Kazia Therapeutics Limited
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Ticker (Exchange)	KZIA (NASDAQ)
Recent Price (11/21/2025)	$8.35
52-week Range	$2.86 - $29.85
Shares Outstanding	~1.62 mm ADS
Market Capitalization	$13.5 mm
Average volume	653,112
EPS (Half year 12/31/24)	(A$2.459)
Employees	7

Source: Google Finance, as of November 21, 2025

PIPELINE		
Drug Candidate	**How It Works**	**Key Differentiator**
Paxalisib	Inhibits the PI3K/AKT/mTOR pathway, a critical signaling route that helps cancer cells grow and multiply.	The only drug of its kind in development that is known to cross the blood-brain barrier.
EVT801	A selective VEGFR3 inhibitor that primarily targets the formation of new lymphatic vessels (lymphangiogenesis) needed by tumors.	Designed to be highly selective to avoid off-target toxicities common in older, similar drugs.

Source: Kazia Therapeutics Limited.

COMPANY DESCRIPTION

Kazia Therapeutics Limited ("Kazia" or "the Company") is a Sydney-based clinical-stage oncology company focused on high-need cancers of the central nervous system (CNS) and select hard-to-treat solid tumors. The portfolio includes two small-molecule programs: (1) paxalisib, a brain-penetrant inhibitor of the **PI3K/AKT/mTOR pathway†**, a critical signaling route that helps cancer cells grow and multiply, licensed from Genentech, and (2) EVT801, a selective **vascular endothelial growth factor receptor 3 (VEGFR3)** inhibitor licensed from Evotec SE. Paxalisib is designed to achieve reliable drug levels in the brain, addressing a central barrier to treatment. It is advancing toward a single pivotal study in newly diagnosed, **MGMT-unmethylated glioblastoma (GBM)** and is being studied across additional settings, including brain metastases, select **gliomas,** such as **Diffuse Intrinsic Pontine Glioma (DIPG)**, primary CNS lymphoma, and certain advanced breast cancer subtypes. Paxalisib has secured multiple FDA designations (**Orphan Drug**, **Fast Track**, **Rare Pediatric Disease**), enhancing regulatory engagement speed and providing potential market exclusivity, priority review, and other incentive benefits. EVT801 targets VEGFR3 to limit **lymphangiogenesis**—the formation of new lymphatic vessels that can enable tumor growth and metastasis—and favorably conditions the tumor microenvironment. Stage 1 of the first-in-human study is complete, with final Phase 1 readout expected in CY2025 and Phase 2 planning underway, initially in **high-grade serous ovarian cancer (HGSOC)** with potential immunotherapy combinations under evaluation.

KEY POINTS

- Kazia runs a lean, partnership-first model. The Company outsources manufacturing and early development, focuses its spending on clinical trials, and pursues non-dilutive capital through regional licenses and research collaborations.
- Selective deals and collaborations include Simcere (Greater China) and Sovargen (select neurology), with research ties to QIMR Berghofer, Pacific Pediatric Neuro-Oncology Consortium (PNOC), and Memorial Sloan Kettering Cancer Center (MSKCC).
- Paxalisib's composition-of-matter patents run to 2031; with process claims and Patent Term Extension (PTE)/Supplementary Protection Certificate (SPC) protection potentially to 2036 in major markets.
- Kazia's leadership has been strengthened with CEO Dr. John Friend and Chairman Bryce Carmine, who bring clinical, operational, and market expertise to support the next phase of development.
- As of December 31, 2024, the Company's cash position was ~A$3.06 million. Since then, Kazia raised $2 million via a registered direct (January 10, 2025), received $1 million from the Cantrixil IP sale (March 30, 2025), and closed a $2 million premium private placement (August 1, 2025), supporting flexible dilutive and non-dilutive funding as late-stage studies advance.

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Executive Overview

All amounts are in U.S. dollars, unless otherwise stated.

Kazia Therapeutics Limited ("Kazia" or "the Company") is a Sydney-based oncology company developing targeted therapies for cancers of the central nervous system (CNS) and other hard-to-treat solid tumors. The lead program, paxalisib, is an oral, brain-penetrant inhibitor of the PI3K/Akt/mTOR pathway licensed from Genentech in 2016. Paxalisib is designed to reach therapeutic levels in the brain, allowing direct treatment of primary CNS tumors and brain-involved solid cancers. Clinical development is currently centered on **glioblastoma (GBM)**, with additional studies in brain metastases, diffuse midline glioma, primary CNS lymphoma, and combination regimens in advanced breast cancer (including **triple negative breast cancer [TNBC]**). Kazia is also advancing EVT801, a selective VEGFR3 inhibitor in-licensed from Evotec SE in April 2021. Preclinical studies suggest broad antitumor activity and synergy with immuno-oncology agents. An overview of Kazia's pipeline is provided in Figure 1.

Figure 1
PIPELINE

Drug Candidate	How It Works	Key Differentiator
Paxalisib	Inhibits the PI3K/AKT/mTOR pathway, a critical signaling route that helps cancer cells grow and multiply.	The only drug of its kind in development that is known to cross the blood-brain barrier.
EVT801	A selective VEGFR3 inhibitor that primarily targets the formation of new lymphatic vessels (lymphangiogenesis) needed by tumors.	Designed to be highly selective to avoid off-target toxicities common in older, similar drugs.

Source: Kazia Therapeutics Limited and Crystal Research Associates, LLC.

Primary Asset: Paxalisib

Paxalisib has been evaluated in ten clinical studies, including **Glioblastoma Adaptive Global Innovative Learning Environment (GBM-AGILE)**, an international Phase 2/3 adaptive platform that tests multiple therapies for GBM in parallel against a shared control, adds or drops arms based on performance, and is designed to generate registrational-quality evidence; results were reported in 2024. Kazia is working toward a potential registrational path in newly diagnosed GBM. The program holds multiple FDA designations: Fast Track and Orphan Drug for GBM; Fast Track for PI3K-altered brain metastases with radiation; and Rare Pediatric Disease and Orphan Drug for select pediatric gliomas, including diffuse intrinsic pontine glioma (DIPG) and **atypical teratoid/rhabdoid tumor (AT/RT)**. These features position paxalisib as a targeted option where reliable brain exposure is essential. After two decades without new drug approvals since temozolomide (branded Temodar) an oral chemotherapy used mainly for brain tumors, advances in genomics, targeted trial design, and regulatory incentives are opening the door for paxalisib and similar agents to gain traction in this expanding market.

Brain Tumor Landscape

Primary malignant brain tumors vary by location, patient, and driver mutations. GBM is the most common and lethal adult glioma, which spreads widely and almost always recurs despite surgery, radiation, and chemotherapy. In children, diffuse midline gliomas (including DIPG) arise in the brainstem and other midline sites and are not resectable. The **blood-brain barrier**, tumor heterogeneity, and resistance limit many drugs, highlighting the need for brain-penetrant agents and rational combinations.

Market Opportunity

Kazia's platform targets several large, under-served markets with clear unmet need. GBM represents roughly a $3.7 billion market in 2024 and is projected to approach $7.9 billion by 2033, where even modest, reliable survival gains can drive adoption (Source: Grand View Research). Pediatric brain cancers are about a $1.3 billion global market in 2024, concentrated in specialized centers and supported by Rare Pediatric Disease incentives that favor focused development (Source: Market Research Future).

Brain metastases account for an estimated $3.9 billion therapeutics market in 2024, and are expected to increase to about $8.8 billion by 2035, with significant populations in breast, lung, and melanoma, where CNS-active combinations with radiotherapy may improve intracranial control (Source: Future Market Insights). In breast cancer, the TNBC segment is estimated at $670.5 million in 2024 and forecast to reach $1.04 billion by 2034 (CAGR ~4.6%), with better intracranial depth and durability of response expanding the opportunity (Source: Fact.MR).

Clinical Highlights and Current Status

- *Glioblastoma and Brain Cancers.* Paxalisib completed participation on the GBM-AGILE platform in newly diagnosed, MGMT-unmethylated GBM. While the primary analysis versus cumulative controls did not reach statistical significance, a prespecified analysis versus concurrent controls showed a trend to longer overall survival (OS) and aligned with Kazia's earlier Phase 2 median overall survival of ~15.7 months. These data support a traditional approval path, and the Company is finalizing a single pivotal Phase 3 study design in consultation with the FDA. Kazia plans to finalize the pivotal GBM protocol and Statistical Analysis Plan (SAP) after recent design alignment. The 350-patient, 1:1 randomization trial is expected to run three to four years; clinical research organizations (CROs) are ready, with start-up depending on funding at $100,000-$150,000 per patient. To enable launch, Kazia is pursuing financing and support from National Cancer Institute/National Institute of Health (NCI/NIH) cooperative groups and potential biotech/pharma partners.

- *Brain Metastases.* A Memorial Sloan Kettering Cancer Center (MSKCC) Phase 1 trial established a 45 mg once-daily dose with concurrent brain radiotherapy in PI3K-altered solid-tumor brain metastases. Safety was manageable, and a high proportion of evaluable patients at the maximum tolerated dose (MTD) achieved intracranial responses by **Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM)**, a standardized set of rules for judging how brain metastases respond to treatment on MRI and in the clinic, supporting follow-on development.

- *Breast Cancer (TNBC and **HER2-negative**).* In 2025, Kazia opened a multi-center Phase 1b trial in advanced breast cancer. Arm A tests paxalisib with olaparib in BRCA-mutated, HER2-negative disease; Arm B evaluates paxalisib with pembrolizumab plus chemotherapy in TNBC. Early TNBC results showed a greater than 50% reduction in circulating tumor cells within 21 days, consistent with immune-modulatory synergy not typically seen with chemotherapy or checkpoint inhibitor alone.

- *Pediatrics.* Paxalisib holds FDA Orphan Drug and Rare Pediatric Disease designations in DIPG and AT/RT. A **Pacific Pediatric Neuro-Oncology Consortium (PNOC)**, an international clinical-trial network focused on bringing new therapies to children and young adults with brain tumors, Phase 2 study in DMG reported median overall survival in the post-radiation cohort above historical benchmarks. AT/RT is next to enter the clinic, with additional separate pediatric study cohorts under evaluation for PI3K/mTOR-activated tumors.

Secondary Asset: EVT801

EVT801 is an oral, selective VEGFR3 inhibitor that targets lymphangiogenesis (the growth of new lymphatic vessels) to normalize tumor lymphatics and reduce hypoxia. In preclinical models, it also shifts the immune microenvironment, with fewer **myeloid-derived suppressor cells (MDSCs)** and greater infiltration of CD8-positive (CD8+) T-cells, which supports use alone and in combination with immunotherapy. Discovered at Sanofi and advanced by Evotec before Kazia licensed it globally, the program completed Stage 1 of its first-in-human study with a maximum tolerated dose (MTD) of 500 mg twice daily (BID) and a recommended Phase 2 dose (RP2D) of 400 mg BID. Early disease-control signals in **high-grade serous ovarian cancer (HGSOC)**, with supportive biomarkers, were presented at the American Association for Cancer Research (AACR) Ovarian Cancer Research Symposium (2024). The Company is planning Phase 2 in ovarian cancer, including combinations with immuno-oncology (IO) agents and **poly (ADP-ribose) polymerase (PARP) inhibitors**, and exploring partnering options while it prioritizes paxalisib.

Intellectual Property

Kazia's base composition-of-matter patents expire in 2031; potential Patent Term Extension (PTE, U.S.) and Supplementary Protection Certificates (SPCs, EU/UK) could add up to five years of protection (plus pediatric extensions where applicable), potentially into 2036 in major markets. Exclusive licenses from QIMR Berghofer add coverage for combination uses, including with immunotherapies and PARP inhibitors. EVT801 is covered by composition-of-matter patents into the early 2030s.

Licenses and Collaborations

Kazia's model blends regional licenses, academic collaborations, and a focused internal team. Multiple FDA designations for paxalisib (Orphan Drug, Fast Track, Rare Pediatric Disease) provide regulatory advantages, potential access to a tradable **Priority Review Voucher** at approval in eligible pediatric indications, and other incentive benefits. Existing agreements include Simcere for Greater China and Sovargen for select neurology indications, along with research collaborations with QIMR Berghofer (an independent research group in Queensland Australia), Pacific Pediatric Neuro-Oncology Consortium (PNOC), and Memorial Sloan Kettering Cancer Center (MSKCC). Kazia builds its pipeline through selective in-licensing from leading research groups. Paxalisib was licensed from Genentech in 2016. EVT801 was licensed from Evotec in 2021. In October 2025, Kazia added an exclusive collaboration and in-licensing agreement with QIMR Berghofer for a first-in-class PD-L1 protein degrader program (lead compound NDL2), alongside worldwide rights to combination IP that covers pairing PI3K inhibitors with immunotherapies and PARP inhibitors.

Strategy, Operating Model, and Funding

Kazia runs a lean, partnership-oriented model that emphasizes capital efficiency and selective risk sharing. The Company outsources manufacturing and much of the early development, focuses internal resources on clinical execution, and seeks non-dilutive income through regional licenses and research collaborations. In November 2023, Kazia delisted from the ASX to concentrate on its NASDAQ listing, improving access to U.S. biotech investors and simplifying administration.

Kazia is advancing paxalisib as a CNS-ready combination backbone across glioblastoma, pediatric brain tumors, brain metastases, and TNBC, while EVT801 targets lymphatic-driven metastasis with immune normalization. With FDA input for a pivotal GBM study, supportive pediatric designations, and early signals in brain metastases and TNBC, the Company has clear clinical milestones ahead. As a pre-revenue issuer, Kazia raised capital in early 2025 through registered directs, private placements, and non-dilutive proceeds from asset sales and grants, and continued access to capital will be important as late-stage trials progress.

Corporate History and Headquarters

Kazia traces its origins to Novogen Limited, an Australian drug developer founded in 1994. Following shareholder approval, the Company rebranded as Kazia Therapeutics in November 2017 to focus on oncology. As part of this transition, Kazia in-licensed GDC-0084 from Genentech in October 2016—now paxalisib—which became the lead asset. Kazia is headquartered in Sydney, Australia, and employs about 7 people.

Intellectual Property

Paxalisib: Patent Protections and Intellectual Property

Paxalisib (GDC-0084) was discovered at Genentech and licensed to Kazia in late 2016. Kazia has secured multiple layers of protection for this asset.

- *Composition-of-matter patents*. Base patents generally expire in December 2031. Kazia expects to pursue patent term extension or supplementary protection certificates in major markets, which could extend effective protection by up to five years.

- *Manufacturing process patents*. Patents covering the synthesis process are granted in the U.S. and India, with applications pending in the EU, China, Canada, Australia, and other regions. Where granted, these are expected to run to 2036 and raise the bar for generic entry by forcing alternative non-infringing routes.

- *New combination-therapy patent family*. Kazia holds an exclusive, worldwide, sublicensable, royalty-bearing license from QIMR Berghofer to a patent family covering PI3K-inhibitor combinations (WO2024/108256 A1; priority November 2022). The claims encompass the use of PI3K inhibitors with immunotherapies, including PARP-inhibitor-based regimens, to treat or delay cancer progression and recurrence. Supporting data indicate PI3K inhibition can epigenetically reprogram repressed T-cells, curb T-cell exhaustion, inhibit cancer stem-cell formation and maintenance, and promote mesenchymal-to-epithelial transition. This portfolio is intended to protect combination approaches with PI3K inhibitors across solid tumors, including recurrent disease.

EVT801: Patent Protections and Inventorship

EVT801 is an oral VEGFR3 inhibitor in-licensed from Evotec SE in April 2021. The molecule originated at Sanofi and transferred to Evotec in 2015. Composition-of-matter filings from the Sanofi/Evotec estate form the core IP. Based on discovery timing, core protection is expected to extend into the mid-2030s. The Evotec agreement grants Kazia an exclusive global license and includes a master services agreement that supports development, manufacturing, and know-how transfer.

