ASX RELEASE

3 December 2021

KAZIA ANNOUNCES POSITIVE FINAL DATA FROM PHASE II CLINICAL STUDY OF PAXALISIB IN NEWLY DIAGNOSED GLIOBLASTOMA

Sydney, 3 December 2021 – Kazia Therapeutics Limited (NASDAQ: KZIA; ASX: KZA), an oncology-focused drug development company, is pleased to announce positive final data from a phase II clinical study of paxalisib as first line therapy in patients with glioblastoma (NCT03522298). The results confirm the previously reported safety and efficacy profile with paxalisib in this high unmet need disease.

Key Points

- The study recruited 30 patients with newly diagnosed glioblastoma and unmethylated MGMT promotor status, a genetic profile which confers primary resistance to temozolomide, the only existing FDA-approved drug treatment for first line treatment.
- 60mg once daily was identified as the maximum tolerated dose (MTD) and selected for future studies.
- Median overall survival (OS) in the intent-to-treat (ITT) population (n=30) was 15.7 months (11.1 – 19.1), which compares very favourably to 12.7 months historically reported with temozolomide in this patient group.[1]
- Median progression-free survival (PFS) in the ITT population was 8.4 months (6.6 – 10.2), representing a substantial increment over the comparable figure of 5.3 months associated with temozolomide.
- In the modified ITT (mITT) population (n=27), which includes only those patients evaluable for efficacy, OS increased to 15.9 months (12.8 – 19.1).
- The safety profile of paxalisib was highly consistent with previous clinical studies: hyperglycaemia, oral mucositis, and skin rash were among the most common drug-related toxicities.
- Kazia expects to receive a final clinical study report in 1Q CY2022 and intends to seek publication of these data in a peer-reviewed scientific journal thereafter.

[1] ME Hegi et al. (2005) *N Engl J Med*. 352:997-1003

Kazia CEO, Dr James Garner, commented, "We are delighted to report positive final data from the completed phase II study of paxalisib. The data continue to demonstrate a clear efficacy signal and favourable safety profile, suggesting a meaningful advantage over temozolomide, the existing standard of care, and validating our decision last year to join the GBM AGILE pivotal study. We have gleaned invaluable insights from this trial, and we are tremendously grateful to the investigators and to the patients who participated. Our task now, as we move rapidly toward a potential marketing authorization, is to confirm and quantify the benefit associated with paxalisib in glioblastoma patients. This indeed is the focus of our participation in GBM AGILE, which commenced recruiting to the paxalisib arm in January 2021. We are increasingly also exploring additional patient populations for which a brain penetrant PI3K/mTOR inhibitor may provide significant advantages over the standard of care."

Professor Patrick Wen, Principal Investigator at Dana Farber Cancer Institute, commented "We are pleased to see the phase II study of paxalisib successfully completed. This data supports the inclusion of paxalisib in the GBM AGILE study, which has recently expanded to Canada. Glioblastoma remains a disease in urgent need of new therapeutic options, and we look forward to seeing further data for paxalisib from GBM AGILE in due course."

Clinical Trial Design

The phase II study of paxalisib was an adaptive trial, conducted in two stages. The first stage sought to determine the most appropriate dose in newly diagnosed patients. The second stage was intended to provide additional information on dosing and to seek a preliminary efficacy signal in order to de-risk transition to a larger, pivotal study.

Consistent with these objectives, the primary objective of the study was to evaluate the safety and tolerability of paxalisib in patients with newly diagnosed glioblastoma. The secondary objectives included typical pharmacokinetic parameters, and efficacy endpoints including overall survival (OS) and progression-free survival (PFS).

The phase II study was conducted in 30 patients at six centres in the United States. It was a single arm study in which all patients received paxalisib as a monotherapy. As such, all data must be interpreted in the context of historical comparators. Specifically, Kazia has referred to the pivotal study of temozolomide, the only existing FDA-approved drug for this patient population. Such comparisons are always inexact, and this study was not designed either to precisely quantify the benefit associated with paxalisib or to demonstrate statistical significance. Rather, these are among the objectives of the ongoing GBM AGILE pivotal trial.

Next Steps

On the basis of earlier interim analyses of this study, Kazia made the decision in 4Q CY2020 to commence participation in the GBM AGILE pivotal study. This global trial recruited its first patient to the paxalisib arm in January 2021 and recruitment is ongoing. Kazia provisionally expects indicative data in CY2023.

