ASX RELEASE

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POSITIVE INTERIM EFFICACY DATA FROM GDC-0084 PHASE II STUDY CONFERENCE CALL RECORDING AND TRANSCRIPT

Sydney, 27 November 2019 – Kazia Therapeutics Limited (ASX: KZA; NASDAQ: KZIA), an Australian oncology-focused biotechnology company, is pleased to provide an audio recording and transcript of the investor conference call on the positive interim data from the GDC-0084 phase II study in glioblastoma, held by Kazia's Chief Executive Officer, Dr James Garner on Tuesday, 26 November 2019.

The recording and transcript are available on the Kazia Therapeutics website via the following link: https://www.kaziatherapeutics.com/investorcentre/corporatepresentations

[ENDS]

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 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, GDC-0084 entered a phase II clinical trial in 2018. Interim data was reported in November 2019, and further data is expected in 1H 2020. GDC-0084 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.

CLINICAL TRIAL SUMMARY

Study Title	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
Phase of Development	Phase II
Investigational Product	Paxalisib (GDC-0084)
Disease Area	Newly-diagnosed glioblastoma (GBM) (WHO grade IV glioma)
Registration	NCT03522298
Study Description	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:- **Stage 1** – 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 **Stage 2** – 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
Number of Subjects	**Stage 1** – 9 patients (enrolment complete) **Stage 2** – 20 patients (enrolment ongoing)
Study Design	This is a single-arm, exploratory study. 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.

	Stage 2 will enroll all patients at the MTD. Half of the patients will receive GDC-0084 with food, and half on an empty stomach, in order to assess potential food effects.
Patient Population	All patients had newly-diagnosed glioblastoma, which had been treated with surgery and radiotherapy according to the standard-of-care 'Stupp regimen'. 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.
Endpoints	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.
Participating Centres	**UCLA – Jonsson Comprehensive Cancer Center** Los Angeles, CA **University of Colorado Cancer Center** Denver, CO **Dana-Farber Cancer Institute** Boston, MA **Massachusetts General Hospital** Boston, MA **John Theurer Cancer Center** Hackensack, NJ **Stephenson Cancer Center** Oklahoma City, OK **MD Anderson Cancer Center** Houston, TX
Start Date	First Patient In: September 2018
Expected Completion	1H CY2020

Q&A

The study has reported a progression-free survival (PFS) of 8.4 months. How should this result be interpreted?

The study had enrolled glioblastoma patients with an unmethylated MGMT promotor. The unmethylated MGMT promotor is a genetic marker that is associated with near total resistance to temzolomide, the only FDA-approved pharmacological treatment for newly-diagnosed glioblastoma. Approximately two-thirds of all glioblastoma patients have an unmethylated MGMT promotor.

For comparative purposes, in this group of patients, temozolomide improves PFS from 4.4 months to 5.3 months[1]. It is difficult to precisely compare results between studies, due to differences in patient population, background standard of care, and calculation methodology, but the magnitude of the difference in this case suggests that treatment with GDC-0084 is associated with a clinically beneficial treatment effect.

Other studies of temozolomide in this patient group have reported a 'headline' PFS of between 5.1[2] and 7.3[3] months, although much of this variability is attributable to differences in study design and calculation methodology.

Given these considerations, it is not yet possible to precisely quantify the potential treatment advantage of GDC-0084 versus temozolomide. However, Kazia considers that the present results constitute a strong qualitative signal that the drug may provide benefit.

What sort of improvement in PFS likely be enough for regulatory approval and for widespread use of the commercial product?

This is early interim data, and potential regulatory approval will almost certainly depend on the findings of a larger, randomised pivotal study.

However, a number of FDA-approved and commercially successful cancer treatments have demonstrated relatively modest improvements in PFS. For example:-

Drug	Indication	PFS Improvement
Avastin (bevacizumab)	Metastatic colorectal cancer	6.2 → 10.6 months
Avastin (bevacizumab)	Recurrent ovarian cancer	3.4 → 6.8 months
Abraxane (paclitaxel)	Pancreatic cancer	3.7 → 5.5 months
Nexavar (sorafenib)	Liver cancer	2.8 → 5.5 months
Stivarga (regorafenib)	Metastatic colorectal cancer	1.7 → 1.9 months

(all figures taken from product Prescribing Information. Nexavar figure is time-to-progression rather than PFS)

[1] ME Hegi, A-C Desirens, T Gorlia, et al. *N Engl J Med* (2005); 352:997-1003
[2] MR Gilbert, MH Wang, KD Aldape, et al. *J Clinical Oncol* (2013); 31:4085-4091
[3] MR Gilbert, JD Dignam, TS Armstrong, et al. *N Engl J Med* (2014); 370:699-708

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

Ideally, the gold standard for definitive determination of efficacy is a randomized, controlled trial (RCT), in which patients are randomly allocated to receive either the treatment under investigation (in this case, GDC-0084), 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 GDC-0084. The reasons for this approach are various, and include both ethical and operational considerations.