Key Licensing and Collaboration Agreements

Kazia's pipeline has been shaped by targeted in- and out-licensing, as described below.

- *Genentech (paxalisib origin).* The exclusive worldwide license was obtained in 2016, transferring patents, data, and know-how to support development across oncology indications.

- *Simcere Pharmaceutical (Greater China).* In March 2021, Kazia out-licensed paxalisib in Mainland China, Hong Kong, Macau, and Taiwan. Consideration included $11 million upfront ($7 million cash and a $4 million equity investment), up to $281 million in milestones for glioblastoma (GBM), and mid-teen royalties. Simcere is responsible for regional development and commercialization.

- *Sovargen Co., Ltd. (rare CNS diseases).* In March 2024, Kazia granted Sovargen an exclusive global license (excluding Greater China) to develop and commercialize paxalisib for intractable seizures due to **focal cortical dysplasia** type 2 and tuberous sclerosis complex, including $1.5 million upfront and up to $19 million in milestones, plus royalties and a share of any sub-license income.

- *Evotec SE (EVT801).* Evotec SE granted Kazia a worldwide exclusive license to EVT801 in April 2021, with €1.0 million upfront, up to €308 million in milestones, and tiered single-digit royalties. The parties also entered a master services agreement to support development activities.

- *QIMR Berghofer (PD-L1 degrader program).* On October 7, 2025, Kazia in-licensed a first-in-class PD-L1 degrader (NDL2) from QIMR Berghofer, gaining exclusive global rights to PI3K-combination IP (WO2024/108256A1; priority November 2022). The IP covers pairing PI3K inhibitors (including paxalisib) with immunotherapies and PARP inhibitors. Preclinical work (Professor Sudha Rao) shows PI3K inhibition can reprogram T-cells, suppress cancer stem cells, and induce MET—supporting trials in solid tumors such as TNBC—while adding combination-use protection that complements paxalisib's core patents.

- *Vivesto AB (Cantrixil).* On March 31, 2025, Kazia sold all remaining Cantrixil (ovarian) IP and trademark rights to Vivesto for $1 million, completing its exit from this legacy program.

Strategic IP Management

Kazia plans to align patent and regulatory exclusivity with its development path, pursuing U.S. Patent Term Extensions (PTE) or EU/UK Supplementary Protection Certificates (SPCs) where available, and U.S. pediatric exclusivity when appropriate. Regional partnerships (for example, Simcere in Greater China) and disease-area out-licenses (for example, Sovargen in rare CNS disorders) expand the commercial reach potential of the Company's IP while allowing internal focus on core oncology programs.

Company Leadership

Kazia is led by an experienced management team, a diverse and active Board of Directors, and a distinguished Scientific Advisory Board. Together, these groups provide deep expertise in biotechnology, oncology drug development, capital markets, and corporate governance. Their combined insight shapes the Company's strategic direction and drives the advancement of Kazia's pipeline, enabling the organization to effectively manage the complexities of cancer research and commercialization. In fiscal year 2024, Kazia strengthened its leadership to support future growth. Dr. John Friend, formerly Chief Medical Officer, was promoted to Chief Executive Officer and Managing Director. Following Mr. Iain Ross's resignation on August 11, 2023, Dr. Friend also served as Interim Chairman until January 18, 2024. On that date, longtime board member, Mr. Bryce Carmine, was appointed Chairman, bringing extensive experience in drug development and global healthcare leadership to the role.

Management

Dr. John Friend, Chief Executive Officer

Dr. John Friend is a highly experienced oncology and hematology drug developer, driven by a passion for improving the lives of cancer patients. In a career spanning more than 25 years, Dr. Friend has worked across a wide range of therapeutic areas in roles from early clinical research through to medical affairs. He was formerly the Senior Vice President of Medical and Scientific Affairs for the U.S. business unit of Helsinn Therapeutics and most recently the Chief Medical Officer at Cellectar Biosciences, a clinical-stage, oncology-focused biotech company in the U.S. Dr. Friend gained his medical degree at Rutgers University (UMDNJ-Robert Wood Johnson) and also holds a BA in chemistry from Southern Methodist University.

Jeffrey Bonacorda, VP Finance and Controller

Mr. Jeffrey Bonacorda is a senior accounting professional with more than thirty years of experience in the pharmaceutical, consumer products, and service industries. Prior to joining Kazia, Mr. Bonacorda held several senior finance positions supporting global R&D development programs and on market pharmaceuticals. Mr. Bonacorda holds a Bachelor of Business Administration from Wilmington University.

Elissa Hansen, Company Secretary

Ms. Elissa Hansen has over 20 years' experience as a company secretary and governance professional for both listed and unlisted companies. She is a Chartered Secretary who brings best practice governance advice, ensuring compliance with the Listing Rules, Corporations Act, and other relevant legislation. Ms. Hansen is a Fellow of the Governance Institute of Australia and a Graduate Member of the Australian Institute of Company Directors. She holds a Bachelor of Commerce and a Graduate Diploma in Applied Corporate Governance.

Board of Directors

Bryce Carmine, Chairman

Mr. Bryce Carmine spent 36 years working for Eli Lilly & Co. and retired as Executive Vice President for Eli Lilly & Co., and President, Lilly Bio-Medicines. Prior to this, he lead Global Pharmaceutical Sales and Marketing and was a member of the company's executive committee. He previously held a series of product development portfolio leadership roles culminating when he was named President, Global Pharmaceutical Product Development, with responsibility for the entire late-phase pipeline development across all therapeutic areas for Eli Lilly. During his career with Eli Lilly, Mr. Carmine held several country leadership positions, including President Eli Lilly Japan, Managing Dir. Australia/NZ & General Manager of a JV for Lilly in Seoul, Korea. He is currently a Board Director of HaemaLogiX Pty Ltd, a Sydney-based privately owned biotech. Mr. Carmine was appointed as Chairman of Kazia in January 2024, having served as a Non-Executive Director of the Company since June 2015. He is a member of both the Audit, Risk and Governance Committee, and Chair of the Remuneration and Nominations Committee.

Steven Coffey, Non-Executive Director

Mr. Steven Coffey is a Chartered Accountant, having spent his career in public practice since graduating from NSW University in 1983. He has been a partner in the chartered accounting firm Watkins Coffey Martin since 1993. Mr. Coffey is a registered company auditor and audits a number of large private companies as well as a number of not-for-profit entities. He has previously served on the board of an Australian listed public company and is currently a board member of two private ancillary funds (PAFs). Mr. Coffey was appointed as a director to the Company in November 2012 and is considered to be an independent director. He is Chair of the Audit, Risk and Governance Committee, and a member of the Remuneration and Nominations Committee.

Ebru Davidson, Non-Executive Director

Ms. Ebru Davidson is a highly experienced corporate lawyer and is currently the General Counsel for QBiotics Group Limited, an unlisted public Australian life sciences company that discovers and develops pharmaceuticals derived from nature to address unmet medical needs in humans and companion animals. As a former partner at Thomson Geer Lawyers, Ms. Davidson brings over 14 years' experience in equity capital markets, private and public mergers and acquisitions, corporate transactions, and corporate governance. Ms. Davidson also has extensive experience in advising listed and unlisted entities on compliance and regulatory matters working closely with the Australian Securities and Investment Commission and Australian Securities Exchange. Ms. Davidson holds a Bachelor of Science degree from the University of Melbourne, and a Juris Doctor (Honours) from Bond University. Ms. Davidson is a Graduate of the Australian Institute of Company Directors and an Associate Member of the Governance Institute of Australia having completed a Graduate Diploma of Applied Corporate Governance. Ms. Davidson was appointed as a Non-executive Director in June 2023. She is Chair of the Remuneration and Nominations Committee and is considered to be an independent Director.

Robert Apple, Non-Executive Director

Mr. Robert Apple has more than 25 years of senior leadership experience in the pharmaceutical industry, including 16 years with Antares Pharma, Inc. as Senior Vice President, Chief Financial Officer, and Corporate Secretary, before going on to become President and Chief Executive Officer from 2016 until its acquisition by Halozyme Therapeutics in 2022. Mr. Apple also served on the Board of Directors at Antares from 2016 until May 2022. He previously served on the Board of Directors of InKine Pharmaceutical, PaxMedica Inc., and Kerathin Inc. Prior to joining Antares, Mr. Apple served as Chief Operating and Financial Officer at InKine Pharmaceutical. He also held prior roles at Genaera Corporation, Liberty Technologies, and Arthur Andersen & Company. Mr. Apple is a member of both the Audit, Risk and Governance Committee, and the Remuneration and Nominations Committee. He holds a B.A. degree in accounting from Temple University, Philadelphia.

Dr. Priscilla Brastianos

Dr. Priscilla Brastianos is director of the Central Nervous System Metastasis Center at Massachusetts General Hospital and leads a multi-R01-funded laboratory. Her research focuses on understanding the genomic mechanisms that drive primary and metastatic brain tumors and she has led studies which have identified novel therapeutic targets in brain tumors. Dr. Brastianos completed her medical school and internal medicine residency at Johns Hopkins School of Medicine and fellowship training in hematology/oncology and neuro-oncology at the Dana-Farber Cancer Institute and Massachusetts General Hospital. She has more than 145 scientific publications and has translated her scientific findings to national multi-center trials. She also leads a multidisciplinary Central Nervous System Metastasis Clinic at Massachusetts General Hospital/Harvard Medical School. She has received a number of awards for her work, including 'NextGen Star' award by the American Association for Cancer Research, Damon Runyon Clinical Investigator Award, Breast Cancer Research Foundation Award, Susan G. Komen Career Catalyst Award, American Brain Tumor Association Joel Gingras Award, and Anne Klibanski Award for Excellence in Mentorship.

Dr. John de Groot

Dr. John de Groot is Division Chief of the Neuro-Oncology Division within the Department of Neurological Surgery at the University of California, San Francisco (UCSF). He is a neuro-oncologist with extensive clinical and translational research experience in the field of glioma, angiogenesis, molecularly targeted therapy, and immunotherapy. Prior to joining UCSF, Dr. de Groot was based at MD Anderson Cancer Center in Houston, TX, where he was co-leader of the GBM Moonshot Program. He has authored over 135 peer-reviewed publications, has been the principal investigator of 44 clinical trials, a collaborator on a further 78 clinical trials, and has been a recipient of multiple NCI, CPRIT, NBTS, and industry-sponsored grants. He has also served as a peer reviewer for 23 scientific journals, and sits on four editorial review boards, as well as holds several leadership positions within the Society for Neuro-Oncology (SNO).

Dr. Alan Olivero

Dr. Alan Olivero is a consultant specializing in drug discovery and development. In 2018, he retired from Genentech, Inc., where he worked for 25 years, rising to the level of Senior Director of Discovery Chemistry and Head of Research Operations. During his time at Genentech, he oversaw much of the medicinal chemistry conducted at Genentech, led research teams for eight clinical candidates and, as Head of Research Operations, additionally oversaw the company's research budget, headcount, and research facilities. Dr. Olivero is an expert on intracellular signaling pathways and was the team leader for Genentech's PI3K franchise. He has a specialist interest in brain cancer and is a co-inventor of paxalisib (formally GDC-0084). He led the early development of paxalisib and was responsible for bringing the drug into human trials. Dr. Olivero has a BS degree in chemistry from Stanford University, completed postgraduate work in synthetic organic chemistry at the Swiss Federal Institute of Technology in Zurich (ETHZ), and received his PhD in organic chemistry from Stanford University in 1988. He has co-authored numerous scientific publications and is a named inventor on over 40 patents.

Dr. Patrick Wen

Dr. Patrick Y. Wen is Professor of Neurology at Harvard Medical School and Director of the Center for Neuro-Oncology at Dana-Farber Cancer Institute. His research interests include novel therapeutics for brain tumors, as well as innovative clinical trial designs, and response assessment and endpoints in clinical trials. Dr. Wen was the President of the Society for Neuro-Oncology (SNO) from 2017-2019. He was formerly the Editor-in-Chief of Neuro-Oncology, and is currently SNO Executive Editor of Neuro-Oncology. He is also a steering committee member of the Response Assessment in Neuro-Oncology (RANO) Working Group and co-chairs the Agents Selection Committee of the GBM-AGILE trial. After receiving his medical degree from the Medical College of St. Bartholomew's Hospital, University of London, Dr. Wen underwent residency training at Harvard Longwood Neurology Training Program, and completed his clinical and research fellowship in neurology at the Center for Neurologic Diseases, Brigham and Women's Hospital, in Boston, Massachusetts.

Core Story

OVERVIEW

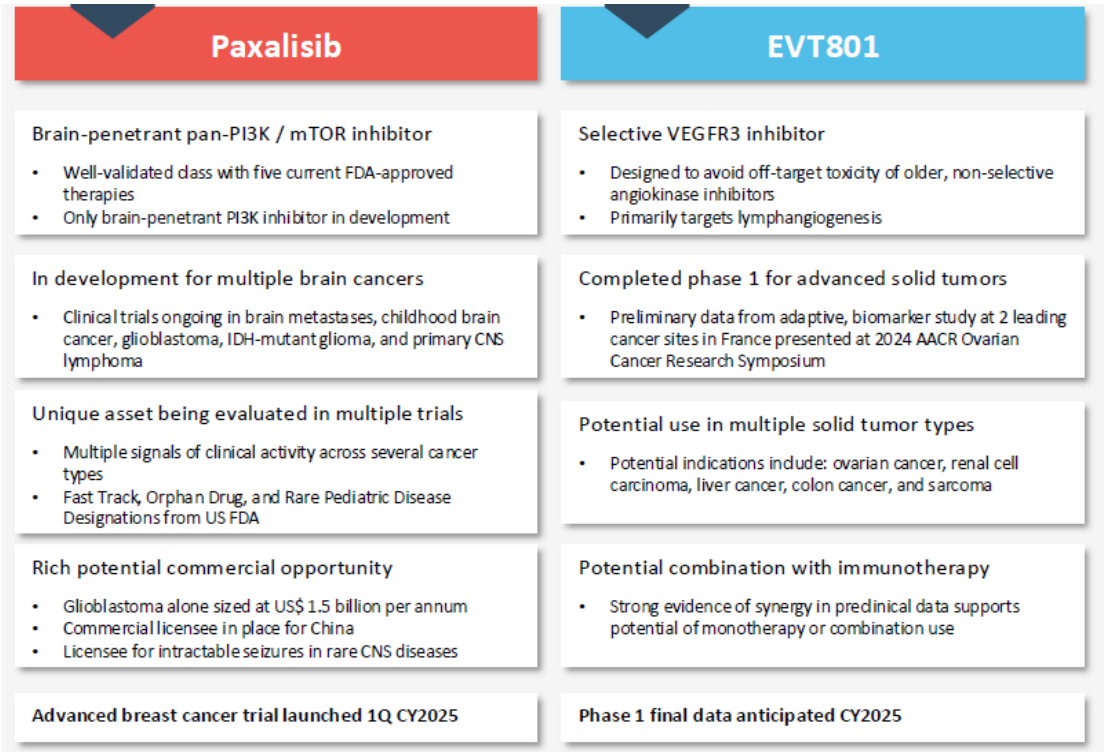
Kazia Therapeutics Limited ("Kazia" or "the Company") is a clinical-stage oncology company advancing two small-molecule programs: paxalisib and EVT801.

Paxalisib is an oral, brain-penetrant inhibitor of the PI3K/AKT/mTOR pathway licensed from Genentech. Development centers on central nervous system (CNS) tumors and other settings where reliable brain exposure matters, including combinations with radiotherapy and immunotherapy, with a recent expansion into advanced breast cancer. Indications under evaluation include glioblastoma (GBM) and **IDH-mutant glioma**; pediatric diffuse midline glioma/diffuse intrinsic pontine glioma (DMG/DIPG) and other pediatric solid tumors; atypical teratoid/rhabdoid tumor (AT/RT); brain metastases; primary CNS lymphoma; and advanced breast cancer subtypes, including triple-negative (TNBC) and HER2-negative disease. The program holds U.S. FDA Fast Track, Orphan Drug, and Rare Pediatric Disease designations.

