Kazia Therapeutics Highlights New Clinical and Translational Findings Demonstrating Paxalisib's Ability to Reinvigorate Anti-Tumor Immunity Across Multiple Advanced Breast Cancer Populations including TNBC and HER2+

First patient from TNBC trial demonstrated 76% tumor volume shrinkage with corresponding reductions in circulating tumor cells (CTC) and clusters

Reinvigoration of immune system + turning cold tumors hot

Preliminary ex-vivo data in HER2+ patients demonstrates immune reinvigoration and reductions in CTC and clusters

Sydney, Australia – December 10, 2025 (NASDAQ: KZIA) – Kazia Therapeutics Limited ("Kazia" or the "Company") today announced new data from two presentations at the 2025 San Antonio Breast Cancer Symposium (SABCS) providing compelling mechanistic and early clinical evidence supporting the activity of paxalisib, the Company's brain-penetrant dual PI3K/mTOR inhibitor, across both HER2-positive metastatic breast cancer and triple-negative breast cancer (TNBC).

The results, originating from advanced liquid biopsy profiling, immune phenotyping, and early clinical readouts, highlight paxalisib's potential to disrupt highly aggressive circulating tumor cell (CTC) clusters, reverse epigenetically-driven resistance pathways, and reinvigorate exhausted T- and B-cell populations, thereby enhancing responsiveness to immunotherapy.

Paxalisib Disrupted Drivers of Metastasis: Vim$^+$/Snail$^+$/NRF2$^+$ CTC Clusters in HER2+ Disease Ex Vivo

In HER2-positive metastatic breast cancer, a population in which nearly all patients eventually relapse despite HER2-directed therapies, investigators observed that even patients who were radiographically responding continued to harbor substantial burdens of therapy-resistant CTC clusters—a key driver of metastatic spread.

Poster Presentation: PS2-10-02 : Liquid Biopsy Tracking of PI3K–mTOR Residual Disease Signatures in Metastatic HER2+ Breast Cancer

Key findings:

- Paxalisib reduced single CTCs by 42% and CTC clusters by 78% ex vivo, including large clusters (≥5 cells), which are strongly associated with metastatic progression.
- CTC clusters expressed a highly aggressive mesenchymal phenotype marked by Vimentin$^+$/Snail$^+$/NRF2$^+$, which paxalisib significantly disrupted.
- Patients with poor clinical response demonstrated impaired cytotoxic function (reduced Granzyme B and Perforin) and expanded exhausted T-cell populations, while paxalisib treatment activated cytotoxic, interferon, chemokine, and inflammatory pathways in samples from these patients, supporting a more immunologically "hot" tumor environment.

"These findings reveal an important biological gap left by existing HER2+ directed therapies," said Prof. Sudha Rao, QIMR Berghofer. "CTC clusters persist even in responding patients, and paxalisib is the first agent we have observed that can directly dismantle this highly aggressive and clinically relevant compartment."

TNBC Phase 1b Trial: Early Clinical Data from First Patient Show Robust Suppression of CTC Clusters and Reversal of T-Cell Exhaustion

Early longitudinal biomarker data from the first patient treated in the PaxPlus-ABC Phase 1b study (paxalisib + pembrolizumab + chemotherapy) indicate that paxalisib has had measurable biological activity after only a single cycle.

Poster Presentation: PS5-08-04: A phase 1b, multi-centre, open-label, randomized study to evaluate the safety, tolerability, and clinical activity of combining paxalisib with olaparib or pembrolizumab/chemotherapy in patients with advanced breast cancer

Highlights from first patient include:

- Marked reduction in CTC clusters following the first cycle of paxalisib.
- Epigenetic reprogramming of CTCs toward less aggressive phenotypes, confirmed through digital pathology and Nanostring profiling.
- Significant reduction of exhausted CD8 T cells, with revitalization of cytotoxic and antigen-presentation pathways.
- CT imaging has demonstrated overall primary tumor volume reduction from baseline 14mm x 11mm (154mm^2) to 12mm x 3 mm (36mm^2)
- Notably, a temporary interruption of paxalisib (necessitated by a chemotherapy-related adverse event) resulted in a rapid resurgence of CTC clusters. Resumption of paxalisib after a short 3-week pause restored suppression of CTC clusters, indicating that pembrolizumab alone could not control these metastatic drivers and highlighting paxalisib's unique mechanistic role.

Pembrolizumab Alone May Not Control CTC Burden; A Mechanistic Opportunity for Paxalisib

Across HER2+ and TNBC ex-vivo datasets, a consistent theme emerges:

- Pembrolizumab monotherapy does not meaningfully reduce CTC burden, and in TNBC, CTC clusters increased when paxalisib was withheld.
- Paxalisib directly targets mesenchymal, metastatic, and epigenetically resistant CTC clusters.
- It also reinvigorates immune effector cells, potentially overcoming the cytotoxic dysfunction and exhaustion that limit checkpoint inhibitor efficacy.

