BELL POTTER

3 July 2020

Speculative

See key risks on Page 3 and Biotechnology Risk Warning on Page 21. Speculative securities may not be suitable for Retail Clients.

Analyst
John Hester 612 8224 2871
Tanushree Jain 612 8224 2849

Authorisation
TS Lim 612 8224 2810

Kazia Therapeutics

5 month survival extension

Recommendation
Buy (Initiation)
Price
$0.51
Valuation
$1.00 (initiation)
Risk
Speculative

GICS Sector

Pharmaceuticals & Biotechnology

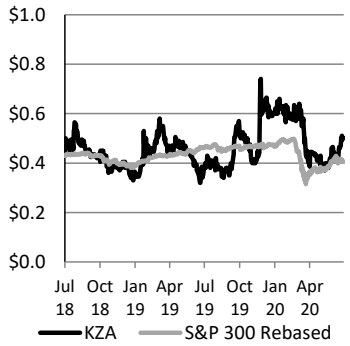
Expected Return	
Capital growth	**96.1%**
Dividend yield	**0.0%**
Total expected return	**96.1%**

Company Data & Ratios	
Enterprise value	**$59.2m**
Market cap	**$48.2m**
Issued capital	**94.6m**
Free float	**100%**
Avg. daily val. (52wk)	**$65K**
12 month price range	**$0.34 - $0.80**

Price Performance

	(1m)	(3m)	(12m)
Price (A$)	0.42	0.43	0.39
Absolute (%)	20.48	17.65	29.87
Rel market (%)	20.01	-5.58	42.44

Absolute Price



SOURCE: IRESS

A breakthrough therapy for brain cancer

Kazia Therapeutics is the developer of paxalisib – a new chemical entity specifically designed for the treatment of Glioblastoma (aka GBM). The drug was licensed to the company from the San Francisco based Genentech in late 2016 and since then has continued development in a phase II clinical program. The interim data shows significant promise with meaningful extension in both progression free survival and overall survival. The trial is now fully recruited and the company has sufficient funding to see it through to the release of at least the next interim update which we expect in early 2021.

Paxalisib is gaining international attention with four additional investigator sponsored studies under way in the US at prominent institutional level hospitals. These investigators are examining the use of the drug in a range of adjacent indications which include childhood brain cancers and brain metastases from other primary tumours. In addition, the company has been invited to join the platform study GBM Agile. This is an ongoing study for the simultaneous investigation of multiple drug candidates in glioblastoma. The platform uses a common control group and therefore, is expected to save millions of dollars in development costs and months if not years in the development timetable. GBM Agile is intended to become the approval study for paxalisib with enrolment of the first patient expected in 2020.

Investment view – Buy (Speculative)

While Paxalisib is unlikely to be curative for GBM, the clinical data suggests it is effective in providing meaningful extension to overall survival with an acceptable safety risk. GBM is an orphan indication in both the US and Europe, however, despite the smaller market, peak revenues are estimated at several hundred million dollars annually. Key intellectual property protection extends to at least 2030 in key markets. The next milestones for the company are the enrolment of first patients in GBM Agile and a further update on key survival data from the phase II study. We initiate coverage with a Buy (speculative) recommendation and valuation of $1.00

Earnings Forecast

June Year End	FY19	FY20e	FY21e	FY22e
Revenues	1.5	4.0	3.7	7.2
EBIT $m	-10.7	-10.2	-20.3	-18.8
NPAT (underlying) $m	-10.3	-10.1	-20.4	-18.9
NPAT (reported) $m	-10.3	-10.1	-20.4	-18.9
EPS underlying (cps)	-16.6	-10.7	-12.9	-11.9
EPS growth %	nm	nm	nm	nm
PER (x)	nm	nm	nm	nm
FCF yield (%)	nm	nm	nm	nm
EV/EBITDA (x)	nm	nm	nm	nm
Dividend (cps)	-	-	-	-
Franking	0%	0%	0%	0%
Yield %	0%	0%	0%	0%
ROE %	-73%	-59%	-71%	-195%

SOURCE: BELL POTTER SECURITIES ESTIMATES

Contents

Investment Thesis

Overview

The lead program is paxalisib (aka GDC-0084), a small molecule inhibitor of the PI3K-AKT- mTOR pathway, which is being developed to treat glioblastoma (GBM), the most common and most aggressive form of primary brain cancer in adults. Licensed from Genentech in late 2016, paxalisib entered a phase II clinical trial in 2018 and was granted orphan designation for glioblastoma by the US FDA in February 2018.

With optimal therapy (surgical resection, radiation and chemotherapy) patients with unmethylated MGMT promotor status have a median survival of approximately 12.7 months[1]. Nearly 100% of GBM tumours recur after first-line therapy. The five year survival rate is ~5%.

Paxalisib is an adjuvant therapy following surgery to remove the tumour. Interim data from the phase II trial showed encouraging extensions in both progression free survival and overall survival. The median extension in overall survival was approximately 5 months.

Based on these results the company was invited to join the GBM Agile study in the United States. GBM Agile is a collaborative research effort between government, industry and researchers to facilitate a faster path to market for promising therapies in this indication. GBM Agile will serve as a pivotal study for registration. The key advantages of this route are reduced cost and a common control group with the result that the time taken to complete the study is potentially accelerated by years. The readout from the current phase II study is not due until 2H CY2021, notwithstanding the first patients on the GBM Agile study are likely to start therapy in late 2020.

In addition to the phase II and GBM Agile, several investigator sponsored studies are underway at prestigious hospitals in the US. These include Memorial Sloan Kettering (NYC) and Dana Farber - Boston, Massachusetts. The results from these studies are due to readout from next year albeit the data is owned by the investigators.

The company's second asset is Cantrixil. Cantrixil (TRX-E-002-1) is a third-generation benzopyran that targets slower dividing 'tumour-initiating cells' thereby helping combat the problems of resistance and recurrence that occur with chemotherapy. The first indication is advanced ovarian cancer. Headline data from the phase 1 study in 9 patients showed one complete response and 2 partial responses. The company is yet to make further commitment to this development program.

Funding

KZA recently raised $9m from shareholders and we expect it will have ~$11m in cash as at 30 June 2020. The addressable market for GBM in the US is estimated at ~8,125 patients annually in the US market alone, with peak sales in the US estimated at US$487m in 2027. The rest of the world market is estimated to be approximately the same in terms of volume, but at a lower price. On a global basis peak sales are estimated in the range of US$700 - $900m. There is further potential for growth once additional indications are considered and these included metastatic disease from other primary tumours.