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.

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.

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.

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.

In general, OS is regarded by regulatory agencies as the 'gold standard' for approval of new cancer therapies. However, PFS is a faster and arguably more sensitive measure, and is often predictive of OS. Consequently, PFS is finding increasing favour for oncology clinical trials and has been the basis of approval for a number of commercial products. PFS is less robust than OS in that it requires interpretation of MRI scans to determine progression, but it is arguably

more specific in that it is not affected by treatments that are administered following progression.

Overall survival (OS) could not be calculated. Does that mean GDC-0084 does not show a survival benefit?

No. Six of eight evaluable patients remain alive at the time of analysis cut-off (late October 2019), and so a median figure (representing the point at which half of patients are deceased) has not yet occurred. Given the small number of death events, it is not possible to use parametric techniques to extrapolate an OS figure at this stage.

The majority of these patients continue to be actively followed up and one patient remains on study drug after more than sixteen months of continuous treatment. It will be possible to determine an OS figure once 50% of patients are deceased. Given the duration of treatment and follow-up to date, it is likely that this will compare favourably to historical controls.

For future comparison, the Hegi paper reports an improvement in OS from 11.8 months to 12.7 months for treatment with temozolomide in newly-diagnosed patients with unmethylated MGMT promotor status.

Why was one of the nine 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 GDC-0084 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.

Is this final data from this part of the study?

No. This is an early interim analysis.

The majority of the 9 patients in Stage 1 remain in follow-up for survival, and so further data from the group of patients will be available at a future date.

The study is currently enrolling an additional 20 patients to Stage 2, a dose expansion cohort, and this data will also be reported at a future date.

The final results of the study may change as additional patients are included in the analysis, and as additional data is collected from these patients over time.

How do these patients compare to those envisaged for Stage 2 and for the pivotal study?

The patients in both stages of this study are exactly consistent in all material respects with the target population of the planned pivotal study: newly-diagnosed GBM patients with an unmethylated MGMT promotor (i.e. resistant to temozolomide).

In Stage 1 of this study, 3 of the 9 patients received a dose of 60mg, and 6 of the 9 patients received a dose of 75mg. The higher dose was subsequently determined to be poorly tolerated. This is an expected finding – the intention of a dose escalation study is to push the dose to the limit to determine how much can safely be administered. However, the consequence is that some of the patients receiving 75mg may have terminated treatment early due to side effects, and therefore received less overall benefit from treatment with GDC-0084. In Stage 2, all patients will receive the 60mg dose, which is expected to be well-tolerated, and this may be associated with greater efficacy.

In the planned pivotal study, it is expected that all patients will also receive the 60mg dose.

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.

This is described as a phase IIa study. Does that mean that a phase IIb study is required before GDC-0084 can commence a phase III study?

No. The 'phase' nomenclature is largely a matter of industry convention and is regarded as increasingly old-fashioned. It has limited regulatory significance. Kazia expects that the next study of GDC-0084 in GBM will be a pivotal study for registration, or what FDA would refer to as a 'substantial evidence' study. This may be designated phase II or phase III, or some combination thereof.

When will the pivotal study start? Is it necessary to complete the current study prior to starting the pivotal study?

The pivotal study is expected to commence in CY2020. While certain data from the current study is required for the pivotal study, it is not necessary for the current study to be fully completed prior to initiation of the pivotal study. Kazia considers that the positive signals seen to date are sufficient for internal decision-making purposes and is therefore accelerating planning for the proposed pivotal study.

Is it possible to seek registration for GDC-0084 on the basis of this data, given the unmet need in glioblastoma?

The present data is likely insufficient for registration. Kazia anticipates that a randomized controlled study against temozolomide will be required to achieve registration, with either OS or PFS as a primary endpoint. Moreover, new cancer drugs typically require several hundred patients of data prior to registration and GDC-0084 has, to date, been administered to a little fewer than 100 patients. However, the signal seen here does suggest the possibility of a smaller pivotal study, or an adaptive design, which may reduce the total number of patients required relative to the company's initial forecasts.

What does this data mean for the other ongoing studies of GDC-0084?

In addition to this clinical trial, four other studies with GDC-0084 are underway in DIPG and in brain metastases. Each of these diseases are different, and so success or failure in one study does not guarantee a corresponding result in the other studies. However, the positive signals seen here provide strong evidence that GDC-0084 is clinically active, which may be taken to increase the likelihood of success in the other ongoing studies.

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 GDC-0084, and (c) which shows superior evidence of activity on currently available data.

What is the level of partnering interest for GDC-0084? Is Kazia in discussion with pharma partners?

Kazia expects GDC-0084 to be a highly attractive asset to pharmaceutical companies. The company has proactively been making potential future partners aware of the GDC-0084 story for some time and will be discussing this data with interested parties in coming weeks, and at the JP Morgan conference in San Francisco in January. While no specific transaction is currently on foot, Kazia will continue to cultivate interest in the GDC-0084 program, with the aim of maximizing long-term shareholder value.