

ASX RELEASE

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## KAZIA'S PAXALISIB SHOWS POSITIVE OVERALL SURVIVAL SIGNAL IN PHASE II GLIOBLASTOMA STUDY

*Overall survival (OS) of 17.7 months, vs. 12.7 months for existing standard of care*

*Longest-treated patient remains progression-free 19 months after diagnosis*

**Sydney, 7 April 2020** – Kazia Therapeutics Limited (ASX: KZA; NASDAQ: KZIA), an Australian oncology-focused biotechnology company, is pleased to share positive interim data from its ongoing phase II study of paxalisib (formerly GDC-0084) in glioblastoma, the most common and most aggressive form of primary brain cancer.

### Key Points

- Interim analysis of Part A (escalation cohort) (n=9) showed median overall survival (OS) of 17.7 months, representing a clinically meaningful extension of life when compared to the 12.7 months associated with the existing standard of care, temozolomide
- Interim analysis of all evaluable patients (Part A = 9; Part B = 21) shows median progression-free survival (PFS) of 8.5 months, broadly in line with previous analysis, and comparing favourably to the 5.3 months associated with temozolomide
- The longest-treated patient remains progression-free 19 months after diagnosis
- Approximately half the enrolled patients remain on drug and both OS and PFS figures may further improve as the trial progresses toward conclusion
- Kazia expects to present further data in 2H CY2020 and final data in 1H CY2021

### Summary of Paxalisib Data in Comparison to Temozolomide (existing standard of care)

	Temozolomide (FDA-approved treatment)	Paxalisib (interim phase II data)
<b>Progression-Free Survival (PFS)</b>		
<i>Measures ability of a drug to slow growth of a tumour</i>	5.3 months	8.5 months
<b>Overall Survival (OS)</b>		
<i>Measures ability of a drug to prolong life</i>	12.7 months	17.7 months

### Board of Directors

**Mr Iain Ross** Chairman, Non-Executive Director

**Mr Bryce Carmine** Non-Executive Director

**Mr Steven Coffey** Non-Executive Director

**Dr James Garner** Chief Executive Officer, Managing Director

Kazia CEO, Dr James Garner, commented, “this is an excellent result, and we are delighted with the emerging data. The ‘gold standard’ for any new cancer treatment is the ability to extend life - an especially challenging goal in a disease such as glioblastoma - and this data provides our first evidence that paxalisib may achieve this objective in a very challenging patient population.”

He continued, “there have not been any new drug treatments for newly-diagnosed glioblastoma patients for over twenty years, and we aspire to change that situation. We believe that paxalisib is rapidly becoming one of the most promising drug candidates in the global pipeline for this very challenging disease and we will be working strenuously to make it available to patients as quickly and efficiently as possible. The study continues to follow a number of patients who remain on treatment, and we currently expect to report a further data read-out in the second half of the year.”

## **Background**

The reported overall survival (OS) figure of 17.7 months represents a strong signal of clinical efficacy. The existing, FDA-approved standard of care, temozolomide, is associated with an OS of 12.7 months in this patient population<sup>1</sup>. Comparison between different studies is always imprecise, but the magnitude of the numerical difference provides powerful evidence that treatment with paxalisib may extend life in this patient group.

The reported progression-free survival (PFS) figure of 8.5 months is slightly better than the figure of 8.4 months previously reported in November 2019. Temozolomide is associated with a PFS of 5.3 months in this patient population.

Before losing patent protection, temozolomide achieved peak sales in excess of US\$ 1 billion per annum, which provides an indication of the commercial opportunity associated with a new treatment for glioblastoma.

Thirty patients were enrolled to this study, comprising 9 in Part A, and 21 in Part B. Data reported here are provisional figures from Part A (for OS) and from the entire study population (for PFS), but may change as ongoing patients proceed through the study. The study has been conducted at leading centers of excellence in the United States.

The safety of paxalisib remained broadly consistent with prior experience, with hyperglycaemia (raised blood sugar), oral mucositis (mouth ulcers), and low-grade rash among the most common drug-related toxicities.

In addition to this phase II study in glioblastoma, four other studies are underway with paxalisib in different forms of brain cancer, and it is anticipated that several of these will provide initial efficacy data during CY 2020.