The short term catalysts for the stock include the headline data from the phase II trial. The trial is fully recruited and due to report in mid CY2021. First patient dosed under GBM Agile will also be a significant item.

[1] 12.7 months is for the unmethylated group only. OS for the broader group including methylated MGMT promotor status is 16.6months. In our view the correct comparison is to the unmethylated group as it is only these patients that will be included in the approval study.

Risk Areas

The key risk include but are not limited to the follow items:

Kazia's ability to achieve profitability is dependent on a number of factors, including its ability to complete successful clinical trials, obtain regulatory approval for its products and successfully commercialise or partner both Paxalisib and Cantrixil. There is no guarantee that the company will achieve these goals.

Kazia does not currently generate revenue from product sales and revenues are not anticipated in the short to medium term. The company is likely to continue to rely on shareholders to fund the business of the foreseeable future.

Clinical trial risk

KZA may be unable to secure necessary approvals from regulatory agencies and institutional bodies (clinics and hospitals) to conduct future clinical trials. There is also no assurance that either of the drugs under development will prove to be safe and efficacious in clinical trials, or that the regulatory approval to manufacture and market its products will be received. Clinical trials might also potentially expose the Company to product liability claims in the event its products in development have unexpected effects on clinical subjects.

Paxalisib and Cantrixil must both undergo a comprehensive and highly regulated development and review process before receiving approval for marketing.

The company is also dependent on commercially attractive markets remaining available to it during the commercialisation phase and there is a risk that, once developed and ready for sale, commercial sales to fund sufficient revenues for continued operations and growth, may not be achieved.

Arrangements with third-party collaborators

Kazia may pursue collaborative arrangements with pharmaceutical and life science companies, academic institutions or other partners to complete the development and commercialisation of its products (including for the GBM Agile study). These collaborators may be asked to assist with funding or performing clinical trials, manufacturing, regulatory approvals or product marketing. There is no assurance that Kazia will attract and retain appropriate strategic partners or that any such collaborators will perform and meet commercialisation goals. If Kazia is unable to find a partner, it would be required to develop and commercialise its products at its own expense. This may place significant demands on the Company's internal resources and potentially delay the commercialisation.

Requirement to raise additional funds

The company may be required to raise additional equity or debt capital in the future. There is no assurance that it will be able to raise that capital when it is required or, even if available, the terms may be unsatisfactory. If the company is unsuccessful in obtaining funds when they are required, it may need to delay or scale down its operations.

Intellectual property

The company's ability to leverage its innovation and expertise depends upon its ability to protect its intellectual property and any improvements to it. The intellectual property may not be capable of being legally protected, it may be the subject of unauthorised disclosure or be unlawfully infringed, or the company may incur substantial costs in asserting or defending its intellectual property rights.

Origins of Paxalisib

Paxalisib was in-licensed by Kazia from Genentech in the US in 2016. KZA paid a US$5m upfront and Genentech will receive performance related consideration linked to regulatory and commercial outcomes. Genentech will also receive a royalty in line with industry benchmarks.

The Investigative New Drug status was transferred to KZA along with the manufacturing analytical processes.

Genentech are a highly renowned drug developer based in San Francisco. The company is a leading developer of medicines for the treatment various cancers including immunotherapy drugs (e.g. Herceptin). Among its highest revenue generating drugs are Herceptin and Perjeta. Genentech is a wholly owned subsidiary of the Swiss pharma giant Roche.

As a rule, none of the monoclonal antibody therapies are effective in controlling brain cancers for the key reason that these molecules are far too large to pass through the blood brain barrier. The scientists at Genentech designed paxalisib specifically to overcome this obstacle.

Paxalisib is in the class of drugs known as PI3K inhibitors which we discuss in the following section and in Appendix A. There are several PI3K inhibitor drugs currently on market for the treatment of solid cancers and blood cancers. These formulations have been studied in brain cancer and been shown to have zero efficacy which was not in least surprising because of the blood brain barrier.

The PI3K- AKT - MTOR is an intracellular signalling pathway known to be critical to cell survival and growth. This pathway is frequently dysregulated (i.e. not functioning in a normal manner) in many human cancers. The abnormal signal transduction result in uncontrolled cell proliferation, loss of apoptosis (programmed cell death) and angiogenesis (enhanced blood supply).

This pathway has been extensively researched and is known to control multiple cellular processes including metabolism, cell proliferation, survival and reducing apoptosis (cell death). Genentech BioOncology developed paxalisib to disrupt this pathway. Appendix 1 contains more detail on the mechanism of action. Suffice to say the MOA is highly complex and is based on decades of accumulated scientific knowledge on human chemistry and biology.

INTELLECTUAL PROPERTY PROTECTION

As GBM is an orphan indication, paxalisib will also get a minimum of 7 years marketing exclusivity in the US from the data of approval.

The key patents on the chemical entity expire in 2030 in the US and 2031 in most other jurisdictions. The key patents relate to the chemical entity and are considered strong IP protection. The expiry on the patents should be around about the same time as the end of the marketing exclusivity.

Paxalisib Clinical Program

In relation to the current phase II study the key points are as follows.

STUDY DESIGN

Key inclusion criteria – the trial only enrolled patients with unmethylated MGMT promotor status (refer appendix 1).

Open label, single arm, multi-centre study in two parts.

- Primary endpoint: safety, tolerability and clinical activity in patients with newly diagnosed GBM;
- Stage 1 (n=9) was a dose escalation cohort which determined the therapeutic dose at 60mg (vs 45mg in the earlier phase 1 study conducted by Genentech in ~2015);
- Stage 2 (n=21), now fully enrolled and awaiting headline data in late 2020 or early 2021 depending on patient survival;
- Patients are dosed daily (via oral dosing) remaining on drug for the duration.

INTERIM DATA FROM PHASE II

The most recent interim data update was provided at ASCO in June 2020.

- The safety profile was adequate. Eight separate patients experienced grade 3 adverse event and 2 patients had grade 4 adverse events (hyperglycemia). Investigators concluded that the toxicities seem broadly consistent with prior clinical experience and with other PI3K targeting agents.

