it probably is not worth spending too much time on it.

VAL-083 (dianhydrogalactitol) – Kintara Therapeutics (NASDAQ: KTRA)

Those familiar with the history of listed Australian drug development companies will recognise the name Dr Dennis Brown. He is the man who founded Chemgenex Pharmaceuticals and merged it with the ASX-listed company, AGT Biosciences, with merged entity taking on the name of Chemgenex, as well. Chemgenex was based around developing a cancer drug, omacetaxine mepesuccinate, that had long been used in China to treat leukaemia. While Chemgenex failed in its efforts to obtain marketing approval for omacetaxine, a couple of transactions and a bit of additional work on the drug, saw it finally approved by the FDA.

VAL-083 or dianhydrogalactitol is what Dr Brown did after Chemgenex. VAL-083 has been used in China to treat various solid tumours for many years and is formally approved by National Medical Products Administration, the Chinese version of the FDA, for the treatment of lung cancer. Dr Brown identified VAL-083 and founded the company DelMar Therapeutics around it in the US. DelMar had been developing VAL-083 for GBM and ovarian cancer, but dropped the ovarian cancer indication, it appears due to a lack of funds. The lack of funds caused DelMar to seek alternatives earlier this year (2020) and in August it completed a merger with Adegro Therapeutics to form Kintara Therapeutics. Just after the merger, Kintara raised USD21.8m to continue the development of VAL-083 to treat GBM.

VAL-083, like temozolomide, is a chemotherapeutic that damages tumour cell DNA resulting in the tumour cells undergoing a cycle of programmed cell death. VAL-O83 also damages the same nucleic acid residue as temozolomide, but it damages it in a different way, such that it is not a target for repair by the MGMT gene product or any of the other DNA repairing enzymes (Zhai et al (2018) Cell Death Dis).

VAL-083 is currently in two studies with GBM patients. Those studies are:

1) NCT02717962: This study is looking at two groups of GBM patients. One group comprises patients whose cancers have recurred or progressed after standard first-line treatment with radiation and temozolomide. The second group comprises patients who have also been treat with the SOC, but they have not received any maintenance therapy with temozolomide, presumably because the patient's tumours were already progressing. Cohort one is expected to comprise up to 83 patients, while 24 patients are expected to be treated in cohort two. This study is being conducted at the University of Texas, MD Anderson Cancer Center. The trial began in January 2017 and is expected to finish enrolling patients soon.
2) NCT03050736: This a safety study very similar in design to Kazia's current trial of paxalisib in GBM. The study is focussed on the first-line treatment of patients whose tumours have unmethylated MGMT promoters. An initial cohort has been treated with VAL-083 to determine an MTD. An expansion cohort has then been enrolled at the MTD. This study commenced in December 2017 and is due to complete soon.

Following is a summary from the most recent conference presentation I could find on each study that contained data.

1) NCT02717962: As of November 15th, 2019, 83 patients had been enrolled in the recurrent arm of the study. However, 35 of these patients had been dosed at 40mg/m^2/day of VAL-083 and the decision was eventually made to lower the dose to 30 mg/m^2/day due to the high levels of myelosuppression (a reduction the number of red blood cells produced by the bone marrow) at 40mg/m^2/day. At the lower dose, 27 of a planned 48 patients have been enrolled. In the adjuvant arm of the study, 5 of a planned 24 patients have been enrolled with all having been treated at the lower dose. The lowering of the dose did appear to resolve the safety issues experienced at the higher dose. Of the patients who received the higher dose in arm 1 of the study, 9 out of 35 or 26% registered a best response of stable disease. At the lower dose, 23 out of the 27 patients currently enrolled in the study were available for data analysis and 6 out of the 23 or 26% registered a best response of stable disease. Overall survival was 6.5 months for the high dose group and 10.6 months for the low. Only one patient was available for data analysis in the adjuvant setting. On May 28, 2020, the overall survival numbers were updated and median overall survival had fallen to 8.5 months in the low dose group.
2) NCT03050736: As of November 2nd, 2019, 23 patients had been treated in this study. 9 patients were enrolled in the dose finding cohort of the study, while 15 patients had been enrolled in the expansion cohort. At the MTD (30mg/m2/day),18 patients were available for analysis and their PFS came out at 10.4 months. An additional patient was available for objective response rate assessments. They showed 9/19 (47%) had complete responses, 8/19 (42%) stable disease and 2/19 (11%) had disease progression.