EVT801 is a selective VEGFR3 inhibitor in-licensed from Evotec. It is designed to modulate lymphangiogenesis and normalize tumor vasculature in solid tumors while aiming to limit off-target toxicities seen with older, non-selective angiokinase agents. The compound has completed Phase 1 in advanced solid tumors, with additional Phase 1 data presented at ESMO 2025. Preclinical data support potential synergy with immunotherapy, and with Kazia positioning EVT801 for solid tumor settings such as ovarian, renal cell, liver, colon, and sarcoma. First-in-human studies were conducted in France at the Institut Universitaire du Cancer de Toulouse and Centre Léon Bérard.

Figure 2 provides a side-by-side overview of each program's core attributes, and Figure 3 (page 12) outlines the clinical pipeline, collaborators, and upcoming data milestones. More extensive details of each program are provided within the accompanying section.

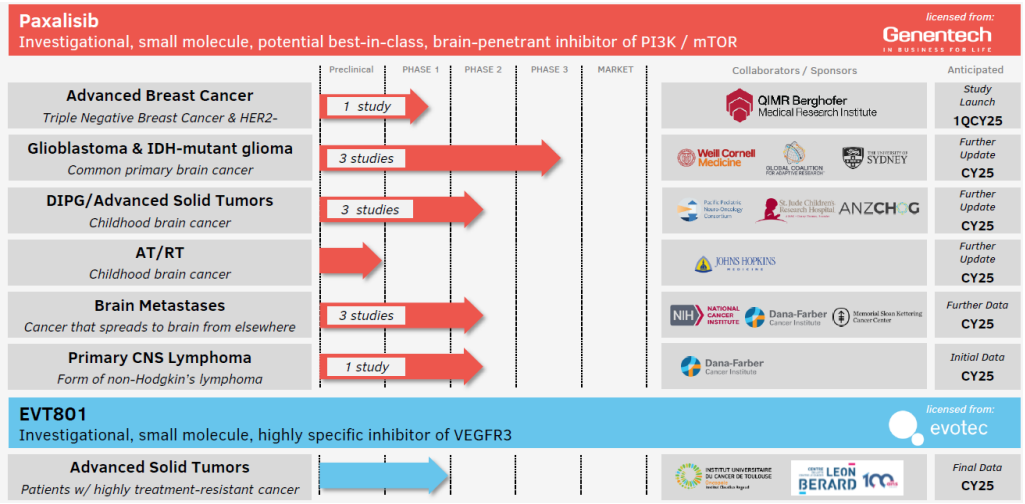
Figure 2
COMPANY OVERVIEW



Source: Kazia Therapeutics Limited.

Figure 3

PIPELINE: TWO DIFFERENTIATED ASSETS CLINICAL PROGRESS



Source: Kazia Therapeutics Limited.

Brain Tumors: Biology, Burden, and Unmet Need

Primary malignant brain tumors differ by where they start, who they affect, and the mutations that drive them. Glioblastoma (GBM), the most common and deadliest adult glioma, usually begins in the cerebral hemispheres. It is a fast-growing cancer that spreads through brain tissue and almost always returns despite surgery, radiation, and the chemotherapy drug temozolomide. Outcomes are influenced by tumor biology, including MGMT promoter methylation (a DNA change that can predict benefit from temozolomide), EGFR amplification (extra copies of a growth-signal gene), PTEN loss (a tumor-suppressor defect), and TERT alterations (telomerase activation).

In children, diffuse midline gliomas, including diffuse intrinsic pontine glioma (DIPG), arise in the brainstem and other midline areas, are often driven by H3 K27 alterations (a histone change that affects gene control), and cannot be removed surgically; radiation typically offers only temporary control. Medulloblastoma, a malignant tumor of the cerebellum, is the most common pediatric brain cancer and includes molecular subgroups such as WNT and SHH that guide prognosis and treatment. In adults, brain metastases from cancers like lung, breast, and melanoma occur more often than primary brain tumors and require treatment that addresses both the body-wide cancer and tumors in the brain.

Across these settings, the blood-brain barrier limits drug entry into the brain, tumors are genetically diverse within the same patient, and resistance to therapy is common. These barriers point to the need for brain-penetrant medicines and smart combinations, such as those being developed by Kazia, which can extend survival and improve quality of life.

PAXALISIB: LEAD CLINICAL ASSET

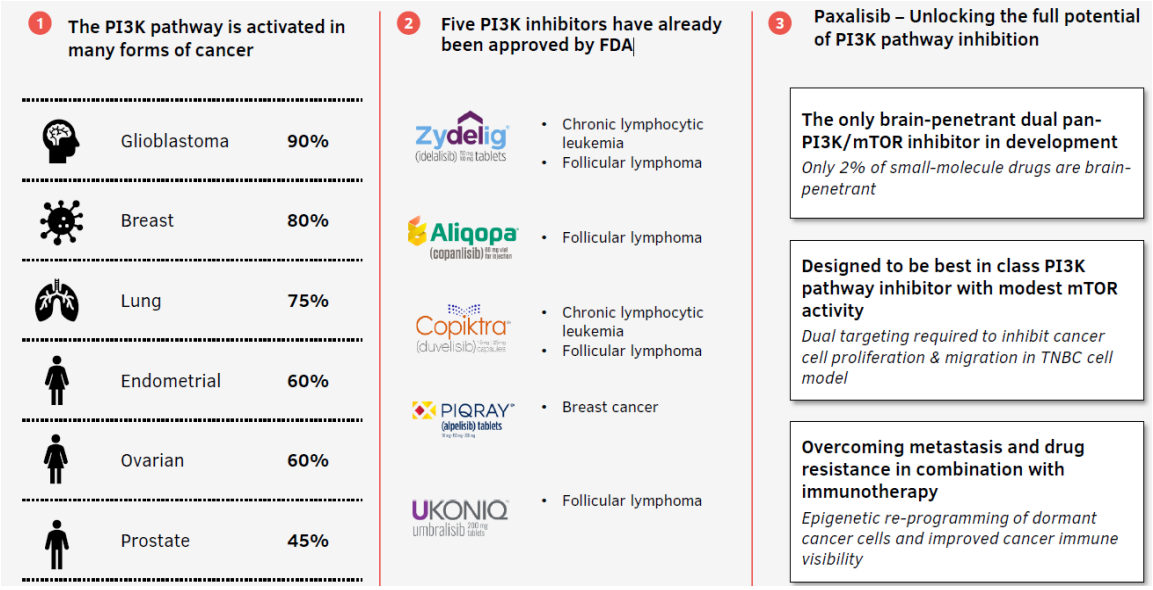
Paxalisib, Kazia's most advanced drug candidate, targets several different and difficult-to-treat cancers as an orally administered PI3K/mTOR inhibitor. This signaling pathway is a central regulator of cell growth and is hyperactivated in approximately 85% to 90% of glioblastoma cases, as well as many other tumor types, driving proliferation, survival, and metastasis. Unlike other PI3K inhibitors approved for peripheral cancers, paxalisib's key differentiator is its ability to cross the blood-brain barrier, a property that allows it to directly act on brain tumors and metastases that are otherwise inaccessible to most systemic treatments, overcoming a major obstacle in CNS drug delivery.

Mechanism of Action

Figure 4 explains why the PI3K pathway is a credible target and how paxalisib is designed to leverage it. PI3K signaling is active in many tumors, including glioblastoma (about 90%), breast (about 80%), lung (about 75%), endometrial and ovarian (about 60%), and prostate (about 45%). The pathway is clinically validated with five PI3K inhibitors having received FDA approvals to date, including idelalisib (Zydelig) for chronic lymphocytic leukemia and follicular lymphoma, copanlisib (Aliqopa) for follicular lymphoma, duvelisib (Copiktra) for chronic lymphocytic leukemia and follicular lymphoma, and alpelisib (Piqray) for breast cancer, with historical approvals also for umbralisib (Ukoniq) for follicular lymphoma (noting that umbralisib's approval was withdrawn in 2022 for safety concerns). This track record confirms that the class is druggable in patients, even as individual labels and indications have evolved.

Figure 4

PAXALISIB: MECHANISM OF ACTION



Source: Kazia Therapeutics Limited.

Paxalisib is a brain-penetrant PI3K inhibitor with some mTOR activity. Because it can cross the blood-brain barrier, it is suited to primary brain tumors and brain metastases. By targeting both PI3K and mTOR, it aims to slow tumor growth and spread where single-pathway drugs have not been enough. Preclinical data suggest that paxalisib can make hard-to-treat tumors more vulnerable to therapy and less prone to spread, especially when used with complementary agents. By blocking the PI3K pathway, paxalisib appears to reduce growth signals, increase the tumor's visibility to the immune system, and impair the cell's ability to cope with treatment-induced damage. These effects provide a rationale for combining paxalisib with checkpoint inhibitors and PARP inhibitors**,** where it may enhance immune attack and limit DNA repair. Because paxalisib reaches tumors in the brain, these findings are particularly relevant to CNS cancers and support ongoing clinical testing of both monotherapy and well-designed combinations.

Paxalisib Development History

Paxalisib's development history, described below, shows a growing body of clinical evidence for activity in GBM, from Genentech's first-in-human work through GBM-AGILE analyses (described on page 15).

- Genentech discovered GDC-0084 in the early 2000s for glioblastoma and ran a Phase 1 dose-escalation study (2012-2015) in 47 patients with advanced high-grade glioma that showed a manageable safety profile and early signs of anti-tumor activity.

- Kazia in-licensed GDC-0084 in 2016 after reviewing Genentech's clinical and animal data, positioning the drug as its lead neuro-oncology asset.

- In February 2018, the FDA granted Orphan Drug Designation for GBM, and in March 2018 Kazia opened a Company-sponsored Phase 2 trial testing first-line use in newly diagnosed GBM alongside standard therapy.

- In August 2020, the program received FDA Fast Track designation in GBM; additional FDA designations include Orphan Drug (GBM, February 2018), Fast Track for PI3K-altered solid-tumor brain metastases with radiation (July 2023), and Rare Pediatric Disease plus Orphan Drug in DIPG (August 2020) and AT/RT (2022).

- On January 7, 2021, the GBM-AGILE adaptive Phase 2/3 platform began recruiting the paxalisib arm, enabling randomized evaluation against a shared control within a multi-sponsor study.

- A December 3, 2021, Company update from a 30-patient Phase 2 monotherapy cohort in newly diagnosed GBM reported a median overall survival of 15.7 months, supporting continued development.

- On August 1, 2022, Kazia reported that the paxalisib arm did not advance from Stage 1 to Stage 2 within GBM-AGILE per the platform's interim algorithm; patients already enrolled continued therapy and follow-up per protocol.

- On July 10, 2024, GBM-AGILE Phase 2/3 results showed a clinically meaningful improvement in a prespecified secondary analysis of overall survival for paxalisib-treated, newly diagnosed MGMT-unmethylated GBM, informing subsequent pivotal-study planning.

Brain Cancers

Clinical development of paxalisib is focused primarily on several forms of brain cancer, as described in the accompanying section, the most advanced being glioblastoma (GBM), where it has demonstrated strong signals of efficacy in multiple trials, and holds potential in pediatric brain tumors and brain metastases.

Glioblastoma (GBM)

Glioblastoma (GBM) is the most common and aggressive primary brain cancer, with an estimated 130,000 to 133,000 new cases worldwide each year within a global cancer burden of approximately 14 million cases annually. There is no clear cause or strong risk profile, and while GBM can appear at any age, it is most frequently diagnosed in people in their 60s. Prognosis remains poor due to limited progress over two decades: survival without treatment is about 3 to 4 months, standard therapy yields a median survival of roughly 15 months, and five-year survival is under 5% (versus roughly 90% in breast cancer). These outcomes underscore the need for better options and the reason why even modest improvements in overall survival are clinically meaningful.

Treatment Landscape

The global GBM treatment market was valued at approximately $3.72 billion in 2024 and projected to reach $7.87 billion by 2033 (CAGR 8.68%, 2025-2033) (*Source: Grand View Research, "Glioblastoma Multiforme Treatment Market Size Report"*). North America holds roughly 40% share, and Asia-Pacific is the fastest-growing region *(Source: Grand View Research, "Glioblastoma Multiforme Treatment Market: Size, Share & Forecast, 2024-2033," 2025).*

Incidence appears to be rising globally, reflecting better diagnostics and aging populations, which increases case counts and strains health systems. Care is intensive and multidisciplinary, typically surgery followed by concurrent radiotherapy and temozolomide. Relapses are common within months, underscoring the need for more effective options. By treatment, surgery accounts for the largest share (about 33%), and hospitals/clinics are the primary end users. Surgical tools such as intraoperative MRI are improving resection quality; a 2024 *Journal of Neuro-Oncology* study reported gross total resection rates increasing from 33.6% to 49.6%, with lower recurrence and longer progression-free survival. Together, these trends point to incremental gains and are a base for broader progress.

That said, therapeutic advances have been limited for more than two decades. Temozolomide received initial FDA approval in 1999 and, based on results published in 2005, became the backbone of modern first-line care. Large studies of bevacizumab and other approaches have not delivered durable overall survival benefits in newly diagnosed or recurrent disease. The result is a persistent unmet need and a clear opportunity for therapies that can extend survival and improve quality of life.

Paxalisib: Lead Brain-Penetrant PI3K Inhibitor

Paxalisib, Kazia's lead brain-penetrant PI3K inhibitor, addresses this critical need through its ability to cross the blood-brain barrier, distinguishing it from other PI3K inhibitors that lack effective CNS penetration. The PI3K pathway is unusually activated in over 85% of GBM patients, providing strong biological rationale for targeting this pathway in the disease.

Paxalisib and GBM AGILE

GBM-AGILE is an international, multi-center, adaptive Phase 2/3 platform study sponsored by the Global Coalition for Adaptive Research (GCAR) to evaluate multiple GBM therapies in parallel. Drugs are randomized against a shared control arm, which reduces the number of patients needed, shortens timelines, and allows head-to-head-like comparisons without running separate trials. The design is not winner-takes-all; more than one drug can succeed. The primary endpoint is overall survival, the FDA's preferred standard for GBM. Paxalisib was one of several arms on the platform alongside regorafenib, VAL-083, troriluzole, and VT1021. Several comparator arms have completed with negative outcomes, while the paxalisib arm reported final top-line data in July 2024, enabling regulatory discussions on next steps.

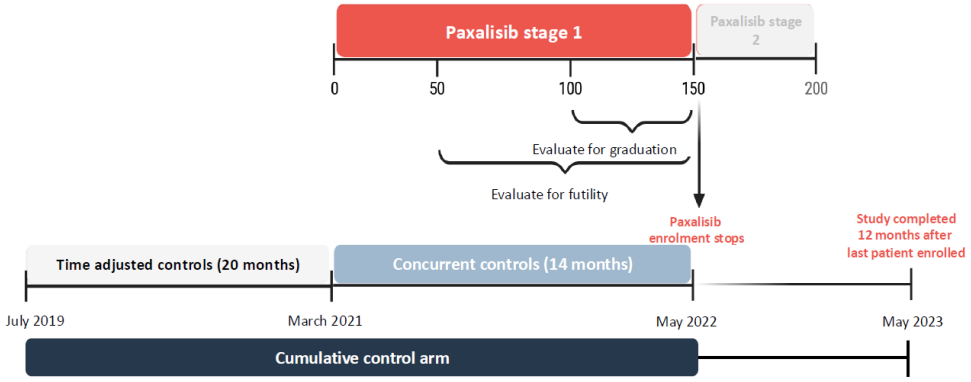
The GBM-AGILE trial tested paxalisib in 154 people with either newly diagnosed unmethylated GBM or recurrent GBM. The paxalisib arm ran through its first stage and then stopped enrolling in May 2022; the trial wrapped up 12 months after the last patient enrolled (May 2023). To judge whether paxalisib helped, the study compared patients on paxalisib to a shared control group made from two sources: (1) "time-adjusted" patients who joined the trial before the paxalisib arm opened, and (2) "concurrent" patients who were treated while paxalisib was enrolling. The main analysis used the combined control pool; a planned secondary analysis used only the concurrent controls (the closest match in time). Anyone still alive was counted up to May 2023. Figure 5 (page 16) outlines the study schema from this trial.