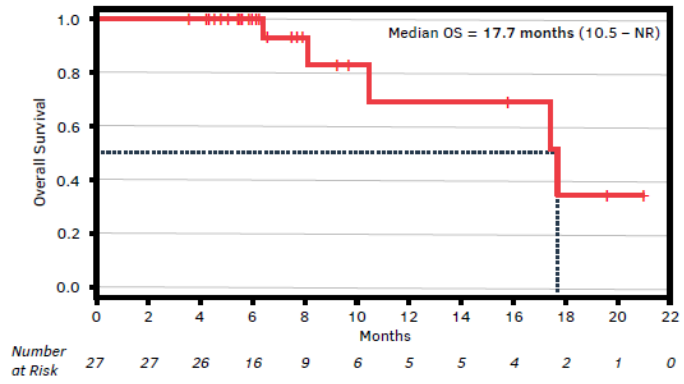
Figure 1 - Summary efficacy data from phase 2 (stage 1 patients)

	Temozolomide	Paxalisib	Δ	% change
Progression free survival (months)	5.3	8.5	3.2	60%
Overall survival	12.7	17.7	5.0	39%

SOURCE: COMPANY DATA

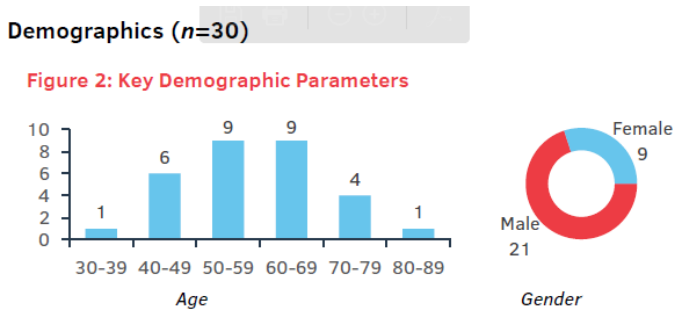
- The survival data for temozolomide is based on previously published clinical trial data;

Figure 2 - Kaplan Meier curve of overall survival



SOURCE: COMPANY DATA

Figure 3 - Key demographic parameters in the PII



SOURCE: COMPANY DATA

- Stage 1 patients achieved median progression free survival (PFS) of 8.4 months and OS of 17.7 months. (figure 2) This is a meaningful extension over the SOC in

both measures. In our opinion, if this benefit were sustained throughout an approval study the drug would almost certainly be approvable.

- Note also from figure 3, the majority of patients are less than 60 years of age. In the broader population GBM effects men and women equally, however the trial population contain an over representation of men.

APPROVAL STUDY

As disclosed in December 2019, Kazia has meanwhile begun preparatory activities in parallel to completion of this phase II study to bring paxalisib into the international platform study, GBM AGILE.

GBM Agile is intended to provide data to support FDA approval for paxalisib in glioblastoma. Subject to completion of contracts, Kazia expects to recruit the first patient in to the paxalisib arm in 2H CY2020 – before the release of headline data from the phase II study.

A key item for investors leading into commencement is certainty over the intellectual property resulting from participation in GBM AGILE. The minimum requirements for Kazia must be:

- Unfettered access to all the data (from both the active and the control arm);
- Specific language to deny the sponsors/funders/other stakeholders of the study any right to the subsequent revenues that may arise from the sale or commercialisation of the product;
- Ownership of the data in the event that GBM Agile is unable to continue (i.e. GBM Agile represents a whole other round of counterparty risk).

Investigator Sponsored Studies

Several hospitals in the US have begun their own investigator sponsored studies with paxalisib across adjacent indications to GBM. We agree with the company's comment that it is a positive reflection of the potential of the drug that it is being trialled alongside drugs from world leading pharmaceutical companies.

The recruitment of these trials is at the discretion of the investigator, hence completion times are less certain. The company's commitment to investigator led studies is for the supply of drug only. Normally the company will get access to the data in exchange for supplying drug.

If the investigator sponsored studies produce results that are worthy of further investigation, the data from these studies would normally become available for the purposes of assisting with registration. The sponsor hospital may be entitled to some form of compensation for their efforts as well.

These hospitals will not normally provide updates on recruitment, therefore we have no insight to their progress.

Figure 4 - Comprehensive Clinical Program for Kazia

	Indication	Stage	n	Progress	Design	Sponsor	Registration
Paxalisib	Glioblastoma	Phase II	27	Completed recruitment	Single Arm, open label	Kazia Thereapeutics	NCT03522298
	Glioblastoma	Phase III	up to 200	Ethics approvals	Randomised Controlled Study	Kazia Therapeutics/GBM Agile	NCT03970447
	Brain metastases - any source	Phase II	150	Recruiting	Three treatment cohorts. Pts receive one of three drugs, one of which is Paxalisib.	Alliance for clinical trials in Oncology and Genentech	NCT03994796
	Brain metastases - breast cancer	Phase II	47	Recruiting	Non randomised, single arm, combination study of Paxalisib with Trastuzumab	Dana Farber Cancer Institute	NCT03765983
	DIPG (childhood brain cancer)	Phase II	41	Recruiting	Various treatment cohorts on paxalisib and radiation therapy	St Jude Children's Research Hospital	NCT03696355
	Brain Metastases - any source	Phase 1	36	Recruiting	3+3 dose escalation cohorts on paxalisib and radiation therapy	Memorial Sloan Kettering	NCT04192981
Cantrixil	Recurrent Ovarian Cancer	Phase 1	28	Completed recruitment	Part A - dose escalation, Part B Expansion Cohort	Kazia Thereapeutics	NCT02903771

SOURCE: COMPANY DATA AND BELL POTTER SECURITIES ESTIMATES

CANTRIXIL CLINICAL DATA

Cantrixil is being studied in the treatment of advanced ovarian cancer in patients that have progressed following multiple lines of therapy. Patients in part A reported median progression free survival of 5.5 months vs std of care (in similar cohorts) of 3.4 months. The company expects to report PFS data for the entire study group in 2H CY2020.

20 of 24 patients were evaluable for efficacy. Of these 1 patient had a complete response, and 2 had a partial response, for an overall response rate of 15%. The safety profile was consistent with prior experience – mostly GI in nature and low grade.

The company is yet to commit to further studies in this indication. In our view one complete response and two partial responses is probably short of a 'clear signal' albeit these patient have been heavily pre-treated and would be considered as salvage. The future of this asset is probably in the balance at this time. Our forecasts do not include any value for it.

GBM AGILE

GBM Agile (**G**lioblastoma **A**daptive **G**lobal **I**nnovative **L**earning **E**nvironment) is uniquely designed as a long-standing platform with the ability to test multiple therapies at the same time against a common control (or standard of care). The purpose is to evaluate multiple investigational treatments for either newly diagnosed or recurrent glioblastoma to determine if any of these study treatment(s) improve overall survival as compared to standard treatments.

