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KAZIA PRESENTS FURTHER PAXALISIB DATA AT SNO, CONFIRMING EARLIER POSITIVE SAFETY AND EFFICACY SIGNALS IN GLIOBLASTOMA

Sydney, 18 November 2020 – Kazia Therapeutics Limited (ASX: KZA; NASDAQ: KZIA), an Australian oncology-focused biotechnology company, is pleased to share a summary of new paxalisib data presented at the Society for Neuro-Oncology (SNO) Annual Meeting, which is being held virtually from 19-21 November 2020.

Key Points

- New interim analysis of paxalisib phase II study in glioblastoma (NCT03522298) is highly consistent with prior data
- Median progression-free survival (PFS) of 8.4 months reported on this analysis (versus 5.3 months for temozolomide, the existing standard of care)
- Median overall survival (OS) of 17.5 months reported (versus 12.7 months for temozolomide)
- First substantial presentation of safety data at a 60mg dose shows profile very similar to prior experience, with the most common toxicities including rash, stomatitis (mouth ulcers), and hyperglycemia (high blood sugar), consistent with other PI3K and mTOR inhibitors
- Phase I study in DIPG (NCT03696355) shows paediatric maximum tolerated dose (MTD) of 27 mg/m^2, with safety profile and pharmacokinetics similar to adult data

Kazia CEO, Dr James Garner, commented, "this is very reassuring data from the glioblastoma study, confirming our earlier results with the data now much more mature. In studies such as this, volatility is the enemy of dependability. From the very first efficacy data we reported from this study, in November 2019, through the ASCO and AACR presentations in June 2020, to today's latest analysis, the PFS and OS figures have remained extremely stable as the study has progressed. This gives us a great deal of confidence that what we are seeing is representative and reliable."

He added, "we expect this study to conclude in the first half of calendar 2021, but it has already provided useful information to guide the development of paxalisib. We have moved into the operational phase of the GBM AGILE pivotal study, and we expect that study to now be the primary focus of our work in glioblastoma from this point forward."

The poster presentation is available for download via the Kazia website at:-

https://www.kaziatherapeutics.com/researchpipeline/paxalisib

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

	Temozolomide[1] (FDA-approved treatment)	**Paxalisib** (interim phase II data)
Progression-Free Survival (PFS)	5.3 months	8.4 months
Overall Survival (OS)	12.7 months	17.5 months

Professor Patrick Wen, the first author on the poster, commented "as this study has matured, we have seen encouraging results that are very stable over successive analyses, and very consistent with prior clinical experience in this drug. Paxalisib is now moving into the GBM AGILE study in glioblastoma, and we expect this to provide definitive data regarding the drug's potential use in this disease and, if successful, a basis for regulatory approval. There remains a profound need for new treatments in glioblastoma, and paxalisib has proven to be an exciting potential candidate."

Initial Data from St Jude Study of Paxalisib in DIPG and Diffuse Midline Gliomas

Dr Christopher Tinkle, lead investigator for the SJPI3K study of paxalisib in DIPG and diffuse midline glioma (NCT03696355), gave an invited oral presentation on interim results from that study.

The SJPI3K study is a first-in-paediatric study, designed to establish the safety and pharmacokinetics of paxalisib in children, and to explore potential early signals of efficacy in this patient population.

The study recruited 27 patients, ranging from 3 to 16 years of age. Four patients discontinued participation prior to receiving a first dose of paxalisib, generally due to disease progression. At the time of analysis, five patients remain on paxalisib treatment, and several patients remain in post-treatment follow-up.

The paediatric maximum tolerated dose (MTD) was determined to be 27 mg/m^2. The dose-limiting toxicities (DLTs) included hyperglycaemia, oral mucositis, and rash, which are entirely consistent with the adult experience.

The pharmacokinetics of the drug, a term which describes the concentration of the drug in plasma over time, was very consistent with the adult experience. The study found no meaningful difference between administration of intact capsules and administration via opening of capsules and sprinkling of contents onto a food carrier.