Seven other studies of paxalisib are ongoing in other forms of primary brain cancer and in various forms of cancer that has metastasized to the brain. The company is working with investigators to crystalise the timing of initial data read-outs from these studies. Kazia had expected at least two further read-outs by the end of CY2021. Clinicians have now indicated that data early in CY2022 is most likely. The company will continue to keep shareholders closely informed as it receives further feedback from investigators.

Having successfully concluded the phase II study in glioblastoma, the investigators are composing a manuscript for submission and publication to a peer-reviewed academic journal in 2022. Once the data has been more thoroughly analysed, Kazia expects to share further detail with investors as it becomes available.

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About Kazia Therapeutics Limited

Kazia Therapeutics Limited (NASDAQ: KZIA; ASX: KZA) is an oncology-focused drug development company, based in Sydney, Australia.

Our lead program is paxalisib, a brain-penetrant inhibitor of the PI3K / Akt / mTOR pathway, which is being developed to treat glioblastoma, the most common and most aggressive form of primary brain cancer in adults. Licensed from Genentech in late 2016, paxalisib commenced recruitment to GBM AGILE, a pivotal study in glioblastoma, in January 2021. Eight additional studies are active in various forms of brain cancer. Paxalisib was granted Orphan Drug Designation for glioblastoma by the US FDA in February 2018, and Fast Track Designation for glioblastoma by the US FDA in August 2020. In addition, paxalisib was granted Rare Pediatric Disease Designation and Orphan Designation by the US FDA for DIPG in August 2020.

Kazia is also developing EVT801, a small-molecule inhibitor of VEGFR3, which was licensed from Evotec SE in April 2021. Preclinical data has shown EVT801 to be active against a broad range of tumour types and has provided compelling evidence of synergy with immuno-oncology agents. A phase I study commenced recruitment in November 2021.

For more information, please visit www.kaziatherapeutics.com or follow us on Twitter @KaziaTx.

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

CLINICAL TRIAL SUMMARY

Study Title	Safety, Pharmacokinetics, and Efficacy of Paxalisib (GDC-0084) in Newly-Diagnosed Glioblastoma
Phase of Development	Phase II
Investigational Product	Paxalisib (GDC-0084)
Disease Area	Newly diagnosed glioblastoma with unmethylated MGMT promotor status (representing resistance to temozolomide)
Registration	NCT03522298
Study Description	This is an exploratory study to identify the optimal dose for further investigation, further characterise the safety profile in newly diagnosed patients, and to seek preliminary signals of efficacy.
Number of Subjects	30 patients
Study Design	This is a single-arm study, in which all patients received paxalisib. **Stage 1** is a dose escalation component, designed to determine the maximum tolerated dose in newly diagnosed patients. **Stage 2** is an expansion cohort, designed to provide further safety and pharmacokinetic data, explore the effect of taking paxalisib with food versus on an empty stomach, and to identify preliminary signals of clinical efficacy.
Patient Population	Newly diagnosed glioblastoma with unmethylated MGMT promotor status
Endpoints	The primary endpoints of this study were safety and tolerability.
Start Date	May 2018
End of Recruitment	February 2020

Q&A

How much confidence do these results provide in relation to the likely outcome of the GBM AGILE study?

This phase II study is exploratory in nature, and was designed to provide, among other information, a preliminary signal of clinical efficacy in order to de-risk further development. In Kazia's view, the final data clearly provides that signal, and strongly suggests that paxalisib improves the clinical outcome for patients with newly diagnosed glioblastoma. On that basis, the decision in 4Q CY2020 to move the drug into a pivotal study appears to be fully validated. Kazia remains of the view that the probability of technical success in GBM AGILE remains favourable and is largely unchanged for better or for worse on the basis of the final data from the phase II study.

This phase II study was not designed to precisely quantify the benefit that paxalisib provides in this patient population. Kazia has consistently stated that this question can only be meaningfully resolved by a larger, randomised controlled study. This is, in effect, the role of the GBM AGILE trial, which commenced recruitment to the paxalisib arm in January 2021.

How do the final results compare to previous interim analyses from this study?

The progression-free survival (PFS) observed in this study is highly consistent with previous interim analyses, which have reported median PFS of 8.4 – 8.5 months. The overall survival (OS) of 15.7 months seen in the final data is modestly lower than the interim result of 17.4 months reported at the Society for Neuro-Oncology Annual Meeting in November 2020.