The trial is made possible by a partnership between a collaboration of clinicians, researchers, governments, regulatory agencies, pharmaceutical companies (including KZA) and patient advocacy groups. The prominent partners included in the United States the National Brain Tumour Society and the National Foundation for Cancer Research.

The study is managed by the Global Co-alition for Adaptive Research being a not for profit group.

GBM AGILE is designed as a learning system to more efficiently and rapidly identify effective therapies for GBM patients. GBM AGILE's nimble model enables multiple drugs (and combinations of drugs) to be screened simultaneously. Drugs that show initial evidence of benefit to patients will seamlessly transition to a confirmatory stage designed to support drug approval. Drugs that are underperforming are dropped. The intent is to lower the cost, time, and number of patients required to evaluate potential new, effective therapies for patients with GBM.

GBM AGILE is open in over 40 academic medical centers and community-based institutions across the United States, with plans to expand across Europe, China, Canada, and Australia through 2020.

Professor Tim Cloughesy (UCLA) is the Principle Investigator for GBM Agile. He also happens to be one of the investigators on the Paxalisib phase II study.

CLINICAL PROGRAM

The first drug in the program was Bayer's Regorafenib (being repurposed for GBM). Regorafenib was originally approved in metastatic colorectal cancer (for liver mets).

Each drug in the trial has its own dosing protocol, however, the results will be compared to a common control arm. We expect the protocol for the paxalisib trial will look very similar to the phase II study. (Refer to page 6).

We understand a detailed contractual arrangement is close to being signed and this should see enrolment of the paxalisib arm commencing 2H CY20 (August/September).

ADVANTAGES

Cost

We estimate the fully sunk cost of a 500 patient randomised controlled study inclusive of the hire of numerous key personnel, the CRO and all the other hidden costs would be at least ~US$200k per patient. (US$100m). We expect the cost to the company will reduce by at least 60% via inclusion in the GBM Agile program.

Time

The savings in recruitment and time to approval will be measured in months if not years (compared to a standalone phase III program run by Kazia). Because there is a common control group, the 200 patient study becomes the equivalent of a 400 patient study, hence the time to recruit is cut by at least half. Other factors include:

- Kazia is a minnow in the field of Oncology and would struggle to gain traction with KOL's and institutions for recruitment;

- GBM Agile avoids the lengthy process of CRO selection, site recruitment plus a host of administrative tasks involved with establishment of a clinical trial;

Common Control Group

The trial will utilise a common control group and this will also save many months if not years of recruitment time.

GBM Agile will enrol patients into one of three parallel groups:

- Newly diagnosed unmethylated;
- Newly diagnosed methylated; and
- Recurrent (patients have been treated with temozolomide and the disease has progressed).

The first priority for KZA is the newly diagnosed unmethylated patients. The paxalisib data will be compared against only those patients in the control group who are newly-diagnosed unmethylated.

The actual parameters of the approval study can't be determined until after the results from the current phase II are finalised. At that point the statistical analysis will determine the size of the approval study.

The Trial Will Utilise An Adaptive Design

Meaning that it will likely recruit up to 200 patients in the active arm. There will be a data safety monitoring committee in place. The DSMC will monitor the progress of the study.

OTHER FACTORS

Potential for Accelerated Approval

The results from the first 9 patients in the phase II study were encouraging. Should these results be sustained throughout the remainder of the study (21 patients) then the company could conceivably talk to the FDA about an accelerated approval.

While the interim data for safety and efficacy is encouraging, the trial is small at only 30 patients and even though GBM is an orphan indication the agency is likely to want to see safety data in more patients before an accelerated approval.

On the other hand, there are 4 (refer figure 5) other on market drugs in this class (none of which are able to cross the blood brain barrier) and the safety profile of paxalisib is consistent with or may be considered cleaner than the others. Zydelig for example carries a black box warning regarding fatal GI effects. Copiktra also carries box warnings for fatal and serious toxicities. Paxalisib has so far been a cleaner drug with a less severe side effects profile by comparison. The safety profile for Paxalisib will continue to be a major focus area for investigators and regulators.

As the outlook for these patients is poor with death (within months) virtually inevitable, in these circumstances the FDA may allow early access to the drug.

The company may make an application for an accelerated approval at any time, including part way through the approval study.

Other drugs in the same class have also been granted accelerated approvals.

Figure 5 - PI3K Pathway Approvals

SOURCE: COMPANY DATA

PIQRAY APPROVAL PATHWAY

This section contains a brief review of the regulatory pathway used by Novartis in the registration of Piqray (see above). It is the least toxic of the four PI3K inhibitors mentioned above, yet still with significant side effects. We included this section for purposes of highlighting the safety and toxicity risk attached to this drug class. Safety will be a key focus of all ongoing studies.

Piqray is indicated for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

The approval followed **a 572 patient trial** of patients with metastatic breast cancer who had advanced after endocrine therapy (aromatase inhibitor)[2]. Results from the trial showed the addition of Piqray to fulvestrant significantly prolonged progression free survival (median of 11 months vs. 5.7 months) in patients whose tumours had a PIK3CA mutation. The study did not report on survival.

The main side effects in the clinical trial were severe hypersensitivity, severe cutaneous reactions, hyperglycemia, pneumonitis and diarrhoea. Grade 3 and 4 severe reactions were relatively rare except for hyperglycemia where this condition occurred in 33% and 4% of patients respectively.

Piqray was the first new drug application for a new molecular entity approved under the Real-Time Oncology Review (RTOR) pilot program, which permits the FDA to begin analysing key efficacy and safety datasets prior to the official submission of an application, allowing the review team to begin their review and communicate with the applicant earlier.

Piqray also used the updated Assessment Aid (AAid), a multidisciplinary review template intended to focus the FDA's written review on critical thinking and consistency and reduce time spent on administrative tasks. As a result of these measures Piqray was approved approximately three months ahead of the Prescription Drug User Fee Act (PDUFA) VI deadline of August 18, 2019.

The FDA granted this application Priority Review designation.

[2] SOLAR 1 - A Phase III Randomized Double-blind, Placebo Controlled Study of Alpelisib in Combination With Fulvestrant for Men and Postmenopausal Women With Hormone Receptor Positive, HER2-negative Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment

Overview of Glioblastoma and its treatment

Glioblastoma

Gliomas (astrocytomas and oligodendrogliomas) are the most common types of malignant brain tumours. Together, they make up about 40% of all primary brain tumours and around 70% of all primary malignant brain tumours. Astrocytomas can occur in any part of the brain or spinal cord.