In GBM-AGILE, paxalisib was compared with two versions of the study's control arm. The cumulative control includes all patients randomized to control from the start of GBM-AGILE in June 2019 up to the date the last patient was randomized to paxalisib; these patients were followed (censored) through May 2023. The concurrent control is the subset enrolled during the same window that the paxalisib arm was open (March 2021 to the last paxalisib randomization), also censored in May 2023.

In survival analysis, “censored” means a patient’s follow-up ended before the event of interest occurred, so the exact survival time is unknown. These patients are counted up to their last confirmed status, such as being alive at data cutoff, lost to follow-up, or withdrawn, and their observation is censored at that point. Standard survival methods, including **Kaplan-Meier** and **Cox models**, incorporate censoring so estimates remain unbiased.

Figure 5

PAXALISIB & GBM-AGILE STUDY SCHEMA: PAXALISIB ARM (N=154) ENROLLED NEWLY DIAGNOSED UNMETHYLATED GBM PATIENTS (NDU) & RECURRENT GBM PATIENTS



Source: Kazia Therapeutics Limited.

Summary of OS in Newly Diagnosed, Unmethylated GBM

GBM-AGILE tested paxalisib in patients with newly diagnosed, MGMT-unmethylated GBM—a group that responds poorly to current therapy. In GBM, MGMT promoter methylation reduces the tumor’s MGMT repair enzyme, making temozolomide more effective and linked to longer survival, whereas unmethylated tumors retain MGMT activity, respond less to temozolomide, and have poorer outcomes. Results are summarized in Figure 6.

The main (primary) analysis compared paxalisib with a large “cumulative” control group and did not reach statistical significance. A preplanned secondary analysis that compared paxalisib only with patients treated during the same time period (“concurrent” controls) showed a clear trend to longer survival. This pre-specified secondary analysis comparing paxalisib with concurrent temozolomide controls showed a consistent ~1.5 to 3.6-month improvement in median overall survival (mOS). By contrast, the broad, protocol-wide analysis from the start to the end of the study period showed an ≈1-month difference, highlighting greater benefit in the concurrent-control comparisons.

Figure 6

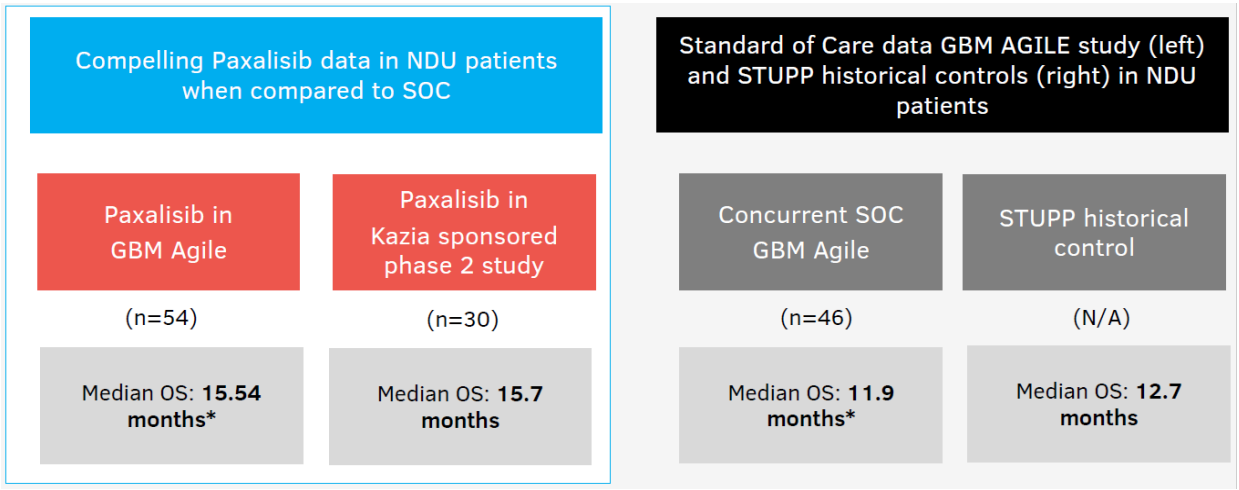
PAXALISIB AND GBM-AGILE SUMMARY OF OS IN NDU PATIENTS: PRIMARY AND SECONDARY ANALYSES

	Primary OS analysis	Prespecified Secondary OS analysis		
		Main analysis	Sensitivity analysis I	Sensitivity analysis II
Method	Bayesian piecewise exponential model	Frequentist methods and standard Kaplan-Meier curve	Frequentist methods and standard Kaplan-Meier curve	Frequentist methods and standard Kaplan-Meier curve
Population	ITT	ITT	ITT	ITT
Number for analysis	Paxalisib: 54 Cumulative control: 75	Paxalisib: 54 Concurrent control: 46	Paxalisib: 54 Concurrent control: 46	Paxalisib: 54 Concurrent control: 46
Median OS	Paxalisib: 14.77 Cumulative control: 13.84	Paxalisib: 15.54 Concurrent control: 11.89	Paxalisib: 15.54 Concurrent control: 11.70	Paxalisib: 14.39 Concurrent control: 11.89
Hazard ratio	0.89 (0.54, 1.38)	0.76 (0.45, 1.26) 24% hazard reduction	0.67 (0.40, 1.13) 33% hazard reduction	0.73 (0.45, 1.18) 27% hazard reduction

Source: Kazia Therapeutics Limited.

In GBM-AGILE, the prespecified secondary analysis for paxalisib (n=54) showed median overall survival of 15.54 months, closely aligning with Kazia's earlier Phase 2 study (15.7 months, n=30). For context, GBM-AGILE's concurrent temozolomide arm reported 11.9 months (n=46), and the widely cited Stupp historical control is 12.7 months. While not head-to-head, the convergence of two independent paxalisib readouts around ~15-15.7 months versus ~11.9-12.7 months for controls suggests a consistent survival advantage in this high-need subgroup; clinician feedback indicates that an improvement of ~2 months in median overall survival can be decision-influencing. A summary of the primary and secondary analysis is provided in Figure 7.

Figure 7
CONSISTENT MOS IN NDU GBM



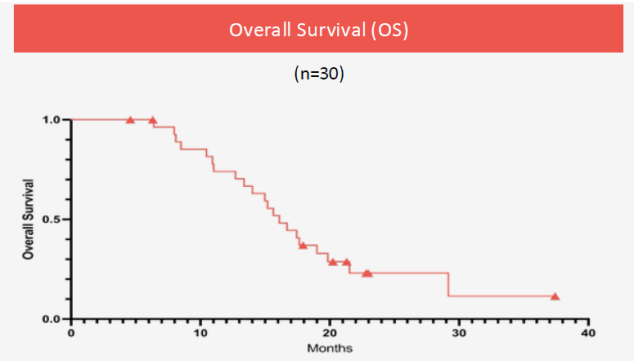
Source: Kazia Therapeutics Limited.

The drug was generally well tolerated with no new safety signals. In newly diagnosed, MGMT-unmethylated GBM, paxalisib's side-effect profile was consistent with PI3K inhibitors and no new safety concerns were seen. The most common events on paxalisib (n=52) were high blood sugar (65%), fatigue (60%), low lymphocytes (50%) and low white blood cells (40%), plus nausea (38%), reduced appetite (37%), diarrhea (37%), mouth sores (33%), and constipation/low platelets/rash (each 31%). By comparison, the concurrent standard-of-care arm (n=44) most often had fatigue (48%), nausea (43%), constipation (39%), and vomiting (25%). Overall, events were generally manageable and aligned with the expected class effects of PI3K pathway inhibition.

Paxalisib in GBM Phase 2 Clinical Study

Figure 8 (page 18) shows overall survival from Kazia's Phase 2 study of paxalisib in newly diagnosed, MGMT-unmethylated glioblastoma (n=30). The median overall survival was 15.7 months (95% CI 11.1-19.1). For context, the often-cited historical benchmark for standard therapy is 12.7 months (Hegi et al., 2005). These are not head-to-head data, but the Kaplan-Meier curve and median suggest survival with paxalisib in this small study was longer than the historical control used for comparison.

Figure 8
PAXALISIB IN GLIOBLASTOMA PHASE 2 CLINICAL STUDY



Median OS: 15.7 months (11.1-19.1)

Historical mOS for existing therapy: 12.7 months (Hegi et al. 2005)

Source: Kazia Therapeutics Limited.

Paxalisib in NDU GBM Phase 3 Planning Update

In October 2025, Kazia said it will request a follow-up Type C meeting with FDA to discuss overall survival findings in newly diagnosed, unmethylated GBM (NDU GBM) and to seek feedback on a conditional approval path aligned with the Oncology Center of Excellence's Project FrontRunner. Under this approach, Kazia would initiate a randomized Phase 3 confirmatory study before submitting an NDA.

The briefing package will center on overall survival as the primary endpoint, consistent with FDA's draft guidance that prioritizes overall survival in oncology. Kazia plans to present survival analyses, safety, and the proposed confirmatory trial design. As disclosed previously, a prespecified secondary analysis in up-front unmethylated GBM showed median overall survival of 15.54 months with paxalisib (n=54) versus 11.89 months with standard of care (n=46).

This represents an evolution from the December 2024 Type C feedback, which pointed toward a traditional approval pathway. Kazia is now pursuing an overall survival-driven, FrontRunner-aligned strategy aimed at conditional approval in first-line GBM, with the confirmatory Phase 3 starting prior to filing. Final protocol details, enrollment targets, timelines, and Contract Research Organization (CRO) engagement remain subject to FDA discussion and financing; the Company continues to explore capital and strategic partnerships (including NCI/NIH-funded groups) to support execution.

Primary Market Research Outcomes

Company-sponsored market research with 15 neuro-oncologists performed in 2021 indicated that for newly diagnosed, unmethylated GBM, physicians would consider adopting a new therapy if it delivers a minimum median overall survival gain of two to three months, with an optimal target near seven months. In stated-intent testing, adoption of a paxalisib-like product was projected to be high even at the minimum benefit and very high if the optimal benefit is achieved, assuming FDA approval. Thus, given the unmet need in this subgroup, clinicians would use a brain-penetrant option with a modest but reliable survival improvement, with uptake rising as the effect size increases.

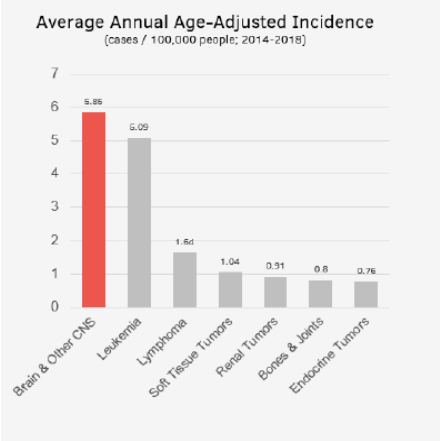
GBM Market Dynamics

The increased incidence of GBM, driven by aging populations and improved diagnostics, coupled with high unmet medical needs, positions this market as a prime target for innovative therapies. Despite the long-standing absence of new approvals—over 20 years since temozolomide—advances in molecular profiling, biomarker-driven trials, and regulatory incentives (such as FDA Fast Track and Orphan Designations) are opening pathways for innovative agents like paxalisib to secure a significant share of this expanding market.

Childhood Brain Cancer

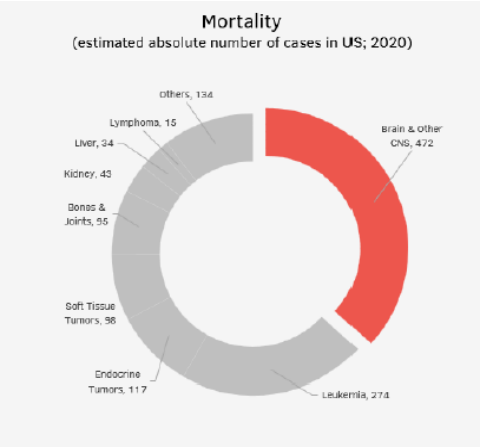
Brain tumors are the leading cause of cancer death in U.S. children and teens and currently represent about a third of all childhood cancer deaths (Figures 9 and 10). Outcomes differ by type and age, where many kids with low-grade glioma live for years, though treatment can be long. By contrast, **diffuse midline glioma (DMG)**—which includes Diffuse Intrinsic Pontine Glioma (DIPG)—has survival measured in months.

Figure 9
BRAIN CANCER IS MOST COMMON MALIGNANCY OF CHILDHOOD



Source: Kazia Therapeutics Limited.

Figure 10
BRAIN CANCER REPRESENTS ABOUT 1/3 OF CHILDHOOD CANCER DEATHS



Source: Kazia Therapeutics Limited.

Treatment Landscape

Standard of care is surgery when possible, followed by radiation and multi-drug chemotherapy; targeted drugs are added only when there is a clear, druggable mutation. Because the blood-brain barrier excludes many medicines, CNS-penetrant agents matter. Long-term side effects are common, so families and clinicians look for options that work without unnecessary toxicity. Recent estimates place the global pediatric brain-tumor treatment market at between $1.3-1.7 billion, with mid- to high-single-digit growth expected over the next several years (Source: The Business Research Company, *Pediatric Brain Tumors Global Market Report 2025*).

Diffuse midline glioma (DMG) arises in midline structures (pons, thalamus, spinal cord), infiltrates normal tissue, and is rarely resectable, with median survival being ~9-11 months. The WHO now classifies these tumors as “diffuse midline glioma, H3 K27-altered,” most often driven by the H3 K27M alteration. In medulloblastoma, where molecular subgroups guide therapy, pediatric glioma trials increasingly test targeted agents (for example, MAPK-pathway drugs) and rational combinations with radiation or immunotherapy.

In pediatric low-grade glioma (pLGG), the FDA has cleared two BRAF-pathway options: tovorafenib (Ojemda) for patients ≥6 months with relapsed or refractory pLGG harboring a BRAF fusion/rearrangement or BRAF V600 mutation, and dabrafenib + trametinib for children ≥1 year with pLGG and a BRAF V600E mutation who require systemic therapy. Tissue-agnostic TRK inhibitors extend this precision approach to rare fusion-driven tumors that can occur in the brain: larotrectinib is approved for adult and pediatric NTRK-fusion cancers, and entrectinib covers pediatric patients older than 1 month with NTRK-fusion solid tumors. In neuro-oncology-adjacent care for children with NF1 and symptomatic, inoperable plexiform neurofibromas, selumetinib (Koselugo) now includes patients ≥1 year. On August 6, 2025, the FDA granted accelerated approval to dordaviprone (ONC201), Modeyso, for H3 K27M-mutant diffuse midline glioma in patients 1 year and older after prior therapy; continued approval requires confirmatory trials.

Despite these gains, the greatest unmet need remains high-grade glioma and DMG/DIPG, where effective targeted options are still limited. This report focuses on CNS-penetrant agents with validated targets and safety profiles suitable for growing children. Programs may also benefit from Rare Pediatric Disease status, which can lead to a tradable Priority Review Voucher. Paxalisib crosses the blood-brain barrier, inhibits the PI3K pathway, and is being studied in aggressive pediatric brain cancers, including DMG, aligning with the field's direction where options are limited.

Paxalisib Pediatric Program: Three Ongoing Paths In Childhood Brain Cancer

Kazia is advancing a pediatric program for paxalisib across three disease areas: diffuse midline gliomas (DMG/DIPG), atypical teratoid/rhabdoid tumors (AT/RT), and broader PI3K/mTOR-activated childhood cancers, as summarized in Figure 11 and described below.