This mechanistic direct suppression of metastasis-initiating cells plus restoration of immune function positions paxalisib as a potentially transformative immunotherapy-enhancing agent.

Expanding Opportunity Across Breast Cancer: HER2+, TNBC, BRCA-Mutated, and Beyond

Because mesenchymal CTC clusters and T-cell exhaustion are shared resistance mechanisms across multiple breast cancer subtypes, paxalisib's effects are highly relevant beyond TNBC.

Emerging data suggest:

- In HER2+ patients, despite targeted therapy, residual disease persists in the form of aggressive CTC clusters—a new therapeutic window for paxalisib.

- In TNBC, paxalisib's epigenetic and immunologic effects provide a strong rationale for combination with pembrolizumab, PARP inhibitors, and chemotherapy.
- In BRCA-mutated and homologous recombination–deficient tumors, PI3K/mTOR inhibition may synergize with synthetic lethal strategies such as olaparib.

"Kazia's recent clinical and translational findings point to a unifying biology across breast cancer subtypes," said Dr. John Friend, CEO of Kazia Therapeutics. "Paxalisib appears capable of disrupting metastatic machinery that is not adequately addressed by current HER2-targeted therapies, checkpoint inhibitors, or chemotherapies. We believe these discoveries meaningfully expand the potential utility of paxalisib beyond our current development programs."

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About Kazia Therapeutics

Kazia Therapeutics Limited (NASDAQ: **KZIA**) is an oncology-focused drug development company, based in Sydney, Australia. Our lead program is paxalisib, an investigational brain penetrant inhibitor of the PI3K / Akt / mTOR pathway, which is being developed to treat multiple forms of cancer. Licensed from Genentech in late 2016, paxalisib is or has been the subject of ten clinical trials in this disease. A completed Phase 2/3 study in glioblastoma (GBM-Agile) was reported in 2024 and discussions are ongoing for designing and executing a pivotal registrational study in pursuit of a standard approval. Other clinical trials involving paxalisib are ongoing in advanced breast cancer, brain metastases, diffuse midline gliomas, and primary central nervous system lymphoma, with several of these trials having reported encouraging interim data. Paxalisib was granted Orphan Drug Designation for glioblastoma by the U.S. Food and Drug Administration (FDA) in February 2018, and Fast Track Designation (FTD) for glioblastoma by the FDA in August 2020. Paxalisib was also granted FTD in July 2023 for the treatment of solid tumor brain metastases harboring PI3K pathway mutations in combination with radiation therapy. In addition, paxalisib was granted Rare Pediatric Disease Designation and Orphan Drug Designation by the FDA for diffuse intrinsic pontine glioma in August 2020, and for atypical teratoid / rhabdoid tumors in June 2022 and July 2022, respectively. 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 tumor types and has provided evidence of synergy with immuno-oncology agents. A Phase I study has been completed and preliminary data was presented at 15th Biennial Ovarian Cancer Research Symposium in September 2024. For more information, please visit **www.kaziatherapeutics.com** or follow us on X @KaziaTx.

Forward-Looking Statements

This announcement contains forward-looking statements, which can generally be identified as such by the use of words such as "may," "will," "plan," "intend," "estimate," "future," "forward," "potential," "anticipate," or other similar words. Any statement describing Kazia's future plans, strategies, intentions, expectations, objectives, goals or prospects, and other statements that are not historical facts, are also forward looking statements, including, but not limited to, statements regarding: additional confirmatory data, imaging and analysis of the phase 1 TNBC clinical study, the timing for results and data related to Kazia's clinical and preclinical trials, the upcoming scientific presentations, Kazia's strategy, plans and next steps with respect to its

paxalisib program, including enrolling patients in the PaxPlus-ABC Phase 1b study, the potential benefits, effects and utility of paxalisib, timing for any regulatory submissions or discussions with regulatory agencies and the potential market opportunity for paxalisib. Such statements are based on Kazia's current expectations and projections about future events and future trends affecting its business and are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements, including risks and uncertainties associated with clinical and preclinical trials and product development, including the risk that interim or early data may not be consistent with final data, risks related to regulatory approvals, risks related to the impact of global economic conditions, and risks related to Kazia's ability to regain and/or maintain compliance with the applicable Nasdaq continued listing requirements and standards. These and other risks and uncertainties are described more fully in Kazia's most recent Annual Report on form 20-F filed with the SEC, and in subsequent filings with the United States Securities and Exchange Commission. Kazia undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise, except as required under applicable law. You should not place undue reliance on these forward-looking statements, which apply only as of the date of this announcement.