The study has not at this stage shown a clear survival benefit for paxalisib in comparison to historical controls. In terms of PFS, the proportion of patients alive and progression-free at

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

six months (PFS6) was 96%, which compares favourably to an historical control of 58%[2]. However, the authors note that PFS can be a complex endpoint to interpret in DIPG trials due to the confounding effect of incidental radiological changes associated with radiation therapy.

Dr Tinkle commented, "my colleagues and I are very pleased with the outcome of this study. We have determined an appropriate dose for future paediatric work, established an acceptable tolerability profile in children, and demonstrated pharmacokinetic equivalence between intact capsule and open and sprinkled administration, which are critical steps in the development of any new drug for paediatric cancer."

He added, "DIPG is an extremely treatment-resistant disease, and no drug has ever shown convincing efficacy as a monotherapy. Our view has always been that the treatment of this disease will consist in combination therapy, and we have shown that paxalisib is eminently suitable to now be evaluated alongside other agents. We look forward to discussing follow-on work that will explore these opportunities and further investigate paxalisib's potential."

Dr Garner commented, "we are grateful to have had the opportunity to collaborate with one of the world's leading paediatric oncology hospitals in this study. The results provide an excellent foundation for the further development of paxalisib in DIPG, and we will be excited to discuss the next phase of work with our collaborators in coming months."

Next Steps

The paxalisib phase II study remains ongoing, with final data expected in 1H CY2021. The paxalisib arm of the GBM AGILE study has moved into an operational phase, and first patient in is expected early in 1Q CY2021.

The St Jude study in DIPG remains ongoing, with final data expected during 1H CY2021.

Investor Conference Call

Kazia is pleased to invite investors to attend a conference call to discuss the results further.

The call will be held on Thursday 19 November 2020 at 12:00pm, Sydney time (AEDT), which is 5pm on Wednesday 18 November 2020 in San Francisco (PST) and 8pm on Wednesday 18 November 2020 in New York (EST).

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

https://s1.c-conf.com/diamondpass/10011029-8iqiBr.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.

[2] T Cooney, A Lane, U Bartels, et al. *Neuro-Oncology* (2017); 19(9):1279-1280

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, the most common and most aggressive form of primary brain cancer in adults. Licensed from Genentech in late 2016, paxalisib entered GBM AGILE, a pivotal study in glioblastoma, in October 2020. Five additional studies are active in other 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.

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 has completed a phase I clinical trial in Australia and the United States with the final data expected in the second half of calendar 2020. Interim data was presented most recently at the AACR conference in June 2020. Cantrixil was granted orphan designation for ovarian cancer by the US FDA in April 2015.

For more information, please visit www.kaziatherapeutics.com.

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

Q&A

How do the latest efficacy results from the phase II GBM study compare to previous interim analyses?

The results of this analysis are highly consistent with previous analyses, which are summarized below:-

	November 2019 (SNO)	**June 2020** (AACR)	**November 2020** (SNO)
PFS	8.4 months	8.5 months	8.4 months
OS	–	17.7 months	17.4 months

For a study at this stage, the primary focus is on the consistency of results. Any substantial change from one analysis to the next, be it in a positive or a negative direction, raises the question of why earlier patients respond differently to later patients. The fact that the data from this study remains highly stable provides encouragement that it is representative and not a statistical quirk.

Are the results from the phase II GBM study 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 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 approved of temozolomide in the late 1990s. A recent meta-analysis found no convincing trend over time[3]. 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 up to 14.7 months for unmethylated patients treated with standard of care. Kazia is not aware of any studies reporting median overall survival with standard of care treatments which is comparable to the figure of 17.5 months seen in this study.

Is it possible that the data from the phase II GBM study could provide a basis for accelerated approval in GBM?