Figure 11
SUMMARY OF PAXALISIB IN CHILDHOOD BRAIN CANCER

	Diffuse Midline Gliomas (DMG, DIPG)	Atypical Teratoid / Rhabdoid Tumors (AT/RT)	Advanced Childhood Cancer (PI3K/mTOR activated)
Preclinical Research	*Positive preclinical data in combination with ONC201*	*Positive preclinical data as monotherapy and in combination (AACR 2022, 2023, 2024)*	*Research proposals under discussion*
Clinical Trials	*Phase 1 monotherapy clinical trial at St Jude Children's Research Hospital completed*	*Clinical trial design/execution discussions ongoing between PNOC and Kazia*	*Additional clinical trial opportunities under discussion for medulloblastoma and HGG*
	PNOC022, Phase 2 clinical trial in combination with ONC201, ongoing		*Phase 2 clinical trial in combination with chemotherapy for treatment of high-risk malignancies commenced 2024*
Regulatory Interaction	*Orphan Drug Designation (ODD) and Rare Pediatric Disease Designation (RPDD) granted by FDA in Aug 2020*	*ODD and RPDD granted by FDA in June and July 2022, respectively*	*Regulatory strategy under discussion*

Source: Kazia Therapeutics Limited.

- *DMG/DIPG.* A fast-growing brain tumor that starts in the "midline" parts of the brain (like the pons, thalamus, or spinal cord), DMG spreads into nearby brain tissue, so surgery usually is not possible, and outcomes are poor even with treatment. A type of DMG, DIPG begins in the pons (brainstem), affects mostly children, cannot be removed by surgery, and typically has a short survival despite radiation. In the U.S., there are roughly 300 new pediatric DIPG cases each year, and an estimated ~200-400 pediatric DMG cases overall, based on NCI/NIH guidance and the American Brain Tumor Association. Paxalisib has shown positive preclinical activity in DMG/DIPG, including in combination with ONC201. A Phase 1 monotherapy study at St. Jude Children's Research Hospital has been completed, and the multi-center PNOC022 Phase 2 trial combining paxalisib with ONC201 is ongoing. This program already carries FDA Orphan Drug Designation and Rare Pediatric Disease Designation, both granted in August 2020.

    - *Recent Approval for DMG from Jazz Pharmaceuticals.* The FDA recently approved therapy for DMG is dordaviprone (ONC201), brand name Modeyso from Jazz Pharmaceuticals. It received accelerated approval on August 6, 2025 for adults and children ≥1 year with H3 K27M-mutant diffuse midline glioma whose disease has progressed after prior therapy—the first FDA-approved systemic treatment for this tumor type. As an accelerated approval, continued approval may depend on confirmatory evidence from ongoing studies.

- *AT/RT.* An atypical teratoid/rhabdoid tumor (AT/RT) is a fast-growing CNS cancer. In the U.S., pediatric AT/RT is very rare, with roughly 50 to 80 new cases per year (often summarized as fewer than 100 annually), corresponding to an incidence of ~0.9 per million children. Preclinical data in AT/RT support activity as monotherapy and in combinations, with results presented at American Association for Cancer Research (AACR) in 2022, 2023, and 2024. Kazia and the Pacific Pediatric Neuro-Oncology Consortium (PNOC) are in active discussions on clinical trial design and execution, and the program holds FDA Orphan Drug Designation and Rare Pediatric Disease Designation, granted in June and July 2022, respectively.

- *PI3K/mTOR-activated advanced pediatric cancers.* For PI3K/mTOR-activated advanced pediatric cancers, research proposals are under review, additional clinical opportunities are being discussed for medulloblastoma and high-grade glioma, and a Phase 2 chemotherapy-combination study for high-risk malignancies began in 2024, with the regulatory plan under development.

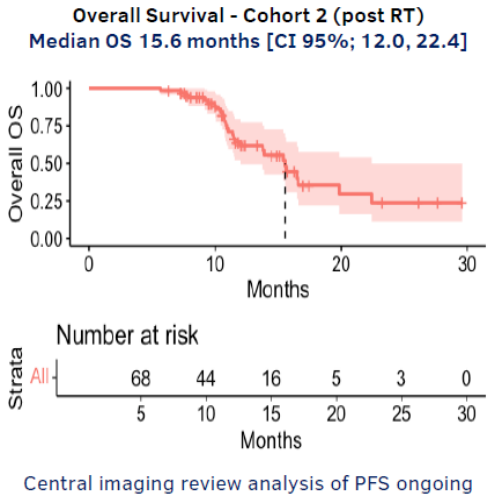
Kazia holds pediatric FDA designations for two indications—DIPG/DMG and AT/RT—and is participating in PNOC022, a Phase 2 adaptive platform in DMG (drug-supply role) that establishes clinical feasibility for paxalisib in pediatrics. AT/RT is next to enter the clinical phase, with design and execution discussions ongoing with PNOC, backed by multi-year preclinical work. Additionally, an Australian cooperative-group program is evaluating PI3K/mTOR-activated pediatric cancers to explore expansion into other high-need tumors (OPTIMISE). Taken together, this gives Kazia multiple pediatric opportunities and several potential near-term catalysts in childhood brain cancer.

Paxalisib In Diffuse Midline Glioma (DMG): ISPNO 2024 Update

The PNOC Phase 2 study enrolled 68 biopsy-confirmed DMG patients (median age ~9 years) between November 2021 and June 2023. In the post-radiation cohort (Cohort 2), median overall survival was 15.6 months (95% CI 12.0-22.4) from diagnosis—longer than the historical 9-11 months typically seen in DMG (Figure 12). In the recurrent cohort (Cohort 3; n=30, treated with paxalisib plus radiation), median overall survival was 8.7 months. The most common grade ≥3 treatment-emergent events included low neutrophils, mucositis, and less frequently colitis, drug-reaction with eosinophilia/systemic symptoms, low lymphocytes, hyperglycemia, and low potassium. A blinded central review of progression-free survival (PFS) is ongoing, with additional PK/biomarker analyses and a clinical update expected in CY2025.

Paxalisib in pediatric DMG holds FDA Orphan Drug and Rare Pediatric Disease designations (August 2020), which can provide incentives such as seven years of U.S. exclusivity upon approval and eligibility for a Priority Review Voucher that can be sold to generate non-dilutive funding.

Figure 12
PAXALISIB IN DIFFUSE MIDLINE GLIOMAS FOLLOW-UP PHASE 2 DATA PRESENTED AT ISPNO 2024 ANNUAL MEETING



Source: Kazia Therapeutics Limited.

Brain Metastases

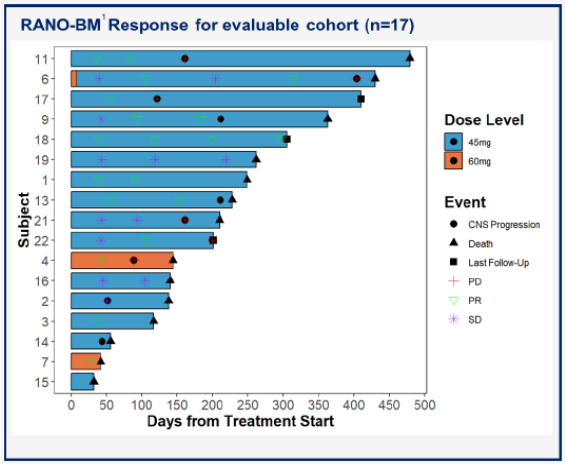
Brain metastases occur when cancer spreads from another part of the body to the brain and are a common and difficult-to-treat complication.

Paxalisib in Brain Metastases: Interim Phase 1 (MSKCC): Activity with Radiation Therapy (NCT04192981)

A Phase 1 trial sponsored by Memorial Sloan Kettering Cancer Center (MSKCC) (NCT04192981) tested paxalisib in combination with brain radiotherapy in patients with PI3K-altered solid-tumor brain metastases and showed encouraging activity. On the strength of safety and early responses, the study closed early to further accrual.

In August 2022, Stage 1 data were first presented at the CNS Clinical Trials and Brain Metastases Conference where all nine efficacy-evaluable patients showed a clinical response by Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) criteria, with breast cancer as the most common primary. Based on these interim results, the FDA granted Fast Track designation in July 2023 for paxalisib in combination with radiation in this setting. In February 2024, the study was concluded early on the strength of positive Stage 2 safety findings and promising clinical responses to date. Preliminary updates were then presented at two scientific meetings in 2024, (American Society for Radiation Oncology [ASTRO] and Society for Neuro-Oncology [SNO} Annual Meeting).

Figure 13
PAXALISIB IN BRAIN METASTASES INTERIM PHASE 1



Source: Kazia Therapeutics Limited.

This MSKCC Phase 1 study tested daily paxalisib given concurrently with brain radiotherapy in patients with solid-tumor brain metastases harboring PI3K-pathway alterations. The trial met its primary goal by identifying a maximum tolerated dose (MTD) of 45 mg once daily oral dose, which was generally well tolerated. Among the 17 evaluable patients (shown in Figure 13), more than two-thirds treated at the maximum tolerated dose (MTD) achieved an intracranial response by RANO-BM, comparing favorably with historical whole-brain radiotherapy response rates of ~20-40%. These data support that paxalisib can be safely combined with radiation and may add meaningful activity in this genotype-selected setting.

Kazia is working with key investigators and the FDA to define the next clinical study. While early and non-randomized, the signal is consistent with CNS activity for paxalisib in combination with radiation and provides a rationale for a follow-on trial in brain metastases. The investigators plan to build on this by testing longer PI3K inhibition across treatment windows (neoadjuvant, adjuvant, and maintenance), pairing with appropriate systemic therapies, and exploring use in other CNS tumors with the same pathway drivers, including potential combinations with stereotactic radiosurgery.

Market Dynamics: Brain Cancers and Beyond

Paxalisib's advanced clinical development demonstrates its potential to serve broad indications. In GBM, the drug's ability to cross the blood-brain barrier and its promising median overall survival benefits position it as a potential new standard of care. The recent GBM-AGILE trial's results, showing a median overall survival increase of nearly four months in a key patient subgroup, support ongoing FDA dialogues for pivotal registration. The broader oncology market for CNS tumors, including metastatic brain cancers, diffuse midline gliomas, and primary CNS lymphomas, is also expanding rapidly as research validates targeting the PI3K pathway and leveraging CNS penetrance. Specifically, the Orphan Drug and Fast Track designations improve regulatory prospects and market access prospects.

Expanding Therapeutic Utility

The Company's strategic expansion beyond brain cancer leverages paxalisib's unique properties across multiple oncology indications. Preclinical research with QIMR Berghofer (further described on page 31) has demonstrated that paxalisib combination with immunotherapy produces consistent efficacy signals in triple-negative breast cancer (TNBC) models, including reductions in tumor volume, metastases, and inflammatory markers, while reinvigorating immune cells, as described in the accompanying section.

Furthermore, the Parkinson's disease research initiative (Michael J. Fox Foundation [MJFF] grant, described on page 32), represents potential first-in-class application of PI3K pathway modulation in neurodegenerative diseases, exploring whether pathway dysregulation contributes to neurodegeneration. This research, supported by non-dilutive funding, could unlock significant additional market opportunities beyond oncology.

Advanced Breast Cancer

Breast cancer is the most common cancer in women worldwide, with more than 2.3 million cases each year. Incidence has risen about 1% annually over the past decade, with a faster increase in women under 50. In the U.S., more than 300,000 new invasive cases are expected this year, with about 1 in 8 women developing invasive breast cancer over a lifetime (Figure 14) and 1 in 43 women dying from breast cancer. The global breast cancer drugs market was $29.26 billion in 2022 and is projected to reach $58.69 billion by 2030 (CAGR 9.1%) (Source: Grand View Research's *Breast Cancer Drugs Market Size, Share & Trends Analysis Report, 2022-2030*, 2023).

Figure 14
BREAST CANCER RISK BY AGE (10-YEAR RISK UNLESS NOTED)

Current age	Diagnosed with invasive breast cancer	Dying from breast cancer
20	0.1% (1 in 1,344)	<0.1% (1 in 19,247)
30	0.5% (1 in 198)	<0.1% (1 in 2,192)
40	1.6% (1 in 62)	0.1% (1 in 723)
50	2.5% (1 in 41)	0.3% (1 in 348)
60	3.6% (1 in 28)	0.5% (1 in 217)
70	4.2% (1 in 24)	0.7% (1 in 141)
80	3.1% (1 in 32)	1.0% (1 in 103)
Lifetime risk	**13.1% (1 in 8)**	**2.3% (1 in 43)**

Source: DevCan, Version 6.7.5., American Cancer Society Surveillance and Health Equity Science.

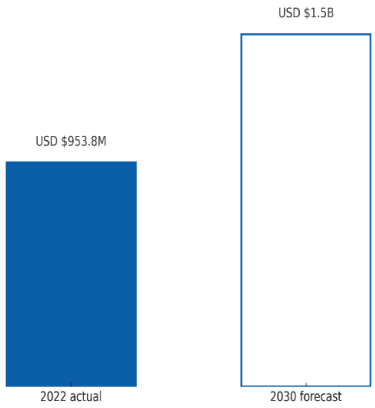
HER2-positive tumors overexpress or amplify the HER2 receptor and often respond to HER2-targeted therapies; HER2-negative tumors lack this driver and are managed with chemotherapy, immunotherapy, PARP inhibitors for eligible BRCA-mutated disease, or other non-HER2 approaches, with a HER2-low subset that may benefit from certain antibody-drug conjugates (ADCs). Despite major advances in HER2-positive disease, outcomes for HER2-negative subtypes—especially triple-negative breast cancer (TNBC)—remain poor, with high relapse and metastasis rates and only modest survival benefits from current options. Addressing this persistent clinical gap is central to Kazia's breast-cancer strategy.

Drivers of Recurrence and Metastasis

Advanced breast cancer often recurs or spreads because tumors adapt on several fronts. They lower antigen presentation and sometimes carry fewer recognizable neoantigens, which diminishes T-cell recognition. The tumor microenvironment becomes immunosuppressive, leaving T-cells exhausted and checkpoint signals persistently active. In parallel, subsets of cells adopt stem-like programs that tolerate therapy and repopulate disease. Tumors also show lineage flexibility, including shifts toward epithelial-to-mesenchymal behavior, which reduces immunogenicity and supports invasion. Together, these adaptations limit the durability of current treatments and support the rationale for combination approaches that restore immune visibility and target resistant cell states.

Unmet Need and Market Opportunity

Figure 15
TNBC MARKET GROWTH FORECAST



Source: National Institutes of Health (NIH): Current and future burden of breast cancer: Global statistics for 2022 and 2030.

TNBC is the most aggressive breast-cancer subtype, representing about 15%-20% of all cases and carrying a high unmet need. The TNBC therapeutics market was valued at roughly $953.8 million in 2022 and is projected to exceed $1.5 billion by 2030 (Figure 15), implying a compound annual growth rate of about 5.8% and emphasizing both the scale of impact and the commercial relevance of effective new therapies. This growth reflects rising incident case recognition, broader testing and guideline-driven use of newer therapies, expansion of treatment into both early-stage and metastatic settings, and continued pipeline activity that targets TNBC's distinct biology.

Current Challenges with Immunotherapy in Advanced Breast Cancer

Checkpoint inhibitors have shown limited benefit in many advanced breast cancers because two reinforcing problems persist: cancer stem cells (CSCs) and exhausted T-cells. CSCs are slow-cycling, therapy-resistant, and able to shift phenotype, which helps tumors seed and maintain metastases while staying "invisible" to the immune system. At the same time, chronic tumor inflammation drives T-cell exhaustion, characterized by inhibitory receptors such as PD-1, LAG-3, and TIM-3, which weakens antitumor responses. The result is a rising metastatic load and a steadily declining immune system.