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<sup>1</sup> ME Hegi, A-C Desirens, T Gorlia, et al. *N Engl J Med* (2005); 352:997-1003

This data had been accepted for presentation at the annual meeting of the American Association of Cancer Research (AACR) in San Diego, CA from 24 -29 April 2020. However, given the cancellation of the AACR meeting due to the COVID-19 outbreak, Kazia has determined to provide an update to investors via this ASX announcement.

### **Next Steps**

The phase II study remains ongoing, with approximately half of the total enrolled patient population still receiving drug at the time of analysis and a number of additional patients still in follow-up. At this stage, Kazia expects to present further data in 2H CY2020, and final data in 1H CY2021.

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, which is intended to provide data to support FDA approval for paxalisib in glioblastoma. This work has been proceeding on schedule, and Kazia continues to expect first patient in to the paxalisib arm in 2H CY2020.

### **Investor Conference Call**

An investor conference call will be held on Thursday 9 April 2020 at 8:30am, Sydney time (AEDT), which is 3:30pm on Wednesday 8 April 2020 in San Francisco (PST), 6:30pm on Wednesday 8 April 2020 in New York (EST), and 6:30am on Thursday 9 April 2020 in Hong Kong SAR (HKT) to allow for further discussion of these results.

Participants will need to **pre-register** for the call via the following link:

<https://s1.c-conf.com/DiamondPass/10005482b-invite.html>

Click the 'Register Now' button and follow the prompts to complete pre-registration. You will then receive a calendar invite with dial in numbers, a passcode and a PIN to dial into the conference call.

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## **About Kazia Therapeutics Limited**

Kazia Therapeutics Limited (ASX: KZA, NASDAQ: KZIA) is an innovative oncology-focused biotechnology company, based in Sydney, Australia. Our pipeline includes two clinical-stage drug development candidates, and we are working to develop therapies across a range of oncology indications.

Our lead program is paxalisib (formerly GDC-0084), a small molecule inhibitor of the PI3K / AKT / mTOR pathway, which is being developed to treat glioblastoma multiforme, 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. Interim data was reported in April 2020, and further data is expected in 2H 2020. Paxalisib was granted orphan designation for glioblastoma by the US FDA in February 2018.

TRX-E-002-1 (Cantrixil), is a third-generation benzopyran molecule with activity against cancer stem cells and is being developed to treat ovarian cancer. TRX-E-002-1 is currently undergoing a phase I clinical trial in Australia and the United States. Interim data was presented at the ESMO Congress in September 2019, and the study remains ongoing. Cantrixil was granted orphan designation for ovarian cancer by the US FDA in April 2015.

This document was authorized for release to the ASX by James Garner, Chief Executive Officer, Managing Director.

## CLINICAL TRIAL SUMMARY

<b>Study Title</b>	A Phase 2 Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of the PI3K/mTOR Inhibitor GDC-0084 Administered to Patients With Glioblastoma Multiforme Characterized by Unmethylated O6-methylguanine-methyltransferase Promoter Status Following Surgical Resection and Standard Concomitant Chemoradiation Therapy With Temozolomide
<b>Phase of Development</b>	Phase II
<b>Investigational Product</b>	Paxalisib (GDC-0084)
<b>Disease Area</b>	Newly-diagnosed glioblastoma (GBM) (WHO grade IV glioma)
<b>Registration</b>	NCT03522298
<b>Study Description</b>	<p>This is a two-part study intended to support transition from an advanced recurrent disease population (as investigated in the phase I study) to newly-diagnosed patients (the target population for commercial launch). It is designed in two stages:-</p> <p><b>Stage 1</b> – a dose escalation component to establish a maximum tolerated dose (MTD) and recommended dose for further study in newly-diagnosed patients; groups of patients will be administered increasing doses of GDC-0084 until unacceptable toxicity is encountered</p> <p><b>Stage 2</b> – a dose expansion cohort, in which all patients will be treated at the MTD, and which is designed to elicit confirmatory signals of clinical efficacy</p>
<b>Number of Subjects</b>	<p><b>Stage 1</b> – 9 patients (enrolment complete)</p> <p><b>Stage 2</b> – 21 patients (enrolment complete)</p>
<b>Study Design</b>	<p>This is a single-arm, exploratory study.</p> <p>Stage 1 is designed as a standard ‘3+3’ dose escalation protocol. The first cohort of 3 patients receive 60mg of GDC-0084, once daily in capsule form. If this dose is tolerated for at least 28 days, an additional 3 patients will receive 75mg, and subsequent cohorts may increase at 15mg intervals until unacceptable toxicity occurs. If a dose-limiting toxicity (DLT) is observed in a given cohort, it will be expanded to 6 patients, and if two DLTs are observed at a given dose level then the previous dose will be declared the MTD.</p>