On initial examination, it appears that several of the last few patients recruited to the study experienced rapidly progressive disease, thereby pulling down the overall result. In open label studies such as this one, clinicians do sometimes recruit more challenging patients in the later part of the study, and Kazia intends to examine this hypothesis in further discussion with investigators. However, the final figure of 15.7 months continues to represent a substantial increment over the existing standard of care, which is associated with a median OS of 12.7 months in this patient group and should therefore be considered a very encouraging result.

Are the OS and PFS data statistically significant?

In clinical trials, the concept of 'statistical significance' refers to the likelihood that the difference between two arms of the study is due to chance rather than to the effects of the therapy under investigation. Since this was a single-arm study, statistical significance is not applicable here.

Did the study meet its primary objective?

Yes. The primary objective of this study was safety and tolerability, and that outcome was fully met. While several efficacy endpoints were included as secondary objectives, there were no specific pre-defined hurdles for those outcome measures.

What is the difference between the ITT and mITT populations?

The 'intent-to-treat' (ITT) population of a clinical trial typically captures all patients who provided informed consent to participate, regardless of how much study drug they received (or even if they received any at all), and irrespective of how much data they provided. In this study, the ITT population includes all 30 patients who were enrolled. Most endpoints are derived from the ITT population, since it provides the broadest dataset and minimises the risk of bias associated with the exclusion of individual patients.

Clinical studies commonly also examine a modified ITT (mITT) or efficacy evaluable (EE) population, which typically includes only those patients who provide data that is likely to be meaningful, and which is included as a sensitivity analysis. In this study, Kazia has separately conducted all analyses on an mITT population of 27 patients, who received at least one dose of paxalisib and provided at least one efficacy assessment. In this group, the OS improves from 15.7 months to 15.9 months.

Is the Hegi paper the most appropriate historical control for the phase II GBM study? It was published fifteen years ago and the outcomes for GBM may have improved in that time.

In general, there is limited evidence of an improvement in GBM prognosis since the approval of temozolomide in the late 1990s. A recent meta-analysis found no convincing trend over time[2]. In addition, few studies of newly diagnosed patients separately report data for patients with unmethylated MGMT promotor status, and so their results cannot readily be compared to the results of this study. In general, other studies have reported median overall survival between 11.2 and 13.8 months for unmethylated patients treated with temozolomide, the existing standard of care. Kazia is not aware of any study reporting median overall survival with temozolomide which is comparable to the figure of 15.7 months seen with paxalisib in this study, which supports a positive interpretation of this data.

Overall Response Rate (ORR) is a common endpoint for phase II oncology trials. Why has that not been reported in this study?

ORR is a common exploratory endpoint in phase II cancer studies. In essence, it measures the change in size of a tumour while a patient undergoes treatment. Meaningful shrinkage is described as 'response'.

In this study, the majority of patients had undergone complete surgical resection prior to study entry and so had no measurable tumour at baseline. It is impossible to measure shrinkage from a baseline of zero, and so ORR is not a viable endpoint for this study. PFS and OS are considered stronger and more meaningful endpoints, because they represent more patient-relevant outcomes.

[2] L Marenco-Hillenbrand, O Wijesekera, P Suarez-Meade, et al. *Journal of Neurology* (2020). 147:297-307

Why did this study only contain a single arm, when randomised data is considered more reliable?

This study was intended to serve several purposes. The primary objective was to determine the most appropriate dose in newly diagnosed patients, and this task only requires a single-arm design.

Although the trial also included exploratory, efficacy endpoints, these were signal-seeking in intent, and the study was not intended to provide definitive quantification of clinical efficacy. Kazia viewed the efficacy components of this study as a de-risking step, prior to committing substantial investment toward a pivotal study. A well-powered, randomised study would have provided greater de-risking, but at very substantially greater cost, and so the company took the view that the single-arm study design represented the optimal balance between cost and risk reduction, with the randomised design deferred to a pivotal study.

How does the safety profile reported in the phase II GBM study compare to FDA-approved PI3K inhibitors?

Paxalisib appears to have a very favourable safety profile for use in advanced cancer. The key toxicities observed with the drug include hyperglycaemia, oral mucositis (mouth ulcers), rash, and fatigue.

While hyperglycaemia is a common side effect of all drugs inhibiting PI3Kα, the rates of serious hyperglycaemia seen with paxalisib are approximately half those seen with comparable agents. Rash and mucositis are believed to be primarily mTOR-driven toxicities, and so are not directly comparable with approved PI3K inhibitors, which do not have mTOR activity. Other less common, but serious, toxicities that have been seen with other agents, such as pneumonitis, infection, liver toxicity, hypertension, and GI toxicity, have not been seen with paxalisib. On present evidence, the drug has the potential to achieve a best-in-class safety profile.