Rationale for Combination Approaches

Epigenetic agents can "reset" tumor and immune cell programs, pushing CSCs from mesenchymal, immune-evasive states toward more epithelial, immune-visible states and priming exhausted T-cells for PD-1/PD-L1 reinvigoration. When this reprogramming is paired with antibodies that block inhibitory checkpoints, T-cells recover function and tumor burden falls in preclinical models.

Where PI3K/mTOR Inhibition Fits

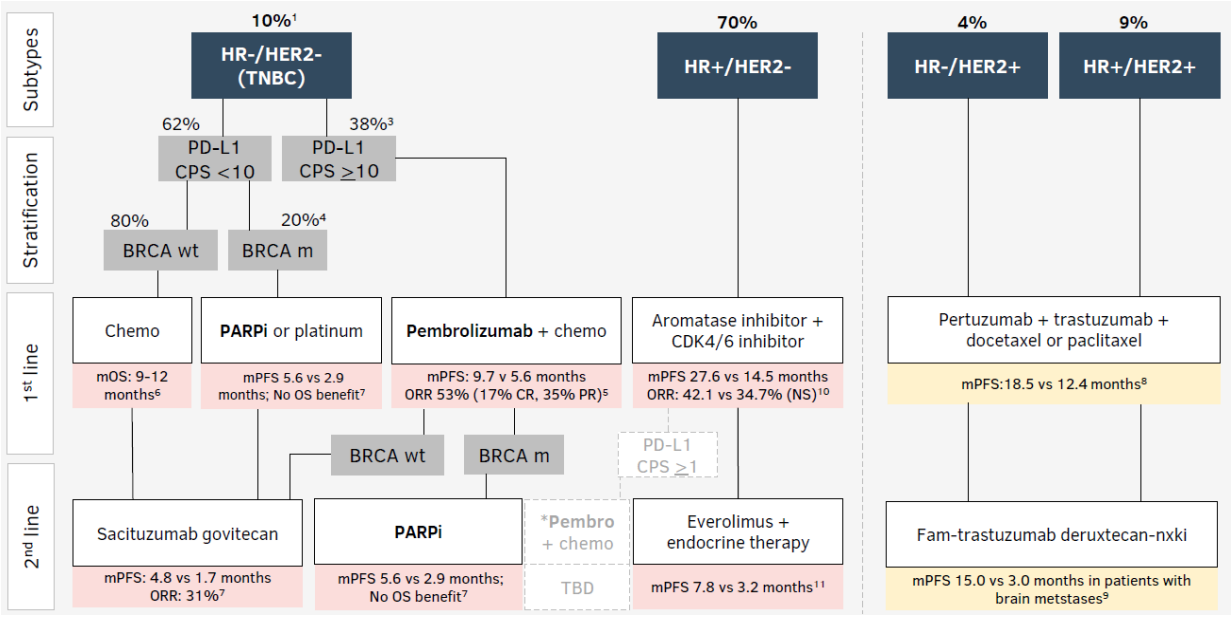
Targeting the PI3K/mTOR axis—the pathway that supports inflammatory signaling, survival, and stemness—may amplify these effects. Inhibition can suppress pro-inflammatory "switch" signatures, induce viral-mimicry signals that increase tumor immunogenicity, make both bulk tumor cells and CSCs more visible to the immune system, and help re-educate the CSC epigenome. In parallel, it can support T-cell reinvigoration, creating a mechanistic basis for combining a brain-penetrant PI3K/mTOR inhibitor like paxalisib with epigenetic modulators and checkpoint antibodies in hard-to-treat metastatic breast cancer.

Current Treatments and Rationale for Paxalisib Combinations

Figure 16 summarizes current treatment paths for advanced breast cancer by subtype and line of therapy. Roughly 10% of cases are TNBC, about 70% are hormone-receptor positive/HER2-negative (HR+/HER2-), and the remainder are HR2-/HER2+ or HR2+/HER2+.

Figure 16

ADVANCED BREAST CANCER TREATMENT LANDSCAPE



Source: Kazia Therapeutics Limited.

In TNBC, first-line care is typically chemotherapy, with pembrolizumab added when tumors express PD-L1. Patients with **BRCA mutations** may receive PARP inhibitors, and sacituzumab govitecan is a frequent second-line option. HR+/HER2- disease usually starts with endocrine therapy plus a CDK4/6 inhibitor, then moves to later-line combinations, such as everolimus with endocrine therapy. HER2-positive disease begins with pertuzumab + trastuzumab plus a taxane, with antibody-drug conjugates like trastuzumab deruxtecan used in later lines. Across these settings, median progression-free survival remains modest for many patients, and outcomes are particularly limited in TNBC and in cases with brain involvement.

Kazia's approach is to layer paxalisib, a brain-penetrant PI3K inhibitor, onto these standard regimens to address resistance biology that current therapies do not fully control. Preclinical work shows synergy when paxalisib is combined with checkpoint inhibitors and with PARP inhibitors, and early clinical experience in TNBC has demonstrated rapid reductions in circulating tumor cells after one cycle. If confirmed in larger studies, paxalisib-based combinations could enhance depth and durability of response in TNBC and potentially extend to other subtypes, with particular relevance where the risk of metastasis is high.

Paxalisib: Target Product Profile

Kazia's paxalisib is a dual inhibitor of PI3K and mTOR designed for oral administration, typically given once daily, while pembrolizumab, an anti-PD-1 checkpoint inhibitor used in combination with paxalisib, is delivered intravenously following standard schedules alongside chemotherapy. The mechanism of action involves inhibiting both PI3K and mTOR pathways, which leads to reprogramming the tumor microenvironment, reducing immune suppression, and enhancing T-cell infiltration and activation. This dual therapy aims to overcome immunotherapy resistance, particularly in patients with advanced or metastatic Stage IV TNBC.

Paxalisib is positioned for first-line therapy targeting adults with advanced TNBC, with ongoing Phase 1b clinical trials sponsored by Kazia and more trials anticipated. The intended benefit is improved tumor response rate, progression-free survival, and overall survival for patients with limited treatment options.

Paxalisib distinguishes itself as the only oral dual PI3K/mTOR inhibitor in clinical development for TNBC, addressing key mechanisms of immunotherapy resistance and demonstrating synergistic activity with pembrolizumab in preclinical models. It also has the potential to cross the blood-brain barrier, indicating promise as a therapy for brain metastases. The commercial opportunity is significant, centered on high unmet need in Stage IV TNBC, with potential label expansion to earlier stage TNBC and other solid tumors resistant to checkpoint inhibitors, including HER2-negative breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, and colorectal cancer.

Paxalisib: Differentiation and Root-Biology Approach

Paxalisib's clinical positioning goes beyond being just another targeted agent, it is designed as a root-biology therapy, directly targeting persister cells underlying resistance and metastatic dissemination, while also revitalizing anti-tumor immunity. Consequently, paxalisib aims to enhance both the efficacy and durability of checkpoint and PARP inhibitor regimens. It remains the only oral dual PI3K/mTOR inhibitor in clinical development for TNBC and uniquely offers consistent brain penetration, positioning it for potential use in CNS/brain metastasis indications as well.

Paxalisib in TNBC

New preclinical and translational work in TNBC strengthens the case for dual PI3K/mTOR inhibition with paxalisib. The global TNBC treatment market is estimated at $670.5 million as of 2024 and is forecast to reach $1.04 billion by 2034 (CAGR 4.6%) (Source: Fact.MR. *Triple-Negative Breast Cancer Treatment Market Outlook, 2024-2034*, 2024).

In vitro, paxalisib slowed proliferation and migration and shifted cells toward a less invasive epithelial state, while reducing markers tied to metastasis-initiating and drug-resistant phenotypes, including a 67% drop in the CD44^high/CD24^low ratio and lower ABCB5, ALDH1, SNAIL, and persister-cell programs, such as NF-κB p65, FOXQ1, NNMT, and NRF2; similar marker decreases were seen in treated 4T1 tumors in vivo. Paxalisib also increased "immune visibility." In circulating tumor cells from patients with TNBC, paxalisib reduced IL-6 protein by about 72% in ABCB5+/EpCAM+ cells and induced a viral-mimicry signature in TNBC lines, most notably upregulating GBP2. These immune-stimulatory effects were specific to dual PI3K/mTOR inhibition rather than PI3K-only blockade.

Monotherapy did not shrink primary tumors in the 4T1 TNBC model, but combinations mattered. Kazia identified 7.5 mg/kg as the optimal oral dose with a favorable toxicity profile. Pairing paxalisib with anti-PD-1 reduced systemic inflammatory features, cut extramedullary hematopoiesis, lowered circulating tumor cells by an order of magnitude, and limited lung metastases. Adding Abraxane to paxalisib + anti-PD-1 produced the largest primary-tumor reductions without added toxicity.

Mechanistically, the data place paxalisib upstream of EZH2, disrupting both the classic repressive p85β-EZH2-H3K27me3 axis and a non-catalytic EZH2-NF-κB program that drives inflammatory, drug-resistant states. Also proposed is PIK3R2 (p85β) as a potential precision biomarker, with higher expression linked to worse outcomes in TNBC, pointing to a way to enrich future studies. This is preclinical/translational, but it supports paxalisib's differentiation as a brain-penetrant dual PI3K/mTOR inhibitor that can reprogram aggressive TNBC biology and remodel the tumor-immune microenvironment. The clearest clinical path is in combinations, especially with checkpoint inhibitors and, where appropriate, chemotherapy. The EZH2 link and PIK3R2 signal provide testable hypotheses for patient selection and trial design.

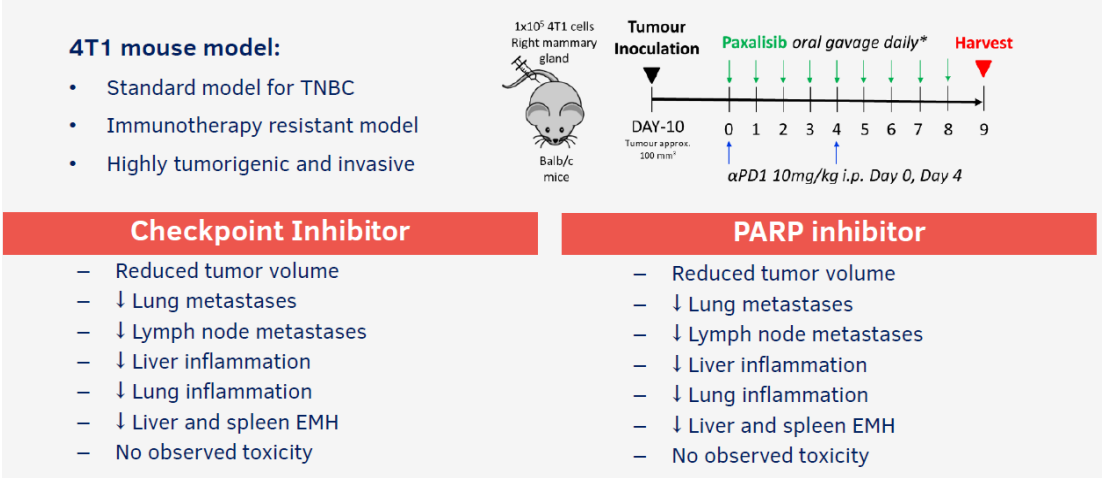
Mechanism of Action, Immune Modulation, and Preclinical Rationale

Paxalisib is a brain-penetrant, oral, once-daily dual inhibitor of PI3K and mTOR, specifically designed to address mechanisms of cancer resistance and immune evasion. Collaborative research with QIMR Berghofer Medical Research Institute (described on pages 31-32) explains how paxalisib alters the tumor immune microenvironment: reinvigorating cytotoxic T-cells, reducing immune suppression, and enhancing tumor susceptibility to immunotherapy.

Preclinical models of immunotherapy-resistant TNBC demonstrated that paxalisib, both alone and in combination with checkpoint (pembrolizumab) or PARP (olaparib) inhibitors, significantly diminishes tumor burden and metastatic spread (Figure 17). Mechanistically, this is linked to the suppression of inflammatory signaling (e.g., via decreased NF-κB and IL-6 activity), reduced metastasis-initiating cell populations, inhibition of epithelial-mesenchymal transition, and increased tumor-infiltrating lymphocytes.

Figure 17

PAXALISIB COMBINATIONS SHOW CONSISTENT EFFICACY



Source: Kazia Therapeutics Limited.

PI3K/mTOR Inhibition and Drug Resistance

PI3K/mTOR inhibition by paxalisib targets multiple mechanisms that drive metastasis and resistance to immunotherapy in breast cancer. It suppresses aggressive, metastasis-initiating cancer stem cells and reverses epithelial-mesenchymal transition (EMT), which limits tumor spread. This inhibition also reduces inflammation by blocking IL-6 and NF-κB signaling pathways that promote tumor survival. Additionally, it reprograms repressed T-cells epigenetically and increases infiltration of immune cells into the tumor microenvironment, helping to overcome immune evasion. By enhancing tumor immune visibility through upregulation of viral mimicry genes, the cancer becomes more recognizable to the immune system. In combination with immunotherapy, PI3K/mTOR inhibition not only reduces the primary tumor burden but also prevents metastatic progression. This multifaceted approach highlights paxalisib's potential to improve treatment outcomes in patients with advanced or resistant breast cancer.

Paxalisib Differentiation: Clinical Profile and Comparative Advantages

Figure 18 (page 28) provides a comparative overview of paxalisib and other relevant PI3K inhibitor programs for breast cancer. Paxalisib is highlighted as a best-in-class pathway inhibitor due to its potent, selective, and oral once-daily dosing with no unexpected toxicities. Uniquely, it offers pan-PI3K inhibition with designed modest mTOR activity, which is essential for blocking both cancer cell proliferation and migration. Another significant differentiator is paxalisib's robust brain penetration, granting potential access to CNS metastases, a common problem in advanced breast cancer.

The right side of Figure 18 compares paxalisib to leading alternatives, including Novartis's Alpelisib and Celcuity's Gedatolisib. Unlike Alpelisib (limited to PI3Kα only, intravenous administration, and associated with severe hypersensitivity), paxalisib targets both PI3K and mTOR pathways, is orally administered, and lacks notable safety concerns in over 550 adult and pediatric patients across multiple clinical phases and expanded access programs. Gedatolisib, which also inhibits PI3K/mTOR, is associated with grade 4 neutropenia when combined with palbociclib and demonstrates only partial brain penetration. By contrast, paxalisib excels in both safety and CNS delivery. This comparative analysis underscores paxalisib's favorable profile for advanced and metastatic breast cancer, especially where brain involvement and multi-pathway resistance are factors.

Figure 18

PAXALISIB: DESIGNED TO BE BEST IN CLASS PI3K PATHWAY INHIBITOR WITH MODEST mTOR ACTIVITY

Paxalisib

- Potent, selective, oral, once a day dosing, no unexpected toxicities
- Pan PI3K inhibitor activity and modest mTOR, by design
  - Dual targeting required to inhibit cancer cell proliferation and migration in vitro
- Robust brain penetration
- More than 550 adult and pediatric patients have received paxalisib through phase 1-3 clinical trials or expanded access programs (8 clinical trials ongoing)

Relevant marketed or active clinical PI3K inhibitor programmes

	Paxalisib (Kazia)	Alpelisib (Novartis)	Gedatolisib (Celcuity)	WXFL-10030390 (Jiatan)[2]
Targets	Pan-PI3K / mTOR	PI3Kα only	Pan-PI3K / mTOR	PI3K / mTOR
Development stage	P3 (GBM) P1 (TNBC & HER2- BC)	Marketed (HER2- BC)	P3 (HER2- BC)	P2 in China (solid tumors)
Safety	No unexpected toxicities	Severe Hyper-sensitivity warning[3]	Grade 4 neutropenia reported in combo with palbociclib[1]	Unknown
RoA	Oral (QD)	IV	IV	Oral
Brain penetration	Yes	Poor	Partial	Unknown

Source: Kazia Therapeutics Limited.