	<p>Stage 2 will enroll all patients at the MTD. Half of the patients will receive paxalisib with food, and half on an empty stomach, in order to assess potential food effects.</p>
<b>Patient Population</b>	<p>All patients had newly-diagnosed glioblastoma, which had been treated with surgery and radiotherapy according to the standard-of-care 'Stupp regimen'.</p> <p>All patients had unmethylated MGMT promotor status, which renders them essentially resistant to temozolomide, the only FDA-approved drug treatment for newly-diagnosed glioblastoma. This group represents approximately two thirds of the total GBM population.</p>
<b>Endpoints</b>	<p>The primary endpoint of Stage 1 was safety and tolerability, since it is a dose escalation study. PFS and OS were included as exploratory efficacy endpoints.</p> <p>The primary endpoints of Stage 2 were PFS and OS.</p>
<b>Participating Centres</b>	<p><b>UCLA – Jonsson Comprehensive Cancer Center</b> Los Angeles, CA</p> <p><b>University of Colorado Cancer Center</b> Denver, CO</p> <p><b>Dana-Farber Cancer Institute</b> Boston, MA</p> <p><b>John Theurer Cancer Center</b> Hackensack, NJ</p> <p><b>Stephenson Cancer Center</b> Oklahoma City, OK</p> <p><b>MD Anderson Cancer Center</b> Houston, TX</p>
<b>Start Date</b>	First Patient In: September 2018
<b>End of Recruitment</b>	Last Patient In: February 2020

## Q&A

### **What is the significance of the data reported here? How should these results be interpreted?**

Kazia has previously referred to the published paper by Hegi et al. on temozolomide, which reports a median PFS of 5.3 months and a median OS of 12.7 months<sup>2</sup>. This paper remains the definitive reference point for this patient population when treated with temozolomide, the existing standard of care. In effect, it shows that patients receiving standard treatment will typically progress in about 5.3 months and will pass away in little over a year.

The current phase II study of paxalisib has reported a PFS of 8.5 months and an OS of 17.7 months. Comparisons between studies are always confounded by differences in patient population, study design, calculation methodology, and other variables. However, the magnitude of these differences strongly suggests that paxalisib is offering superior benefit to patients. Were this difference in OS to be replicated in a randomized, controlled trial, the magnitude of improvement would represent approximately a 40% increase in life expectancy. As previously noted, the precise quantification of this benefit will be the focus of the planned GBM AGILE study.

OS has long been considered the ‘gold standard’ measure of effectiveness for a new cancer drug<sup>3</sup>, although a number of novel therapies have been approved in recent years without demonstrating an OS benefit. The implication that paxalisib may be able to achieve this objective provides a powerful endorsement to its further development.

### **Are the results statistically significant?**

‘Statistical significance’ is a mathematical term that refers specifically to a comparison between different arms in a single study. In common with most oncology studies at this stage of development, this study is only a single-arm study and so it is not possible to formally assess statistical significance.

### **Is it possible that this study could provide a basis for product approval without conducting a further pivotal study?**

While these data are highly encouraging, Kazia expects that confirmation from a larger number of patients in a randomized, controlled trial will be required to secure product approval from FDA and other regulatory agencies.

In December 2019, Kazia announced that it had begun setup work to bring paxalisib into GBM AGILE, an ongoing platform study designed to provide data for registration of new drugs in glioblastoma. Our plan is to use GBM AGILE as a path-to-market for paxalisib, and recruitment is expected to commence in 2H CY2020.