If GBM AGILE demonstrated an improvement in overall survival associated with paxalisib of approximately three months (the difference between this result and the historical data for temozolomide), what would this mean for paxalisib's commercial prospects?

For newly diagnosed patients, the only existing FDA-approved standard-of-care drug treatment is temozolomide. In this patient population (those with unmethylated MGMT promotor status), temozolomide is associated with an improvement in survival from 11.8 to 12.7 months, or about four weeks. Although this study was not designed to precisely quantify treatment benefit, the implicit survival extension associated with paxalisib would be approximately four times greater than the existing standard of care (four months rather than four weeks). Before it lost patent protection, temozolomide achieved peak sales in excess of US$ 1 billion per annum.

In the recurrent setting, Avastin (bevacizumab) is approved in certain markets. This drug has never demonstrated any survival benefit in glioblastoma.

Primary market research commissioned by Kazia Therapeutics in mid-2021 found that a survival benefit of 2.6 months versus standard of care would be expected to yield an adoption rate of 84% among clinicians in the United States. This is an exceptionally high market penetration. A survival benefit of 7 months was associated with only an additional 10% adoption. In short, paxalisib has excellent commercial prospects if it is able to show any meaningful evidence of efficacy whatsoever in this patient population.

How do the final data from this study compare to other treatments in development for glioblastoma?

In general, it is extremely difficult to compare results across different phase II studies because they are conducted in different ways with slightly different patient populations.

Two other therapies are under investigation in GBM AGILE alongside paxalisib: Bayer's regorafenib and Kintara Therapeutics' VAL-083.

In the REGOMA study of regorafenib in recurrent glioblastoma, treatment was associated with a survival advantage of approximately 1.8 months in comparison to lomustine.[3] No published data is available in newly diagnosed patients.

For VAL-083, interim data from two ongoing single-arm phase II studies were the subject of poster presentations (CTNI-21 and CTNI-26) at the Society for Neuro-Oncology (SNO) Annual Meeting in November 2021.[4] The first of these reported OS of 19.1 months in an efficacy evaluable population of 25 patients from a study performed entirely in China. The second reported on 36 efficacy evaluable patients in a single-centre study in the United States and determined an interim OS of 16.5 months. There are material differences in study design and patient population, but Kazia considers this second study to be more closely comparable to the paxalisib data. Given the relatively small number of patients in each study, and consequently wide confidence intervals, the results may be considered approximately equivalent.

Few other drugs under investigation report data specifically in the newly diagnosed unmethylated population. In the universe that Kazia tracks, Inovio reported interim data at SNO in November 2020 from a phase II study involving a combination of INO-5401 (a gene therapy encoding hTERT, WT1, and PSMA), INO-9012 (a gene therapy encoding IL-12, a T-cell activator), and cemiplimab (a PD-1 inhibitor), delivered via intramuscular injection with electroporation to achieve temporary blood-brain barrier penetration. This data reported median OS in 32 patients of 17.9 months.[5]

[3] G Lombardi et al. (2019) *Lancet Oncol.* 20(1):110-119
[4] Kintara Therapeutics press release of 18 November 2021
[5] Inovio press release of 20 November 2021

In May 2019, Bristol Myers Squibb announced that a phase III study of Opdivo® (nivolumab) in patients with newly diagnosed glioblastoma with unmethylated MGMT promotor status, the Checkmate-498 study, failed to meet its primary endpoint of overall survival.[6]

What would the approval of another novel glioblastoma therapy, either before or after paxalisib, mean for paxalisib's commercial prospects?

Most cancers are treated with a wide range of therapies. For example, in the last decade, around twenty new drugs have been approved by FDA for lung cancer. Almost no drug treatment is curative, and so clinicians typically use drugs in different sequences and combinations to maximise patient benefit.

It is highly likely that this will also be the trajectory for glioblastoma. At present, there is only one FDA-approved drug for first line use, temozolomide. In a disease with as high an unmet need as glioblastoma, this represents an extraordinary paucity of treatment options. Kazia expects and hopes that multiple new therapies will become available over coming years. In general, such therapies will be used in combination regimes, and so there is likely to be relatively less intense competition for market share.

[6] Bristol Myers Squibb press release of 9 May 2019