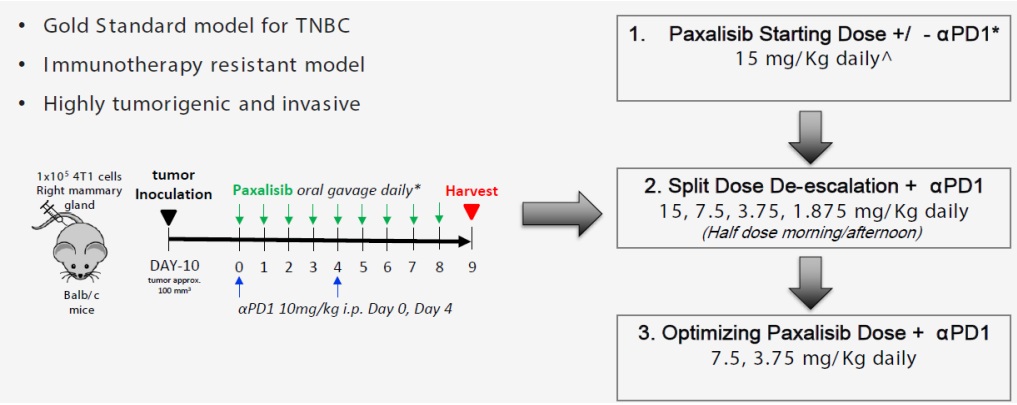
Paxalisib Administration Protocol in 4T1 TNBC Preclinical Model

Kazia employed a rigorous protocol for evaluating paxalisib in a preclinical model of TNBC using the 4T1 cell line in Balb/c mice, which is recognized as a gold standard for studying aggressive and immunotherapy-resistant TNBC. Tumors were established by inoculating $1x10^5$ 4T1 cells into the right mammary gland, with experimental treatments commencing once tumors reached approximately 100 mm^3. Paxalisib was administered daily via oral gavage on days 0 to 9, and several dosing strategies were explored to determine the optimal therapeutic window.

The study began with a starting dose of 15 mg/kg/day, with or without co-administration of the immune checkpoint inhibitor αPD1 (pembrolizumab), which was delivered intraperitoneally at 10 mg/kg on days 0 and 4. To address potential toxicity and refine therapy, subsequent groups received de-escalating doses of paxalisib (15, 7.5, 3.75, and 1.875 mg/kg/day) split between morning and afternoon administrations. Dose optimization continued with intermediate regimens (7.5 and 3.75 mg/kg/day) in combination with αPD1 to assess synergy and tolerability. This comprehensive approach is designed to identify the most effective combination strategy for overcoming immunotherapy resistance and supporting paxalisib's development in difficult-to-treat TNBC settings. A summary of the administration of paxalisib in 4T1 TNBC model in combination with immunotherapy is provided in Figure 19 (page 29).

Figure 19

ADMINISTRATION OF PAXALISIB IN 4T1 TNBC MODEL IN COMBINATION WITH IMMUNOTHERAPY



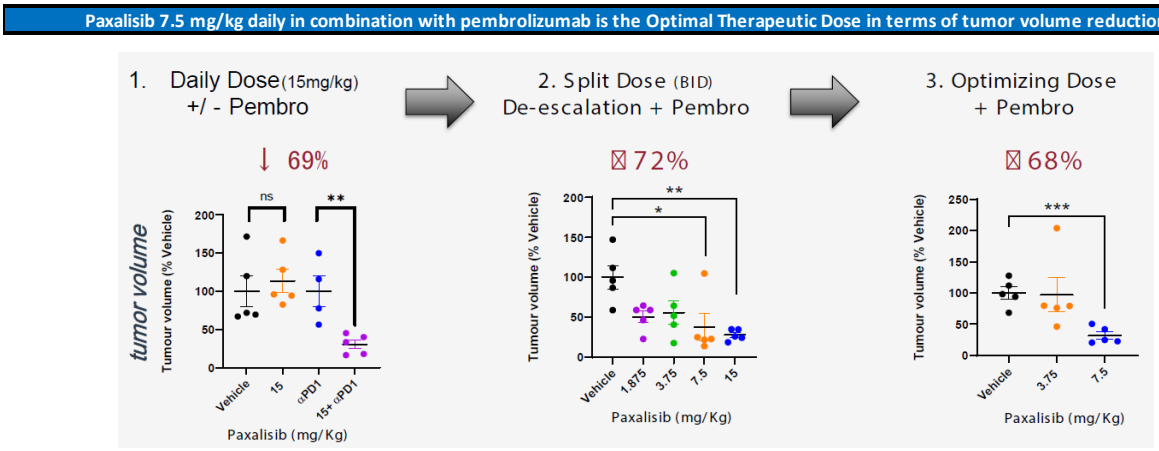
Source: Kazia Therapeutics Limited.

Paxalisib: Tumor Volume Efficacy Combined with Immunotherapy in 4T1 TNBC Model

Figure 20 presents the tumor volume efficacy of paxalisib in combination with immunotherapy, pembrolizumab (Pembro), in the 4T1 TNBC mouse model.

Figure 20

4T1 TNBC MODEL PAXALISIB IN COMBINATION WITH PEMBROLIZUMAB: TUMOR VOLUME EFFICACY



Source: Kazia Therapeutics Limited.

The study evaluates three dosing strategies:

- First, a daily dose of 15 mg/kg with or without pembrolizumab results in a 69% reduction in tumor volume when both drugs are combined.

- Second, a split-dose (BID) de-escalation regimen with pembrolizumab tests Paxalisib at 15, 7.5, 3.75, and 1.875 mg/kg daily and demonstrates up to 72% tumor volume reduction, highlighting increased efficacy at certain dose levels.

- Third, a focus on optimizing dose with pembrolizumab (testing 7.5 and 3.75 mg/kg) results in a 68% reduction in tumor volume compared to vehicle.

The data indicate that paxalisib at 7.5 mg/kg daily combined with pembrolizumab provides optimal therapeutic tumor reduction in this TNBC model. These findings are supported by statistical significance testing and are sourced from Melino et al., Molecular Cancer Therapeutics, 2025. This demonstrates that both dose optimization and combination immunotherapy can significantly improve anti-tumor effects of paxalisib in resistant TNBC settings.

Paxalisib Clinical Program: Phase 1b Study Design and First Results

Following promising preclinical results, Kazia's Phase 1b study (KZA-0084-ABC001) is a multi-center, open-label, randomized trial launched in Australia in about 24 patients with advanced breast cancer. The trial stratifies patients into two distinct arms to target clinically relevant populations (Figure 21):

- *Arm A* enrolls patients with HER2-negative metastatic breast cancer carrying confirmed BRCA1 or BRCA2 mutations, who receive paxalisib in combination with olaparib.

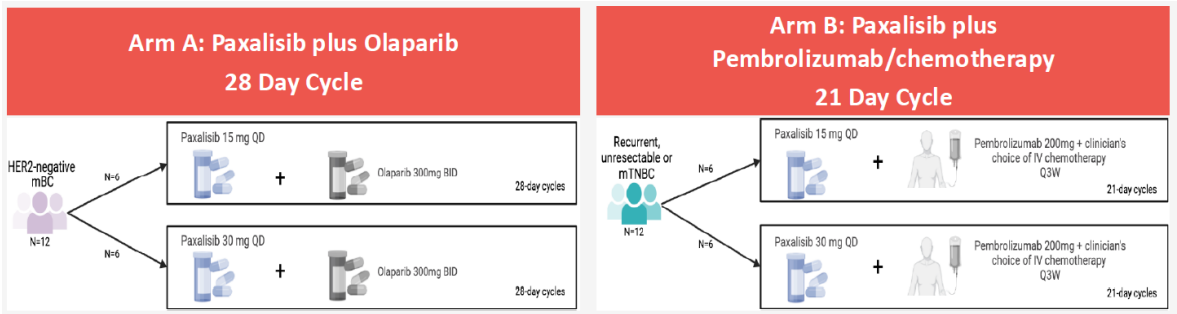
- *Arm B* includes individuals with recurrent or metastatic TNBC who have not previously received PD-1 or PD-L1 therapy, treated with paxalisib alongside pembrolizumab and chemotherapy.

The trial evaluates the safety, tolerability, and early clinical activity of paxalisib in combination with either olaparib or pembrolizumab plus chemotherapy.

- *Primary objectives* are to assess safety and tolerability and to establish a recommended Phase 2 dose for daily paxalisib in each combination.

- *Secondary objectives* include using liquid biopsy to track circulating tumor cells as a predictor of recurrence, examining immune cell signatures as a marker of immune reinvigoration, and documenting clinical activity such as progression and response rates.

Figure 21
KAZIA-SPONSORED CLINICAL STUDY OVERVIEW: KZA-0084-ABC001



Source: Kazia Therapeutics Limited.

This study design aims to rigorously explore the therapeutic benefit and safety profile of paxalisib in combination approaches across key subgroups of advanced breast cancer, as described below.

- Eligible participants for Arm A are required to have a diagnosis of HER2-negative stage IV (metastatic) breast cancer established by prior histopathology and imaging. They must have a confirmed germline BRCA mutation (gBRCAm), (BRCA1, BRCA2, or both), have previously received chemotherapy for metastatic disease, and meet all current criteria for initiating olaparib therapy.

- Eligible participants for this cohort must have recurrent, unresectable, or metastatic TNBC, as established through documented histopathology and imaging. Their tumors must express PD-L1 with a combined positive score (CPS) of 10 or higher, and they must not have received prior therapy targeting PD-1 or PD-L1. Additionally, all participants must qualify under current prescribing guidelines for initiating pembrolizumab therapy.

Paxalisib: Phase 1b TNBC: >50% Drop in Circulating Tumor Cells (CTC)

In Kazia's Phase 1b TNBC trial, the first patient, a 61-year-old woman with lung metastasis, received paxalisib plus pembrolizumab and standard chemotherapy. By Day 21 (end of cycle 1), total circulating tumor cells (CTCs) and CTC clusters fell by more than 50%, and the remaining CTCs shifted away from a mesenchymal phenotype associated with aggressive spread. According to the Company, responses of this magnitude are uncommon after a single cycle of chemotherapy or checkpoint inhibitor alone. Separately, ex vivo analyses showed that paxalisib monotherapy disrupted highly metastatic CTC clusters in HER2-positive Stage IV breast cancer samples, suggesting potential relevance beyond TNBC. This first-in-human data reflects mechanistic synergy consistent with the preclinical data.

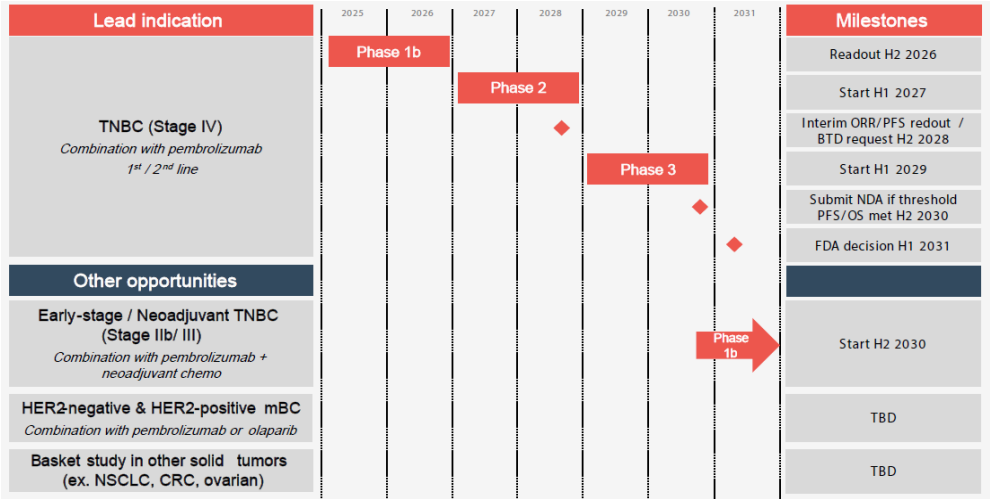
Paxalisib Disrupts CTC Clusters Ex Vivo in HER2+ mBC

In September 2025, Kazia reported ex vivo data showing that paxalisib monotherapy reduced single circulating tumor cells and completely disrupted (100%) large CTC clusters ≥3 cells in blood samples from Stage IV HER2-positive metastatic breast cancer patients. Because CTC clusters are linked to metastasis and poor prognosis, the findings suggest a potential anti-metastatic effect and extend paxalisib's relevance beyond TNBC into HER2-positive disease; they also align with initial reductions in CTCs/clusters seen in Kazia's ongoing Phase 1b TNBC study. Detailed datasets have been submitted for presentation at a 2025 oncology meeting.

Development Roadmap and Upcoming Milestones

Kazia's clinical strategy (Figure 22) is to advance from the Phase 1b safety run-in toward Phase 2 expansion in TNBC, with interim efficacy readouts targeted for 2028, Phase 3 initiation in 2029, and a potential NDA submission in 2030. Early-stage and neoadjuvant TNBC combinations with pembrolizumab plus chemotherapy are being considered for future trials, as are potential **basket studies** in additional PI3K/mTOR-driven malignancies.

Figure 22
DEVELOPMENT PLAN AND TIMELINE



Source: Kazia Therapeutics Limited.

Paxalisib in Triple-Negative Breast Cancer (QIMR Berghofer Collaboration)

Kazia and QIMR Berghofer are evaluating paxalisib in the aggressive 4T1 mouse model of TNBC. Early data from preclinical TNBC models show reductions in primary tumor burden and metastasis. According to QIMR's Professor Sudha Rao, the effect appears to reflect a property of PI3K inhibition that modulates immune activity within the tumor and its microenvironment. When given at doses and schedules that differ from conventional PI3K use, paxalisib seems to reinvigorate antitumor immunity and may increase the tumor's susceptibility to immunotherapy.

Preliminary findings were presented at the San Antonio Breast Cancer Symposium in the fourth quarter of 2024. The collaboration is advancing along three tracks that inform clinical strategy: combination studies with pembrolizumab in TNBC models, combination studies with olaparib in advanced breast cancer models, and mechanistic profiling of how paxalisib shifts immune cell populations, including T-cells, B cells, and NK cells, within the tumor and across the microenvironment. Kazia also notes related intellectual property activity tied to these observations.

NDL2 PD-L1 Degrader Program In-Licensed from QIMR Berghofer

On October 7, 2025, Kazia announced an exclusive collaboration and in-licensing agreement with QIMR Berghofer for NDL2, a first-in-class PD-L1 protein degrader. NDL2 is a bicyclic peptide designed to recognize and degrade post-translationally modified PD-L1 found on the cell surface and within the cytoplasm and nucleus, which are enriched in patients who fail or relapse on antibody checkpoint inhibitors. By clearing these resistant PD-L1 pools, NDL2 aims to restore cytotoxic T-cell activity and reduce T-cell exhaustion, potentially overcoming primary and acquired resistance to PD-1 and PD-L1 antibodies.

In preclinical TNBC models, NDL2 reduced tumor growth as monotherapy and in combination with anti-PD-1 therapy, with accompanying signs of reduced T-cell exhaustion and no observed toxicity to date. The initial development focus is advanced breast cancer and non-small cell lung cancer. IND-enabling studies are expected to begin within about six months of the announcement, with first-in-human studies targeted in roughly 15 months. Kazia plans to evaluate combinations with paxalisib and EVT801 given complementary effects on the tumor microenvironment. Financial terms include a one-time payment of approximately $1.39 million due 15 business days after signing, Kazia funding all development costs, and a share of future commercialization revenue, including any out-licensing proceeds.