In addition to the conference presentations above, an article by Guo et al was published on NCT03050736 in the journal Glioma in January of this year (2020). The results in the article were consistent with those in the abstract.

The results produced in the two conference presentations and paper tend to suggest that VAL-083 is having a positive effect in GBM patients, both in the front-line and recurrent settings. I did start to develop some concerns around data integrity, though. The fact that 35 patients were treated at a dose of 40mg/m^2/day before they realised that the levels of myelosuppression were too high raised an initial red flag for me. There also seemed to be some inconsistencies over the years in the data that has been released. It is, however, difficult to say that errors have definitely been made, because the data was often re-cut in different ways when presented. Study NCT03050736 is being conducted in China it is also not unusual for results produced there to be found misleading when drugs are put through more robust studies later on.

There is a reason smaller drug development companies shy away from conducting clinical trial trials in China. With VAL-083 being of Chinese origin, further risks could come to the forefront. The drug is in the hands of those who know how to use it, and, while you might normally want that, if you cannot reproduce the results elsewhere, your drug will not be approved. National pride could also have affected how the trial is being conducted or how the results were reported.

In the end, I think you have to place some big question marks over the quality of the VAL-083 data.

GCAR has invited Kintara to have VAL-083 assessed in GBM AGILE and the company has said they would accept the offer. The raising they did in August is partly intended to cover Kintara's costs for the study. Kintara has also said that VAL-083 will commence AGILE 5 months from the date an agreement is signed with GCAR for VAL-083's participation. Kintara has not announced an agreement has been signed with the group, yet.

Intellectual Property

Paxalisib is covered by patents out until 2032, which include a patent covering the chemical entity that is the drug (patent #: US8883799B2). Kazia will also likely be able to get the term of these patents extended as a result of the time that Kazia and Genentech have spent collecting data for the regulator (FDA). Companies are not allowed to apply for a patent term extension. Most of the large jurisdictions have some sort of mechanism for extending patents to compensate for some of the patent time that is lost while a company collects data to convince the regulator that the drug is safe and effective. Depending on how the patent office and the FDA see things, I am reasonably confident that Kazia will be granted an extension of 4 to 5 years, with 5 being the maximum allowable. This would see paxalisib protected out until 2036 or 37.

To a certain extent, Kazia's patents may end up being redundant, given many of the cancer indications Kazia is going after qualify for ODD. As I said earlier, drugs approved for orphan indications are granted a 7-year period of market exclusivity by the FDA and a 10-year period by the EMA. What is nice about these statutory periods of exclusivity is they are fairly rock solid, whereas patents can be challenged relatively easily. That is not to say that I believe there is anything wrong with the patents covering paxalisib. In fact, given the origins of paxalisib and the quality of the lawyers at large pharmaceuticals companies, the patents on paxalisib are pretty solid.

Capital Sufficiency

In my opinion, rarely do good Australian biopharma companies ever have enough money on hand. Equivalent American NASDAQ-listed companies almost never let their cash fall below USD50 million or USD100 million. There are multiple reasons for this, but they include, the risk associated with the availability of investment funds, the amount of time a company needs to spend raising capital increases at a much lower rate than the size of the raising, a need to be able to fund clinical trials all the way through milestones, junior staff security and so on. In a nutshell, what it comes down to is that the dilution caused by having so much money on the balance sheet is simply worth it. I will rarely be upset with a company raising capital, as long as they are firmly focussed on adding value to their products. Normally, I ask them why they did not raise more?

Investors should also go into biopharma investments expecting to have to contribute to rights issues along the way. That way they can worry less about dilution and companies can pay them back by raising capital through rights issues, knowing they will get the money they need that way.