Astrocytomas are classified by grade from one to four (I–IV) based on how much they look like normal brain tissue. A higher grade means that the tumour is less like normal brain cells and grows faster. Grade I astrocytomas are also called pilocytic astrocytomas. These tumours occur in children and young adults. They are less invasive than other grades and have a relatively good prognosis. Grade III astrocytomas are also called anaplastic astrocytomas. **Grade IV astrocytomas are often called glioblastoma multiforme (GBM).**

RISK FACTORS

Cause is unknown and they appear to occur randomly. Risk factors include age and exposure to ionising radiation (X rays, gamma rays). Non ionising electromagnetic radiation (such as radio waves, microwaves) have long been suspected as a cause of malignant brain tumours but there is no strong evidence to support of an association. Studies in people exposed to high levels of non-ionising electromagnetic radiation, such as electrical workers and heavy users of mobile phones, have mainly shown no effect.

The tumours occur where there is a gene mutation that controls how cells grow and multiply. In GBM the cells with the mutation develop into the tumour.

EPIDEMIOLOGY

Primary malignant tumours of the central nervous system (brain and spinal cord) are rare. Only 7 people out of every 100,000 people in Australia (total of 1,472 people) were diagnosed with primary malignant brain tumour in 2007, the latest year for which national figures are available. In comparison, nearly ten times more people were diagnosed with bowel cancer in the same year (63 people out of every 100,000 people in Australia).

The median age at diagnosis of malignant brain tumours in Australia was 55–59 years for men and 60–64 for women in 1999. Gliomas are slightly more common in men than in women.

We estimate there are between 12,000 to 15,000 new cases of GBM annually in the USA and of these ~65% are unmethylated MGMT.

SYMPTOMS AND DIAGNOSIS

Patients typically present with complaints of blurred vision, dizziness, headaches and seizures. Diagnosis is normally via MRI. Most people with a primary malignant brain tumour are middle-aged adults at the time of diagnosis.

Early detection of brain tumours does not significantly improve the benefit of treatment.

TREATMENT OF HIGH GRADE TUMOURS

Following diagnosis and depending on the grade of the tumour (which is normally assessed via biopsy) first line treatment is surgery to remove the tumour followed by radiotherapy and or chemotherapy. The surgery is rarely curative.

The aim of the chemotherapy following surgery is to prevent or slow the regrowth of the tumour. Temozolomide is the standard of care for GBM patients.

Limitations to Temozolomide

Temozolomide is the standard of care for the treatment of all patients following surgery to remove a GBM. It is an off patent drug and generates ~12,000 prescriptions per month in the US.

Temozolomide has one very specific limitation in that the drug only has efficacy in patients with methylated MGMT promotor status. The drug is generally not effective in patients with unmethylated MGMT promotor status.

MGMT promotor status is a term relating to a certain gene expression for DNA repair. A patient's MGMT promotor status is determined from a biopsy normally collected at the time of the surgery to remove the tumour.

Paxalisib was developed specifically to treat patients with unmethylated MGMT promotor status for which temozolomide has minimal efficacy.

Appendix A contains a more detailed overview of this topic.

Financials

The company under took a substantial refresh from 2015 onwards following two decades as a listed entity. These measures included:

- July 2015 - Appointment of Iain Ross to the Board as NED. Mr Ross initiated a company wide review particularly focussed on the pre-clinical drug pipeline. Over the ensuing 2 years this resulted in the termination or sale of several pre-clinical programs. The only surviving drug from this time is Cantrixil;
- December 2015 - Appointment of James Garner as CEO;
- June 2016 - Iain Ross Appointed Chairman, Board reduced to three NED's plus CEO;
- October 2016 - In licenses GDC-084 (paxalisib) from Genentech;
- November 2017 - Change of company name from Novogen Limited to Kazia Therapeutics Limited;
- November 2017 - 1:10 share consolidation reducing the number of shares on issue to 48.3m;
- December 2017 – The directors cancelled paid-up share capital of $162.2m under section 258F of the Corporations Act. This reduced the value of paid up share capital to $31,575,824 as at 31 December 2017. This effectively re-set the balance sheet to reflect the current state of affairs of the company.

Capital Structure

Figure 6 - Capital Structure and Recent History Of Capital Raises

Fiscal Year		$m	Shares(m)	Issue Price $	Comments
Recent Equity Capital Raisings					
Mar-20		9.0	22.5	0.40	Placement and SPP
Oct-19		4.0	10.0	0.40	Placement
Nov-18		4.2	11.05	0.38	Placement and SPP
		17.2			
Shares on issue June 2020 - KZA		94,598,369			ASX listed
Shares on issue June 2020 - KZIA		3,148,929			NASDAQ listed
Paid up capital	$	36,641,519			
Convertible note	$	464,000			Represented by 1,865,000 unlisted securities

SOURCE: COMPANY DATA

The NASDAQ listing is a legacy of the previous management at Novogen. The American Depositary Reserves (ADR's trade on the NASDAQ). Each ADR represents 10 ordinary shares in the company. Bank of New York Mellon is the Depository for the American Depository Reserves traded on NASDAQ. The ADR's represent ~26% of the ordinary shares on issue.

The former shareholders of Triaxial are the beneficial owners of the convertible notes[3]. There is in fact no interest payable and no liability attached to the CN's. As we understand there may be an obligation to issue some shares in the company if Cantrixil progresses to a phase II trial.

The most recent event to trigger a conversion was the in-license deal on paxalisib in October 2016. The remaining portion of the CN's are exercisable at the holders' discretion

[3] We believe this attaches to Cantrixil only. Triaxial Pty Ltd is a former subsidiary of Kazia Therapeutics which has since been wound up.

on completion of a phase II trial or achieving breakthrough designation, and would convert to 1,856,000 ordinary shares if converted (representing approximately 2% dilution).

The company received a further $2.4m from the sale of surplus assets in March 2019. It is also a significant beneficiary of the Australian Government's R&D Tax Refund Scheme.

Cash Runway

Cash at 31 December 2019 was $6.4m. The net cash burn for the July – December 2019 period was $2.7m. We expect an operating net cash burn in 2H20 in the range of $4m to $5m. The company raised $9m in March 2020 hence we expect a cash balance at 30 June of ~$11m.

Assuming 200 patients are recruited into the active arm of GBM Agile, the starting point for total cost would be US$40m, most of which would be funded by KZA

KZA's financials commitment to GBM Agile are yet to be published, however, we expect it will involve at least 200 patients in the active arm of the randomised trial. Our valuation assumes KZA will be required to fund most of the ~200 patients in the active arm of the study. The forecast includes A$48m over three years for GBM Agile, funded by a further capital raise during the period.