Kazia will evaluate any opportunities deriving from this data once the study is formally completed, which is currently expected to be in 1H CY2021. However, it has always been the company's base case expectation that a randomized controlled trial would be required for any form of approval.

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

Is it possible that the phase II GBM study results will change significantly, for better or for worse, in the final analysis of the complete data set?

These results are not final and may therefore change as the study moves towards completion. However, the fact that the study is at this stage relatively mature, together with the fact that these data have remained extremely stable over time, suggests that the final results will be very similar to the interim analyses that have been presented over the course of the study.

Why is data from 29 patients reported, when 30 were enrolled to the phase II GBM study?

One patient was removed from the study by the principal investigator due to very poor compliance. That patient is believed to have received less than two weeks of paxalisib treatment, and all data was deemed unreliable. Consequently, they have been removed from this and all previous analyses. The impact of their removal on the overall data is minimal.

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

While hyperglycemia is a common side effect of all drugs inhibiting PI3Kα, the rates of serious hyperglycemia 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, including 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.

Overall Response Rate (ORR) is a common endpoint for phase II oncology trials. Will that be assessed in the phase II GBM study?

ORR is commonly used as an endpoint in early-phase studies of cancer therapies. In general, it is considered an inferior endpoint to PFS or OS, and very rarely provides a basis for product approval.

From a technical standpoint, ORR measures the change in size of an existing tumour. 80% of patients in this study had undergone complete resection prior to joining the study, and so had no measurable tumour at study entry, making ORR impossible to determine. The endpoint will be assessed in the final analysis in those patients for whom it can be determined but is unlikely to provide significant additional information.

How should the data from the phase I DIPG study be interpreted?

This is a phase I first-in-paediatric study and the primary objective is to assess safety and tolerability of paxalisb. The study has successfully met those objectives, achieving a paediatric MTD of 27 mg/m^2. This dose will be used in future paediatric studies and has already been adopted for several children who have received the drug on a compassionate use basis.

Moreover, the finding that safety and pharmacokinetics are very consistent with the adult experience is extremely useful for the future development of the drug.

This study has not yet shown a survival benefit for paxalisib in DIPG. This is not unexpected and does not necessarily indicate that the drug has no therapeutic benefit in this disease, simply that the study was not primarily designed to determine efficacy. In addition, it has always been the expectation of Kazia and its collaborators that a disease as aggressive as DIPG would require combinations of several drugs to demonstrate meaningful efficacy. Kazia plans to work with the St Jude team, and with other advisors, in coming months to plan the next stage of the paediatric clinical program.

A number of patients in the phase I DIPG study remain on drug. Is it possible that the data from the study will change as these patients progress through follow-up?

Yes. However, the study data set is relatively mature at this stage, and so it is considered unlikely that there will be a fundamental change in overall outcome.

Does the data from the phase I DIPG study have any bearing on the likelihood of success for paxalisib in glioblastoma?

No. DIPG and glioblastoma are considered distinct diseases and may respond differently to a given treatment. For example, temozolomide has been shown effective in glioblastoma, but has not demonstrated benefit in DIPG[4].

Does the data from the phase I DIPG study have any implication for the likelihood of Kazia achieving a pediatric Priority Review Voucher (pPRV) on approval of paxalisib?

This data has no material impact. This study was not designed to support product registration in this indication, and it is unlikely that any data from it would have been sufficient in isolation to achieve a product registration, especially in the absence of approval in an adult indication. It has always been Kazia's base case expectation that a further study or studies would be required to provide definitive evidence of efficacy.

Will Kazia continue to develop paxalisib in DIPG?

Yes. Kazia is in discussion with several parties regarding potential further studies of paxalisib in DIPG. There is a strong scientific rationale for paxalisib in this disease, there is convincing evidence of therapeutic potential in preclinical data, and the current phase I DIPG study provides highly useful information to guide and inform future studies.

[4] KJ Cohen, RL Heideman, T Zhou, et al. *Neuro-Oncology* (2011). 13(4):410-416