With that in mind, Kazia has just announced a fully underwritten 1 for 3 rights issue. The institutional portion of that issue has already been completed, with the institutions taking up a solid 70% of their rights. Overall, I expect the company to net about $23.7 million from this raise assuming the broker is paid the standard 6% commission. With cash in the bank, this should give Kazia enough money to cover the cost of participating in the GBM AGILE study which I have estimated at USD20 million (AUD27.3 million). Kazia's CEO said pretty much the same during a webinar regarding the raise

One thing that investors can take confidence from is that the raise is underwritten. It is extremely hard for an Australian biopharma to have a raise of any sort underwritten. The reason is that Australian brokers generally do not have balance sheets that allow them to underwrite a raising. The only way they will underwrite a raising is if they can sub-underwrite it first. To do this, the broker will approach larger investors likely to participate or who want to participate in raising and offer them a discount on the shares they purchase if they agree to sub-underwrite a portion of the total raise. Usually, the discount the sub-underwriters receive comes out of the placement fee the broker charges the company. A broker will usually charge the company a total fee of about 6% of the capital raised, passing on 1% to 2% to the sub-underwriters. The point is that an underwritten offer usually indicates strong demand.

One might ask why they have to raise all the money in one hit. Again, there are many reasons for this, but two stand out. The first is that it is ethically extremely poor form to have to stop a clinical trial due to a lack of funds, because patients are involved in the endeavour. Wasting their time is bad enough but having to pull the pin on them when they are half through their treatment is unforgivable. The second reason is that many of those outside groups required to make the trial a success will want to see the company can pay their way. Management which fail to cover the costs of a trial tend to be remembered in the industry.

Valuation Methodology

We have used a probability-adjusted discounted cash flow model to obtain a 12-month price target for the stock, which is the standard method used to value pharmaceutical companies. Investors need to bear in mind that this sort of valuation methodology requires a lot of assumptions and estimates for variables. Moreover, there is very limited data on which to base many of these assumptions and estimates. Key overall assumptions and estimates are given in table 5A, while those for specific programs are in table 5B (see next page, bottom).

Based on experience, there is little to be gained by creating a complex model for a drug development company for the simple reason that the amount of error associated with larger variables tends to swamp lesser variables. I have also tried to keep all assumptions and estimates used in the model as conservative as possible. **I do not believe Kazia will undertake sales and marketing activities for paxalisib. As consequence, one the biggest assumption the model makes is that another company will acquire Kazia over the course of FY25**. That should give prospective buyers plenty of time undertake due diligence post the completion of the GBM AGILE pivotal trial at the end of FY2023. Another big assumption I have made is that the acquirer will be willing to part with 33% of the present value of paxalisib to buy Kazia. This includes the PRV, which will, almost certainly transfer, with the company to the acquirer of Kazia, presuming they come in and take Kazia out before paxalisib is approved by the FDA and the voucher is awarded. While that seems a safe bet, the 33% is very much on the low side, given companies who licence assets at the end of a successful pivotal program are often willing to pay a royalty rate on sales alone of 30%, which doesn't include what would likely be a fairly large upfront payment, a milestone on US FDA approval and sales milestones at certain net sales

thresholds, etc. If any assumption needs to be revised up, it will almost certainly be that one. We have chosen to use a 15% discount rate of 15% to try and err on the side of conservatism, with our own past calculations for companies similar to Kazia and those used by the larger pharmaceutical companies to value programs suggesting that shaving 3% to 4% off the rate we used in this model would not be unreasonable (i.e. a discount rate as low as 11% to 12% would still be quite reasonable). Projected sales revenue for each indication is based on a same generic sales curve that has been developed in-house. Only sales revenues derived from the US have been estimated, with worldwide sales estimated by dividing US sales revenue by the percentage of worldwide sales the US accounts for. To that end, we have assumed US sales represent 55% of the worldwide sales. This percentage is at the higher end of estimates for the US market size. In terms of the clinical trials, the probability of success rates used are generally in-line with those that can be derived straight from the published literature on the topic. The only tinkering with the probabilities I have done is to move them up a bit for each indication, based on the results from Genentech's paxalisib study, the early trial results out of Kazia's ongoing phase II study and the strength of the data supporting the mechanism of action. A good final result out of the ongoing GBM trial and/or a good result out of the DIPG trial, would cause us to have to revisit those probabilities pretty quickly. More mundane things like the amount of the R&D cash rebate Kazia receives have been kept in line with historical percentages, although allowances have been made for expenditures related to GBM AGILE, still they are not that big, because Kazia is getting a very good deal on a very good quality pivotal trial.