Based on these assumption, it is likely that the cash reserves at 30 June 2020 will represent 6 to 10 months of funding depending on the rate of recruitment into GBM Agile and also on the company's funding obligation.

As one would expect the company has not given any guidance on its future funding requirement. Importantly, participation in GBM Agile is unlikely to prevent a partnering transaction, hence there are some options for funding.

Once the data from the approval study is completed, then KZA takes on a new profile. A smaller company could easily market a highly differentiated drug such as paxalisib. It would have seven to eight years of patent protection and a relatively small number of specialist physicians responsible for prescribing the drug.

Addressable Market

The consensus estimate for new GBM cases in the US is ~ 12,500 annually. Of these ~65% have unmethlylated MGMT promotor status, hence the annual addressable market for newly diagnosed patients is ~8,125. We assume a similar market size for the rest of the world.

The annualised costs of the drug is likely to be in the vicinity of US$100K with patients remaining on therapy for 9 months on average. We believe this is an appropriate starting point for pricing based on comparison with the pricing of other drugs in the orphan indications. Based on these assumptions the TAM for the US is ~US$609m annually. Assuming 80% market penetration we estimated peak revenues in 2027 at US$487m.

The ROW market is likely to be approximately the same volume as the US but at a lower price point. On a global basis we estimate peak revenues in the range of US$700m to $900m for GBM alone.

The potential for label extension into adjacent indications is also significant (refer figure 4). None of the investigator sponsored studies listed in figure 4 would be sufficient for a separate approval, nevertheless, if the drug is approved (in GBM) following GBM Agile, off label use in these other indications is highly likely. While the drug cannot be marketed for off label indications, the data from the studies may be presented at conferences and reported in medical journals. In the tight knit community of oncologists responsible for the treatment of these patients, it is certainly possible for a new therapy to gain a profile.

Encouraging results from the investigator led studies will almost certainly lead to further approval studies in these adjacent indications. Further work on a biomarker for these indications also inevitable.

Valuation

Our valuation of the stock is based on the risk/reward profile as at the date of this report. As the drug moves towards the completion of the clinical program the valuation is likely to increase as development milestones are achieved.

Ultimately the value of the company will be influenced by the effect size of the drug, which in turn determines its price. Based on what we know today (i.e. interim data from phase II in 9 patients, the drug increased progression free survival by 3.5 months and overall survival by ~5 months) the effect size is significant. We believe insurers in the US will pay handsomely for such an effective drug.

For comparable transactions in the space, there really aren't any recent deals in GBM. While there have been many deals in oncology over the years, these are across a very wide variety of diseases and treatment types. There have been very large deals worth billions of US$ in the CAR-T space and for immune checkpoint inhibitors (ICI's) as well. These drugs are applicable to a wide variety of cancers – particularly the ICI's.

Paxalisib is a small molecule drug in a relatively small indication, nevertheless the principles for determining its value are unchanged i.e. future revenues determined by market size and effect size.

For completeness, in 2011 Gilead acquired Calistoga for US$375m in cash plus up to US$200m in development milestones. Calistoga's key asset was its PI3K inhibitor – Zydelig, which went on to gain approval for the treatment of certain rare blood cancers. It is a third of fourth line therapy and was a mid-stage asset at the time of the acquisition.

In the Australian context, the most recent transactions in the oncology space include Merck's acquisition of Viralytics in 2018 for ~US$320m and the acquisition of Sirtex in 2017 for A$1.8bn (~US$1.3bn). Sirtex had its SIR spheres for the treatment of mCRC which generated A$200m in revenues, while VLA had its mid stage oncolytic virus for the treatment of melanoma and was being investigated for efficacy in a range of visceral tumours in several phase II trials.

We estimate KZA has spent $20m on the development of paxalisib to this point inclusive of the initial US$5m upfront paid to Genentech.

Our risk adjusted discounted cash flow model uses a discount rate of 15% and term of 9 years with first revenues generated in 2024. The model assumes the drug is partnered following completion of the clinical trial in 2023 with a series of milestone payments as commercialisation hurdles are achieved, together with a royalty on sales of 12%.

As is always the case with the valuation of such assets, the valuation is based on assumptions about outcomes from clinical trials which remain highly uncertain. See also the summary of key risk areas.

We initiate coverage of Kazia with a Buy (Speculative) recommendation a valuation of $1.00 implying an enterprise value of $106m. This represent a large discount to some of the transactions discussed above.

Kazia Therapeutics Board

Mr Iain Ross – Non Executive Chairman

Mr Ross is based in the UK. He is an experienced Board Director and Pharma executive. He has served on numerous company boards both in Australia and the UK with most of these in the biotechnology sector. In his career he has held senior positions in Sandoz AG, Fisons Plc, Hoffmann-La Roche AG and Celltech Group Plc and also undertaken a number of start-ups and turnarounds on behalf of banks and private equity groups.

Dr James Garner – Chief Executive Officer and Managing Director

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 in executive roles with Biogen and Takeda. Prior to joining Kazia in 2016, he led R&D strategy for Sanofi in Asia Pacific.

Mr Bryce Carmine – Non Executive

Mr 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 lead the Global Pharmaceutical Sales and Marketing and was a member of the company's Executive Committee. Mr Carmine previously held a series of product development portfolio leadership roles including Global Pharmaceutical Product Development, with responsibility for the entire late-phase pipeline development across all therapeutic areas for Eli Lilly.

Mr Steven Coffey – Non Executive

Mr Coffey is a Chartered Accountant and has been a partner at Watkins Coffey Martin since 1993.

Figure 7 - Director Shareholdings

	Shareholding (m)	Options (m)
Mr Iain Ross	800,001	-
Mr Steven Coffey	251,474	-
Mr James Garner	200,000	800,000
Mr Bryce Carmine	191,292	-
	1,442,767	800,000
Shares on issue	94,598,369	
Free float	98%	

SOURCE: COMPANY DATA

Substantial shareholders include Platinum Investment Management (9.6%) and the private company Hishenk Pty Ltd with 12%.

Appendix A – MGMT Promotor Status and PI3K Pathway

A number of chemotherapy agents work by damaging DNA. The chemistry dates back to WWI when mustard gas was used as a chemical weapon. One of the effects of damaging DNA is to make it harder for cells to divide and replicate. Cancers usually represent the fastest growing cells in the body, so damaging DNA injures the cancer more than the slower-growing healthy cells (although it is also responsible for some of the side effects in faster-growing healthy cells such as in the bone marrow or the lining of the GI tract). Temozolomide works this way – it causes alkylation of DNA.