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<sup>2</sup> ME Hegi, A-C Desirens, T Gorlia, et al. *N Engl J Med* (2005); 352:997-1003

<sup>3</sup> US Food and Drug Administration. *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics – Guidance for Industry* (December 2018)

## How would a survival benefit of this magnitude compare to other cancer drugs, and would it be sufficient to engage the support of clinicians and payors?

Each disease is specific, and so it is difficult to compare the potential efficacy of paxalisib with other drugs in other disease areas. Nevertheless, Kazia takes the view that, if paxalisib continued to demonstrate in a pivotal study an OS improvement of approximately this magnitude, both in proportional and absolute terms, it would provide the basis of a highly competitive commercial product.

For reference, the OS benefit associated with a number of FDA-approved and commercially successful cancer treatments are indicated below:-

Drug	Indication	OS Improvement
Avastin (bevacizumab)	Metastatic colorectal cancer	15.6 → 20.3 months
Avastin (bevacizumab)	Recurrent glioblastoma	(no improvement)
Abraxane (paclitaxel)	Pancreatic cancer	6.7 → 8.5 months
Nexavar (sorafenib)	Liver cancer	7.9 → 10.7 months
Stivarga (regorafenib)	Metastatic colorectal cancer	5.0 → 6.4 months

*(all figures taken from product Prescribing Information)*

## How robust is the comparison to data from previous clinical studies?

Ideally, the gold standard for definitive determination of efficacy is a randomised, controlled trial (RCT), in which patients are randomly allocated to receive either the treatment under investigation (in this case, paxalisib), or a comparator of some kind (either placebo or an existing treatment). The investigational treatment is then compared with exactly matched patients in the same clinical trial.

However, in common with the majority of cancer studies at this stage of development, the present study only contains a single arm and all patients receive paxalisib. The reasons for this approach are various, and include both ethical and operational considerations. A recent published analysis determined that more than 60% of oncology studies are single-arm rather than RCT<sup>4</sup>. Moreover, a separate analysis demonstrated that success in a single-arm phase II study was strongly predictive of subsequent success in a phase III study, and that an RCT phase II study was not superior to a single-arm design<sup>5</sup>.

As such, the emerging data must necessarily be compared to results from previous studies to assess treatment effect, and this reliance on 'historical controls' is also standard practice in the development of new cancer drugs. Such comparisons are of course imperfect: there are often differences in the way that studies have been run, the statistical calculation of endpoints, and the composition patient population.

<sup>4</sup> BR Hirsch et al. *JAMA Intern Med.* (2013);173(11):972-979

<sup>5</sup> JG Monzon et al. *Eur J Cancer.* (2015);51(17):2501-2507



Nevertheless, the natural history of glioblastoma is generally well-understood, and there have not been significant improvements in the prognosis of the disease since the Hegi paper was published. In this context, Kazia considers the emerging data from this study to be a positive signal.

### **What is the difference between progression-free survival (PFS) and overall survival (OS)?**

For a given patient, progression-free survival (PFS) describes the time until either progression of the disease (recurrence or growth of the tumour) or death, whichever is first. Overall survival (OS) describes the time until death from any cause.

In clinical trials of experimental cancer drugs, median PFS and median OS are commonly used as endpoints. The median PFS is the time point at which 50% of patients have progressed or died. For example, a median PFS of 5.4 months means that half of the patients will progress in less than 5.4 months and half will last longer. The median is used in preference to the more common mean because it reduces the impact of outliers. Similarly, the median OS is the time point at which 50% of patients have passed away.

### **These are interim data. Is it expected that the headline figures (PFS of 8.5 months and OS of 17.7 months) may change substantially in subsequent read-outs?**

As additional patients complete their participation, it is possible that these data points will change, either for the better or otherwise. The PFS data matures more quickly than the OS data, since patients typically progress before passing away, and so this data point may be considered more stable. The fact that inclusion of additional patients in the PFS analysis does not materially change the figure may be interpreted as validating.

### **Why was one of the patients withdrawn from the study, and what is the impact on the results?**

One patient was poorly compliant with study procedures and a decision was made by the Principal Investigator to withdraw that patient from the study. Since the patient's exposure to paxalisib was confined to a matter of days, and given that any data associated with this patient was considered questionable, they have been excluded entirely from this analysis.