Valuation

Based on the valuation methodology as described, my model indicates that a reasonable price to expect per Kazia share in 12-months' time is $2.05.

While this valuation might seem high, volatility alone can account for share price movements of more than 200% with companies like Kazia over the course. A 200% movement upwards would put Kazia's share price at $2.88. Volatility alone can could result in the share the price reaching our target. Of course, we do not set our price targets based on volatility. All the exercise tells us is that the price target is not entirely unreasonable with the movements we could see the stock make. Since the target price is more than 15% above the current share, the model is telling us that the market has not efficiently priced the company. Having said that, we did not need the model to tell us that. Years of looking at comparable companies in the US tells that good companies here are rarely valued efficiently and carry with them an Aussie discount, if you like. That discount is what makes the sector so attractive in our eyes. These stocks are Clinuvel (ASX: CUV), Opthea (OPT) and Viralytics (formerly, VLA), VLA having been boosted by American investors and then, again, when Merck came in and bought it.

A price target is a number spat out by a model, based on, in the case of pre-revenue pharmaceutical, a lot of estimates. The model can provide you with a reasonable idea if the market is fairly valuing the company and, if not, which side it might be sitting on. It cannot tell you if events will conspire over the course of the year to cause the market to correct and revalue the company appropriately. To get a feel for whether the market will correct, you generally look at a combination of macroeconomic factor and company specific factors. As we said in the opening to the report, the only real way a company can add value to a drug is by studying it in clinical trials, to define what the future markets might be for it and the cash flows that might flow from them and move the drug through the regulatory process. With that in mind, think about what Kazia has in front of it for the next 9-months to 1-year.

- Further interim results from the phase II GBM trial later this year, followed by the final results next year,
- The same for DIPG study next quarter, with the possibility, albeit small, that if paxalisib knocks it out of the park, interactions with the FDA and, even, potentially other companies could get very interesting,
- We also have the first interim report on one of the BM studies this side of Christmas, before it starts up, again, next year,
- The other thing that may happen before Christmas is the start of paxalisib's participation in the trial intended to be the one that will take it to market, that trial is GBM AGILE, then Christmas comes, after which,
- Paxalisib commences a study for an indication it looks almost as well built for as GBM, PCNSL, for which it looks highly suited, due to the clinical activity of drugs with which it shares an identical mechanism of action, then, more trial results,
- First interim analyses from the two studies looking primarily at paxalisib's performance as a targeted medicine in treating BMs and, then ,we are likely to see,

Table 5A. Assumptions and Estimates that Apply to the Whole Model.

	Assumptions & Estimates
Overall	Discount Rate: 15%; AUD/USD: $0.72; US % of the World Market: 55%; Paxalisib Pricing List Price: USD150k/year; Gross to Net Discount: 44%; Peak Sales per Indication: 8 years post-approval; Market Penetration at Peak Sales: 80%; Patent Expiry: 2032; Patent Term Extension: 4 years; Value of Cash Flows Acquirer Pays: 33%; R&D Rebate as a % of R&D expenditure: 15%; Intellectual Property Protection Ends: End of 2036; No Difference in Timing between US Sales and Sales in other regions.

Source: M. Sinatra

Table 5B. Program Specific Assumptions & Estimates.

Drug	Indication	Assumptions & Estimates
Paxalisib	GBM	Addressable Market: 7,100 patients per year; Percentage of patients with an Unmethylated Promoter: 60%; Time on Paxalisib: 8 months; Probability of Success: 27.5%; GBM AGILE Costs: USD20m; AGILE Length: 30 months; AGILE Completes: End FY 23; Year Sales Begin: 2025
	DIPG	Addressable Market: 225 patients per year; Time on Paxalisib: 4 months; Probability of Success: 12%; Year Sales Begin: 2025; The value of the possibility of obtaining the priority review voucher associated with this program is accounted for in the acquisition value that is assumed to be paid on a successful outcome to the GBM program
	PCNSL	Addressable Market: 2,297 patients per year; Time on Paxalisib: 4 months; Probability of Success: 12%; Year Sales Begin: 2027
	BM	Addressable Market: 21,501 patients per year; Time on Paxalisib: 4 months; Probability of Success: 12%; Year Sales Begin: 2026
Cantrixil	Ovarian cancer	Not valued. Cantrixil represents unaccounted for upside for investors.