The MGMT gene codes for an enzyme that repairs DNA. In the ordinary course of events, humans incur regular DNA damage from background radiation, toxins, etc., and MGMT is one of the mechanisms by which our body repairs that damage.

Having a 'fully functional' DNA repair mechanism is ordinarily a good thing, but it can be a liability when a patient is being treated with DNA-damaging chemotherapy. The DNA repair mechanisms effectively work against the DNA-damaging chemotherapy, and counteract all or part of its effect. In the case of the MGMT gene, this is relatively binary. Those with an 'unmethylated MGMT promotor' have a well-functioning repair mechanism, while those with a 'methylated MGMT promotor' have a less well-functioning repair mechanism. The methylation essentially refers to a switch beside the gene ('epigenetic') which turns it on or off. Turning it off deliberately is sometimes referred to as 'gene silencing', and has been a therapeutic strategy for companies like Benitec.

For glioblastoma, this has two consequences. First, the patients with the unmethylated promotor (i.e. a fully-functional DNA repair mechanism) generally have a poorer prognosis than those with the methylated promotor (i.e. a deficient DNA repair mechanism), regardless of treatment. The reasons for this are not entirely clear. It does seem very consistent though – glioblastoma with an unmethylated MGMT promotor is a worse disease than glioblastoma with a methylated MGMT promotor.

Second, and perhaps more importantly, because temozolomide works by damaging DNA, those with the unmethylated MGMT promotor effectively repair the damage as fast as temozolomide can cause it, basically cancelling out the effect. In the clinic, this translates to methylated patients getting a meaningful survival benefit from temozolomide (15.3 months -> 21.7 months), while unmethylated patients get no meaningful survival benefit (11.8 months -> 12.7 months).

There are several good assays now available to measure MGMT methylation status, and it is common clinical practice in developed countries. The methylation status of the MGMT promoter is determined by polymerase-chain-reaction (PCR) analysis. PCR is widely used in molecular biology. The tests are 95%+ accurate and require a tissue sample (collected at the time of surgery). Most studies say that about 35-45% of samples are methylated, and 55-65% are unmethylated.

For paxalisib, MGMT methylation status makes no difference per se, because the drug doesn't work by damaging DNA. However, in the unmethylated patients, it is so universally accepted that temozolomide is ineffective and consequently it can be replaced in a clinical study without regulatory, ethical, or clinical concern.

In the methylated patients, temozolomide does offer a benefit so it cannot be easily dropped from clinical trials. For this reason, the clinical trials of paxalisib only recruit patients with unmethylated MGMT.

The definitive work on this topic was done by Hegi et al[4].

The Hegi paper was a retrospective analysis of the original phase III studies that led to the approval of temozolomide. It showed that, although the drug works on average overall, it is only actually the methylated patients that are responding.

The PI3K/AKT/mTOR Pathway

Many cancers result from, or depend on, malfunctions in biochemical signalling pathways in the cell, which ordinarily regulate things like cell growth. When these signalling pathways are disrupted, for example due to a genetic mutation, the cell will often multiply out of control, leading to a tumour.

Broadly speaking, there are two main components to the signalling pathway. Extracellular receptors are situated on the surface of the cell and are activated by signalling chemicals in the blood. For example, the epidermal growth factor receptor (EGFR) is on the surface of many cells and is activated by epidermal growth factor (EGF) in the blood. This signalling mechanism is switched on in a lot of lung cancers, for example.

Once the extracellular receptors are activated, they cascade that signal through intracellular (inside the cell) signal transduction pathways, (which are really just chains of chemical reactions). One of the key such pathways is the PI3K / Akt / mTOR pathway (to give it its full name). This is part of the signal transduction mechanism for many extracellular receptors, including EGFR and HER2, which is particularly relevant in breast and gastric cancer.

Inhibiting the PI3K pathway can help stop tumour growth in a couple of ways. First, it counteracts the effect of any overexpressed extracellular receptors. For example, if a drug inhibits PI3K, then to some extent it doesn't matter how much EGFR you have – because it signals through PI3K, it doesn't have much effect. Second, PI3K itself can get switched on by cancer-causing genetic mutations, and this causes signal transduction (and therefore cell growth, etc.) even in the absence of those extracellular receptors being switched on.

In glioblastoma, the PI3K pathway is activated in 85-90% of patients, either via genetic mutations to extracellular receptors such as EGFR, or via genetic mutations to PI3K itself. This is probably why Genentech considered it a promising target for glioblastoma.

The PI3K pathway contains multiple steps, but the four major components are: activation of extracellular receptor (e.g. EGFR) -> activation of PI3K inside the cell -> activation of Akt -> activation of mTOR. For this reason, it is sometimes referred to more fully as the PI3K / Akt / mTOR pathway.

Paxalisib is a potent inhibitor of PI3K, and it is also a moderate inhibitor of mTOR. In other words, it inhibits the pathway in two separate places. This is deliberate, and intended to reduce some of the risk of bypass and resistance mechanisms.

For readers interested in pursuing further research we recommend the following video presentation in addition to the Hegi paper.

https://www.youtube.com/watch?v=hcGrpd0CRV0

[4] NEJM 352;10 p997 - 1003

Kazia Therapeutics
as at 3 July 2020

Recommendation	Buy, Speculative
Price	$0.51
Valuation	$1.00

Table 1 - Financial summary

	FY18	FY19	FY20e	FY21e	FY22e
Year Ending June					
R&D incentive	2.2	1.4	4.0	3.7	7.2
Total Revenue	**12.9**	**1.5**	**4.0**	**3.7**	**7.2**
COGS	-	-	-	-	-
Gross profit	12.9	1.5	4.0	3.7	7.2
Expenses Net of R&D	-9.8	-6.5	-8.2	-16.0	-16.0
Other expenses	-5.6	-3.9	-5.0	-8.0	-10.0
Total Expenses	-19.3	-12.2	-14.2	-24.0	-26.0
EBIT	-6.4	-10.7	-10.2	-20.3	-18.8
Interest income	0.0	0.0	0.0	-0.1	-0.1
Pre tax profit	(6.3)	(10.6)	(10.2)	(20.4)	(18.9)
Tax expense	0.3	0.3	0.1	-	-
NPAT- normalised	**(6.0)**	**(10.3)**	**(10.1)**	**(20.4)**	**(18.9)**
Reported NPAT	(6.0)	(10.3)	(10.1)	(20.4)	(18.9)