Kazia has conducted sensitivity analyses to explore the impact of including all available data from this patient versus removing them from the analysis, and the impact on PFS and OS is negligible.

### **How does this study compare to the phase I study performed by Genentech?**

Prior to Kazia's licensing of the GDC-0084 asset, Genentech completed a phase I dose escalation study (NCT01547546). There are important differences between this study and the phase I study:-

- The phase I included patients with both grade III and grade IV glioma. Glioblastoma is essentially equivalent to grade IV glioma. This study has only enrolled patients with glioblastoma (grade IV glioma).

- The phase I patients were very advanced and had failed on average three prior lines of therapy, making them an extremely treatment-resistant group. The present study has enrolled newly-diagnosed patients who are expected to respond better to treatment.
- The phase I study included patients with both methylated and unmethylated MGMT promotor status. The unmethylated MGMT promotor is associated with a worse prognosis. This study has only enrolled patients with unmethylated MGMT promotor status.
- The phase I study did not report PFS or OS.

**What are the next steps for the paxalisib program, and what does this data mean for GBM AGILE, the planned pivotal study?**

This phase II study remains ongoing. At present, Kazia expects to report further interim data in 2H CY2020, and final data in 1H CY2021.

In the meantime, as previously indicated, Kazia has begun preparatory work associated with the addition of paxalisib to the ongoing GBM AGILE study in glioblastoma. GBM AGILE is a platform study that is being run independently of any one company, under the leadership of many of the leading world experts in the field. It is designed to provide data to support registration of new drugs in glioblastoma and is strongly supported by the US FDA. It is expected that GBM AGILE will recruit up to 200 patients on paxalisib, in a randomized, controlled trial against temozolomide, the existing standard of care. The patient population will be highly consistent with that examined in this phase II study, and the primary endpoint will be overall survival.

For clarity, GBM AGILE has been adopted in place of a previously-planned company-sponsored phase III study, and it is expected that it will provide the path-to-market for the commercial product.

Investors are referred to Kazia's announcement in December 2019 and its investor newsletter in March 2020 for additional information. At present, Kazia expects that GBM AGILE will begin recruiting paxalisib patients in 2H CY2020, prior to finalization of the ongoing phase II study.

**How is progress on the other paxalisib clinical trials?**

In addition to this clinical trial, four other studies with paxalisib are underway in DIPG and in brain metastases. All of these studies have recruited patients. Kazia is working with investigators in the hope of providing interim data from several of these studies during CY2020 and will update investors accordingly in due course.

**What are Kazia's plans for publication of final data from this study?**

Kazia expects that final data from this phase II study will be published in a peer-reviewed journal in CY2021, after completion of all analyses.

In the meantime, the phase I study originally conducted by Genentech has been accepted for publication by the journal *Clinical Cancer Research*, and publication is expected soon. In

addition, the post hoc analysis of imaging data from that study by Professor Ben Ellingson at UCLA has separately been accepted for publication in the same journal. Professor Ellingson's work was previously the subject of a prize-winning oral presentation at the Society for Neuro-Oncology annual meeting in November 2019, as announced at the time by Kazia.

**What is the competitive landscape for glioblastoma? How do these results compare to other drugs in development for the disease?**

Kazia is not presently aware of any investigational new drug in the global pipeline which is (a) in active development for single-agent adjuvant use in newly-diagnosed glioblastoma patients, (b) further advanced than paxalisib, and (c) which shows superior evidence of activity on currently available data.

**What is the level of partnering interest for paxalisib? Is Kazia in discussion with pharma partners?**

Kazia continues to entertain exploratory discussion with several potential partners for the paxalisib asset. The timing and terms of any future transaction will be designed to ensure the most expeditious development of the drug, and the optimal return to Kazia shareholders.

**Does Kazia expect this or other studies to be affected by the ongoing COVID-19 outbreak?**

Kazia works with large, world-class, highly-experienced partners in the conduct of its studies, and each of these collaborators have put in place measures to mitigate the impact of COVID-19. At this stage, we see minor operational disruption, but no suggestion that the timelines or data integrity of our clinical studies are likely to be fundamentally affected. We will continue to keep investors informed as the situation develops.