Source: M. Sinatra

- Final results from the current phase II trial of paxalisib in treating GBM and the phase I trial in DIPG, and,
- That is all before the md-point of next year.

We think that that there is an extremely good chance that a few trial results will see the wind at Kazia's back and the share price meeting or even exceed our price target

Kazia's Board & Management

Following are the biographies of each director as stated on the Kazia's website. Overall, the company has a nice mix of skills that are relevant to a company that is solely progressing a drug candidate through the clinic. Of course, the Scientific Advisory Board also has a big role to play in a company of Kazia's nature. You can read their biography's by clicking here. If Kazia's activities were broader than they are, perhaps the skill set of the board could be broadened, as well. Right now, however, the balance seems to be just about right.

Iain Ross, BSC (Hons), C.DIR
Chairman & Non-Executive Director
Mr Iain Ross is an experienced multinational pharmaceutical and biotechnology executive and is currently Chairman of Redx Pharma plc (LON:REDX), Silence Therapeutics plc (LON:SLN) and Biomer Technology Limited.

During his career, Mr Ross has held senior positions at multinational companies, Sandoz AG, Hoffman La Roche, and Celltech Group PLC and been a Chairman, CEO and Director of several biotech companies. He is a qualified Chartered Director and former Vice Chairman of the Council of Royal Holloway, London University.
Mr Ross was appointed as a director of the Company in July 2015 and is considered to be an independent director. He is a member of the Audit, Risk and Governance Committee and a member of the Remuneration and Nominations Committee.

Dr James Garner, MA, MBA, MBBS, BSC (Hons), MAICD

Chief Executive Officer & Executive Director

Dr Garner is an experienced life sciences executive who has previously worked with companies ranging from small biotechs to multinational pharmaceutical companies such as Biogen and Takeda. His career has focused on regional and global development of new medicines from preclinical to commercialisation.
Dr Garner is a physician by training and holds an MBA from the University of Queensland. He began his career in hospital medicine and worked for a number of years as a corporate strategy consultant with Bain & Company before entering the pharmaceutical industry. Prior to joining Kazia Therapeutics in 2016, he led R&D strategy for Sanofi in Asia-Pacific and was based in Singapore. Dr Garner is a member of the Australian Institute of Company Directors.

Bryce Carmine

Non-Executive Director

Mr Bryce Carmine spent 36 years working for Eli Lilly & Co. and retired as Executive Vice President for Eli Lilly & Co, and President, Lilly Bio-Medicines. Prior to this he led the Global Pharmaceutical Sales and Marketing and was a member of the company's executive committee. He previously held a series of product development portfolio leadership roles culminating when he was named President, Global Pharmaceutical Product Development, with responsibility for the entire late-phase pipeline development across all therapeutic areas for Eli Lilly.
During his career with Lilly, Mr Carmine held several country leadership positions including President Eli Lilly Japan, Managing Dir. Australia/NZ & General Manager of a JV for Lilly in Seoul, Korea. He is currently Chairman and CEO of HaemaLogiX Pty Ltd, a Sydney-based privately owned biotech.
Mr Carmine was appointed as a director of the Company in June 2015 and is considered to be an independent director. He is a member of the Audit, Risk and Governance Committee and Chair of the Remuneration and Nominations Committee.

Steven Coffey, CA

Non-Executive Director

Mr Steven Coffey is a Chartered Accountant, having spent his career in public practice since graduating from NSW University in 1983. He has been a partner in the chartered accounting firm Watkins Coffey Martin since 1993.
Mr Coffey is a registered company auditor and audits a number of large private companies as well as a number of not-for-profit entities. He has previously served on the board of an Australian listed public company and is currently a board member of two private ancillary funds (PAFs).
Mr Coffey was appointed as a director to the Company in November 2012 and is considered to be an independent director. He is Chair of the Audit, Risk and Governance Committee and a member of the Remuneration and Nominations Committee.