Cashflow (A$m)	FY18	FY19	FY20e	FY21e	FY22e
Gross cashflow	-8.7	-6.7	-7.5	-20.3	-18.8
Net interest	0.0	0.0	0.0	-0.1	-0.1
Operating cash flow	-8.7	-6.7	-7.5	-20.4	-18.9
Proceeds from asset sales	0.0	2.4	0.0	0.0	0.0
Free cash flow	-8.7	-4.3	-7.5	-20.4	-18.9
Business acquistions	0.0	0.0	0.0	0.0	0.0
Proceeds from issuance	0.0	3.8	13.0	32.0	0.0
Movement in borrowings	0.0	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0	0.0
Change in cash held	-8.7	-0.5	5.5	11.6	-18.9
Cash at beginning of period	14.5	6.0	5.4	10.9	22.5
FX adjustment	0.0	-0.1	0.0	0.0	0.0
Cash at year end	**6.0**	**5.4**	**10.9**	**22.5**	**3.6**

Balance Sheet (A$m)	FY18	FY19	FY20e	FY21e	FY22e
Cash	6.0	5.4	10.9	22.5	3.6
Receivables	2.5	1.7	0.5	0.5	0.5
Other current assets	0.7	0.4	0.5	0.5	0.5
Property, Plant and Equipment	-	-	-	-	-
Intangibles	14.6	13.5	13.5	13.5	13.5
Other non current assets	4.3	0.2	0.2	0.2	0.2
Total assets	28.1	21.2	25.6	37.2	18.3
Trade payables	2.1	1.8	3.0	3.0	3.0
Other liabilities	2.5	1.4	1.4	1.4	1.4
Deferred taxes	4.0	3.7	3.7	3.7	3.7
Provisions	0.3	0.1	0.5	0.5	0.5
Total Liabilities	8.9	7.0	8.6	8.6	8.6
Net Assets	19.2	14.2	17.0	28.6	9.7
Share capital	31.6	36.6	49.6	81.6	81.6
Other equity	2.2	2.5	2.4	2.4	2.4
Retained earnings	(14.6)	(24.9)	(35.0)	(55.4)	(74.3)
Reserves	-	-	-	-	-
Shareholders Equity	19.2	14.2	17.0	28.6	9.7

Valuation Ratios (A$m)	FY18	FY19	FY20e	FY21e	FY22e
Reported EPS (cps)	-12.4	-16.6	-10.7	-12.9	-11.9
Normalised EPS (cps)	-12.4	-16.6	-10.7	-12.9	-11.9
EPS growth (%)	nm	nm	nm	nm	nm
PE(x)	**nm**	**nm**	**nm**	**nm**	**nm**
EV/EBIT (x)	nm	nm	nm	nm	nm
P/NTA (x)	5.4	45.2	13.8	5.4	- 21.3
Book Value Per Share (cps)	39.7	22.9	18.0	18.0	6.1
Price/Book (x)	1.3	2.2	2.8	2.8	8.3
DPS (cps)	-	-	-	-	-
Payout ratio %	0%	0%	0%	0%	0%
Dividend Yield %	0.0%	0.0%	0.0%	0.0%	0.0%
Franking %	0%	0%	0%	0%	0%
FCF yield %	nm	nm	nm	nm	nm
Net debt/Equity	0%	0%	0%	0%	0%
Net debt/Assets	0%	0%	0%	0%	0%
Gearing	net cash	net cash	net cash	net cash	net cash
Net debt/EBITDA (x)	n/a	n/a	n/a	n/a	n/a
Interest cover (x)	n/a	n/a	n/a	n/a	n/a

Interim Results	1H20	2H20e	1H21e	2H21e
Revenues	0.6	3.4	0.6	3.1
R&D Expense	-4.2	-4.0	0.0	0.0
All Other expenses	-2.4	-2.6	-4.0	-4.0
EBIT	-6.2	-4.0	-3.4	-0.9

SOURCE: BELL POTTER SECURITIES ESTIMATES

Recommendation structure

Buy: Expect >15% total return on a 12 month view. For stocks regarded as 'Speculative' a return of >30% is expected.

Hold: Expect total return between -5% and 15% on a 12 month view

Sell: Expect <-5% total return on a 12 month view

Speculative Investments are either start-up enterprises with nil or only prospective operations or recently commenced operations with only forecast cash flows, or companies that have commenced operations or have been in operation for some time but have only forecast cash flows and/or a stressed balance sheet.

Such investments may carry an exceptionally high level of capital risk and volatility of returns.

Research Team

Staff Member	Title/Sector	Phone	@bellpotter.com.au
TS Lim	Head of Research	612 8224 2810	tslim
Industrials			
Steven Anastasiou	Industrials	613 9235 1952	sanastasiou
James Filius	Industrials	613 9235 1612	jfilius
Sam Haddad	Industrials	612 8224 2819	shaddad
Alex McLean	Industrials	612 8224 2886	amclean
Hamish Murray	Industrials	613 9235 1813	hmurray
Chris Savage	Industrials	612 8224 2835	csavage
Jonathan Snape	Industrials	613 9235 1601	jsnape
Damien Williamson	Industrials	613 9235 1958	dwilliamson
Healthcare/Biotech			
John Hester	Healthcare	612 8224 2871	jhester
Tanushree Jain	Healthcare/Biotech	612 8224 2849	tnjain
Elyse Shapiro	Healthcare/Biotech	613 9235 1877	eshaprio
Financials			
TS Lim	Banks/Regionals	612 8224 2810	tslim
Lafitani Sotiriou	Diversified Financials/Fintech	613 9235 1668	lsotiriou
Resources			
Peter Arden	Resources	613 9235 1833	parden
David Coates	Resources	612 8224 2887	dcoates
Stuart Howe	Resources	613 9235 1856	showe
Associate			
jJoseph House	Associate Analyst	+61 3 9235 1624	jhouse

Bell Potter Securities Limited
ACN 25 006 390 7721
Level 29, 101 Collins Street
Melbourne, Victoria, 3000
Telephone +61 3 9256 8700
www.bellpotter.com.au

Bell Potter Securities (HK) Limited
Room 1701, 17/F
Posperity Tower, 39 Queens Road
Central, Hong Kong, 0000
Telephone +852 3750 8400

Bell Potter Securities (US) LLC
Floor 39
444 Madison Avenue, New York
NY 10022, U.S.A
Telephone +1 917 819 1410

Bell Potter Securities (UK) Limited
16 Berkeley Street
London, England
W1J 8DZ, United Kingdom
Telephone +44 7734 2929