Kazia Therapeutics

A Laser-Like Focus

Kazia Therapeutics (ASX: KZA)

Market Capitalisation: $75.7

Valuation Data (AUD Million)

Year Ending Jun	FY20A	FY21E	FY22E	FY23E	FY24E
Profit	**(12.5)**	**(12.2)**	**(16.6)**	**(16.2)**	**(8.4)**
EPS (¢)	(11.0)	(13.2)	(12.9)	(17.6)	(17.1)

Balance Sheet (AUD Million)

Year Ending Jun	FY20A	FY21E	FY22E	FY23E	FY24E
Cash & Equivalents	7.6	21.2	7.5	22.4	15.5
R&D Tax Rebate	1.4	1.5	2.1	2.1	0.9
Current Assets	**9.0**	**22.7**	**9.6**	**24.5**	**16.4**
Intangibles	12.4	11.3	10.2	9.2	8.1
Non-Current Assets	**12.4**	**11.3**	**10.2**	**9.2**	**8.1**
Total Assets	**21.4**	**34.0**	**19.9**	**33.6**	**24.5**
Trade & Other Payables	3.5	3.1	4.0	4.1	2.4
Provisions	0.2	0.2	0.2	0.2	0.2
Contingent Consider.	1.4	1.4	1.4	1.4	1.4
Current Liabilities	**5.1**	**4.7**	**5.6**	**5.7**	**4.0**
Deferred Tax	3.4	3.1	2.8	2.6	2.3
Contingent Consider.	0.5	0.6	0.8	1.1	1.5
Non-Current Liabilities	**3.9**	**3.7**	**3.7**	**3.7**	**3.8**
Total Liabilities	**8.9**	**8.4**	**9.3**	**9.4**	**7.8**
Net Assets	**12.5**	**25.6**	**10.6**	**24.3**	**16.7**
Contributed Equity	48.8	72.6	72.6	100.8	100.8
Reserves/Other	2.5	1.5	1.5	1.5	1.5
Accumulated Losses	(36.2)	(48.4)	(65.0)	(81.2)	(89.6)
Total Equity	**14**	**26**	**9**	**21**	**13**

Profit and Loss (AUD Million)

Year Ending Jun	FY20A	FY21E	FY22E	FY23E	FY24E
Total Revenue	**1.0**	**1.6**	**1.6**	**2.3**	**2.3**
R&D Tax Rebate	*1.0*	*1.4*	*1.5*	*2.1*	*2.1*
Expenses	**(13.8)**	**(14.1)**	**(18.5)**	**(18.8)**	**(10.9)**
EBITDA	(11.8)	(11.6)	(15.9)	(15.6)	(7.7)
D&A	(1.1)	(1.1)	(1.1)	(1.1)	(1.1)
EBIT	**(12.9)**	**(12.7)**	**(17.0)**	**(16.7)**	**(8.8)**
Net Interest	0.1	0.2	0.1	0.2	0.2
Profit - Pre-Tax	**(12.8)**	**(12.5)**	**(16.9)**	**(16.5)**	**(8.6)**
Tax	0.3	0.3	0.3	0.3	0.3
Profit - After-Tax	**(12.5)**	**(12.2)**	**(16.6)**	**(16.2)**	**(8.4)**
Comprehensive Profit	**(12.5)**	**(12.2)**	**(16.6)**	**(16.2)**	**(8.4)**

Cashflow (AUD Million)

Year Ending Jun	FY20A	FY21E	FY22E	FY23E	FY24E
Operating Cashflow	**(9.2)**	**(10.2)**	**(13.7)**	**(13.3)**	**(6.8)**
Investing Cashflows	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Financing cashflows	**12.1**	**23.8**	**0.0**	**28.2**	**0.0**
Net Equity Raised	12.1	23.8	0.0	28.2	0.0
ΔCash	2.9	13.6	(13.7)	14.9	(6.8)
Cash	**7.6**	**21.2**	**7.5**	**22.4**	**15.5**

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Sydney

79 Kent St
Millers Point
Sydney NSW 2000

Phone: +61 400 897 559
Email: enquiries@corporateconnect.com.au
https://www.corporateconnect.com.au/