Michael J. Fox Foundation (MJFF) Grant Funds Paxalisib Preclinical Study in Parkinson's Disease

On February 20, 2025, Kazia and the Hebrew University of Jerusalem received a Michael J. Fox Foundation (MJFF) grant to evaluate paxalisib as a potential treatment for Parkinson's disease. The work, led by Professor Ronit Sharon's lab, will test paxalisib in mouse models for effects on survival, motor and non-motor performance, and disease biomarkers. Paxalisib is a brain-penetrant class IA PI3K inhibitor; the study explores whether modulating the PI3K/AKT/mTOR pathway, implicated by prior human and animal data and linked to α-synuclein A53T activity, can impact PD pathophysiology. Results are intended to clarify mechanistic relevance and inform future development outside oncology.

Compassionate Use/Expanded Access

Kazia may provide investigational drugs (paxalisib, EVT801) for individual, named-patient use in rare circumstances after discussion with the treating physician. Eligibility is on a case-by-case and generally requires: a serious or life-threatening condition; no adequate alternatives or trial options; sufficient clinical data to define dose/schedule; a favorable benefit-risk assessment; no negative impact on ongoing trials or reviews; and adequate drug supply with feasible shipping. Requests must be submitted by the treating physician, who is responsible for regulatory/IRB or ethics approvals, informed consent, patient monitoring, and safety reporting. This is not a standing, open-label program; it is individual access evaluated under Kazia's policy and subject to country-specific regulations. Kazia has also disclosed an expanded-access to breast-cancer cases in 2025.

EVT801: TARGETING LYMPHATIC METASTASIS

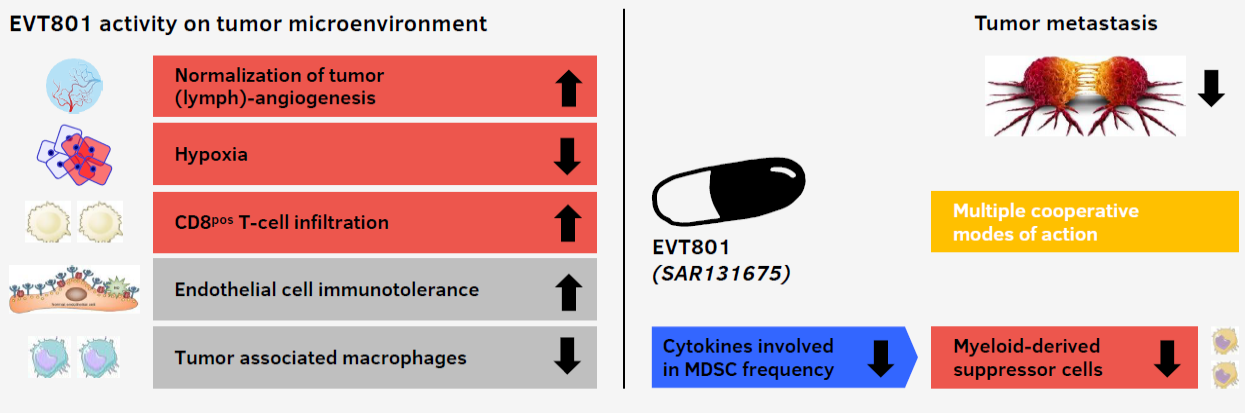
EVT801 is a highly selective VEGFR3 inhibitor that targets lymphangiogenesis, the formation of new lymphatic vessels linked to tumor growth and metastatic spread. Discovered at Sanofi and advanced through IND-enabling studies by Evotec, the program was later licensed worldwide by Kazia, which has progressed EVT801 into clinical development. By focusing on VEGFR3 rather than the broader VEGF axis, EVT801 is intended to limit off-target toxicity and mitigate hypoxia-driven resistance seen with legacy anti-angiogenic agents. Preclinical studies show activity across multiple tumor models and support combination potential with immuno-oncology agents and with paxalisib.

EVT801 is an oral agent (once or twice daily). Composition-of-matter patents extend in most jurisdictions to 2032-2033. The compound has been described as straightforward to manufacture with favorable stability and a low projected cost of goods. One-month GLP toxicology was supportive. A Phase 1 study has been completed, positioning the program for signal-seeking trials, including immuno-oncology combinations.

EVT801 Mechanism of Action

Kazia describes EVT801 as a selective VEGFR3 blocker that reshapes the tumor microenvironment on both the vascular and immune sides. In preclinical models with SAR131675 (the same compound), VEGFR3 inhibition produced features of vascular "normalization," including reduced abnormal lymphatic growth and lower tumor hypoxia, conditions that favor immune attack. These changes were associated with increased CD8+ T-cell infiltration, fewer cytokines that recruit myeloid-derived suppressor cells (MDSCs), and declines in both MDSCs and tumor-associated macrophages. Together, these mechanisms provide a biologic rationale for slowing metastatic spread and for combination strategies with checkpoint inhibitors. Figure 23 schematizes EVT801's mechanism of action based on preclinical data.

Figure 23
EVT801 MECHANISM OF ACTION: SCHEMATIC OVERVIEW BASED ON PRE-CLINICAL DATA



Source: Kazia Therapeutics Limited.

Phase 1 Clinical Trial Results

EVT801 is a differentiated anti-angiogenic that selectively targets VEGFR3 to modulate lymphangiogenesis. In the first-in-human, dose-finding study (KZA-0801-101) in advanced solid tumors, Stage 1 achieved its objectives: dose escalation from 50 mg once daily through twice-daily regimens established a maximum tolerated dose (MTD) of 500 mg BID and a recommended Phase 2 dose (RP2D) of 400 mg BID. Clinical and biomarker data presented in September 2024 showed strong VEGFR3 expression and an encouraging disease-control signal in high-grade serous ovarian cancer (HGSOC), with multiple patients achieving stable disease and at least one partial response. Kazia is planning the next study to consolidate safety at the RP2D and to evaluate HGSOC as the lead indication, either as monotherapy or in combination with standard of care such as a PARP inhibitor. These findings support advancing EVT801 to Phase 2 while continuing to validate the mechanism in the clinic.

Plans for Phase 2 Development

Encouraged by these findings, Kazia intends to advance EVT801 into Phase 2 trials concentrating on advanced ovarian cancer, alongside exploratory combination strategies with immune checkpoint inhibitors. EVT801 offers optionality for broader development, potentially extending into colorectal and other solid tumors where lymphatic metastasis is a driver of poor outcomes. Strategic partnerships are being pursued to accelerate clinical progress and maximize geographic reach, including potential opportunities in China and niche oncology indications.

Strategic Catalysts

A selection of Kazia's catalysts that the Company believes could set the pace for development, partnering, and financing decisions are listed below.

Potential Near-Term Catalysts

Paxalisib: Glioblastoma (GBM) Program

- An FDA Type C meeting (December 2024) confirmed a standard-approval pathway via a single pivotal registrational study in newly diagnosed unmethylated GBM. Kazia seeks to finalize the protocol, assessing cost/timelines, and selecting a strategic Contract Research Organization (CRO) partner.

- Kazia reported (September 2025) ex vivo data in Stage IV HER2-positive mBC show paxalisib alone cut single circulating tumor cells and fully disrupted CTC clusters of three or more cells (100%). Since CTC clusters track with metastatic risk, this supports a metastasis-focused rationale for paxalisib in HER2-positive disease, not just TNBC. Results are consistent with reductions seen in Kazia's Phase 1b TNBC study, with full datasets headed to a 2025 meeting.

Paxalisib: Pediatric and Brain Metastasis Programs

- Pacific Pediatric Neuro-Oncology Consortium (PNOC) expects to complete PK/biomarker analyses and provide an update during CY2025 across pediatric brain cancer studies (e.g., DIPG/DMG).

- The Memorial Sloan Kettering Cancer Center (MSKCC) brain-metastasis study combining paxalisib with radiotherapy is expected to complete analysis and close out.

Paxalisib: Advanced Breast Cancer

- Kazia continues to enroll in a Company-sponsored open-label Phase 1b study (KZA-0084-ABC001) in advanced breast cancer evaluating paxalisib with pembrolizumab or olaparib.

- The Company intends to provide additional preclinical updates from the QIMR collaboration through 2025.

EVT801 (VEGFR3 Inhibitor)

- Stage 1 of the Phase 1 first-in-human study (KZA-0801-101) is expected to complete clinical study report.

- Kazia intends to discuss and plan a Phase 2 study in advanced ovarian cancer, while actively engaging potential partners.

Regulatory Designations (Supporting Catalysts)

- Paxalisib holds Orphan Drug and Fast Track designations in glioblastoma, Fast Track for solid-tumor brain metastases with PI3K-pathway mutations in combination with radiation, and Rare Pediatric Disease designations for DIPG and AT/RT. These programs provide enhanced FDA interaction, fee reductions, potential exclusivity benefits, and eligibility for pediatric priority review vouchers (historically sold for >$100 million).

Corporate and Business Development

- Kazia is opportunistic with regard to global/regional licensing for paxalisib and EVT801.

Licensing and Collaborations

The accompanying section summarizes Kazia's current out-licensing agreements and research collaborations that expand geographic reach, add indication breadth, and bring in non-dilutive capital. The information below indicates who holds which rights, the headline economics, and how each partnership supports development of paxalisib and EVT801.

Licensing

- *Simcere Pharmaceutical Group* (Mainland China, Hong Kong, Macao, Taiwan). Nanjing, China-based, Simcere holds the exclusive Greater China license for paxalisib, leading development, regulatory, and commercialization in its territory while Kazia supplies product and retains rights elsewhere. Financial terms include $11 million upfront ($7 million cash and $4 million equity), up to $281 million in GBM-related milestones (with potential for additional milestones in other indications), and mid-teen tiered royalties on net sales.

- *Sovargen Co., Ltd.* (neurology indications). Sovargen is a Korea-based biotech focused on CNS diseases driven by mTOR-pathway dysregulation. In March 2024, Kazia granted Sovargen an exclusive worldwide license to develop, manufacture, and commercialize paxalisib for intractable epilepsy associated with focal cortical dysplasia type II (FCD-T2) and **tuberous sclerosis complex (TSC)**, except Greater China, which Kazia retains. Terms include $1.5 million upfront, up to $19 million in development/regulatory milestones, royalties on net sales, and a share of any sub-licensing revenue. Sovargen assumes development and regulatory lead for these seizure indications.

Key Collaborations

- *QIMR Berghofer Medical Research Institute (research partner).* Kazia's collaboration with QIMR Berghofer began in 2022 and has produced multiple translational programs, including preclinical and ex vivo work showing paxalisib's potential to enhance immunotherapy and disrupt circulating tumor-cell clusters in breast cancer, led by Professor Sudha Rao. In September/October 2025, the relationship expanded with an exclusive collaboration and in-licensing of NDL2, a first-in-class PD-L1 degrader discovered at QIMR Berghofer, for clinical development by Kazia. QIMR has also highlighted a QIMR-Kazia clinical initiative combining paxalisib with immunotherapy in breast cancer, underscoring the partnership's bench-to-clinic scope.

- *Johns Hopkins University (AT/RT program).* Kazia collaborates with Johns Hopkins (Sidney Kimmel Cancer Center; lead investigator Jeffrey Rubens, MD) on preclinical and translational work in atypical teratoid/rhabdoid tumor (AT/RT) and other pediatric brain tumors. The Johns Hopkins team has presented multiple AACR posters showing paxalisib activity in AT/RT models and combination strategies (for example, with gemcitabine), and Kazia has highlighted a formal collaboration with Johns Hopkins to evaluate paxalisib across pediatric brain-cancer models. These data supported U.S. Orphan Drug Designation for AT/RT and inform plans to advance paxalisib into cooperative-group clinical studies. If approved, Kazia could be eligible for a Pediatric Priority Review Voucher; these vouchers are tradeable and have historically sold for >$100 million.

Competition

Kazia develops drugs within crowded oncology spaces where large, well-funded companies and numerous biotech and pharma entities are active. The Company specifically competes across CNS and metastatic oncology, with its technology centering on paxalisib's reliable CNS exposure and combination potential, and on EVT801's selective VEGFR3 focus that targets lymphatic metastasis. Kazia differentiates paxalisib as a brain-penetrant PI3K-pathway inhibitor positioned for CNS tumors and brain-involved solid cancers; EVT801 is positioned as a selective VEGFR3 approach aimed at lymphangiogenesis and immune reconditioning.

The accompanying section provides an overview of select potential competition Kazia may face within these markets, specifically from multinational companies as well as development stage companies seeking to bring therapeutics to market for the same indications. This is not intended to be an exhaustive collection of potential competitors; however, it is believed to be the type of competition the Company may face as it strives to commercialize its technologies and product candidates.

Paxalisib

Glioblastoma (GBM)

Standard of care (SOC) remains radiation plus temozolomide (Temodar/Temodal), with tumor treating fields (Optune) FDA-approved in both newly diagnosed and recurrent GBM and commonly layered onto standard of care. Development is active across adaptive platforms, DNA-damage backbones (e.g., lomustine), oncolytic viruses, targeted/biomarker subsets, and RT combinations. Potential competition for this indication may include the following companies:

- ***Bayer AG.*** Bayer's multikinase inhibitor, regorafenib, is used off-label in recurrent GBM and showed an overall survival benefit versus lomustine in the randomized REGOMA study, with subsequent prospective and real-world cohorts supporting activity. Bayer AG is headquartered in Leverkusen, Germany.

- ***Candel Therapeutics, Inc.*** Candel is advancing CAN-3110, an HSV-based oncolytic immunotherapy for recurrent GBM, with FDA fast track and orphan-drug designations and positive interim data reported in October 2025. Candel Therapeutics is headquartered in Needham, Massachusetts.

- ***Carthera SAS***. Carthera is a device company developing the SonoCloud-9 implantable ultrasound system to open the blood-brain barrier and enhance chemotherapy delivery; the pivotal SONOBIRD trial in recurrent GBM is underway. Carthera is headquartered in Paris/Lyon, France.

- ***CNS Pharmaceuticals, Inc.*** CNS Pharmaceuticals is developing berubicin, an anthracycline reported to cross the blood-brain barrier, in a late-stage randomized study versus lomustine in recurrent GBM with a primary analysis disclosed in March 2025. CNS Pharmaceuticals is headquartered in Houston, Texas.

- ***Day One Biopharmaceuticals, Inc***. Day One markets tovorafenib (Ojemda) for BRAF-altered pediatric low-grade glioma, making it a relevant neuro-oncology comparator even if not a GBM therapy. Day One Biopharmaceuticals is headquartered in Brisbane, California (South San Francisco area).

- ***Denovo Biopharma LLC.*** Denovo Biopharma applies retrospective biomarker discovery to match legacy drugs with responsive patients, and in high-grade glioma is advancing DB107 (also referenced as DB107-RRV) with CIRM grant support into clinical testing at U.S. academic centers. Denovo Biopharma is headquartered in San Diego, California (with additional operations in Hangzhou, China).

- ***DNAtrix, Inc.*** DNAtrix is developing the oncolytic adenovirus DNX-2401 (tasadenoturev), including combinations with pembrolizumab that have shown signals of activity in recurrent GBM in a Phase 1/2 study published in *Nature Medicine*. DNAtrix is headquartered in Houston, Texas.

- ***Gilead Sciences, Inc. (Kite).*** Gilead and academic partners are testing bivalent CAR-T cells targeting EGFR and IL13Rα2 delivered intracerebroventricularly in recurrent GBM, with early responses reported and additional development planned. Gilead Sciences is headquartered in Foster City, California.

- ***ImmunityBio, Inc.*** ImmunityBio has reported an exploratory case series in recurrent GBM using a chemo-free regimen that combines ANKTIVA (IL-15 superagonist), NK-cell therapy, and Novocure's Optune Gio, with disease control observed in all five initial patients. ImmunityBio is headquartered in Culver City (Los Angeles), California.

- ***Imvax, Inc***. Imvax is running a randomized Phase 2b trial of IGV-001, a personalized autologous cell-based immunotherapy implanted in biodiffusion chambers after resection in newly diagnosed GBM, with enrollment updates in 2024-2025. Imvax is headquartered in Philadelphia, Pennsylvania.

- ***Insightec Ltd.*** Insightec is a device competitor using MR-guided focused ultrasound (Exablate Neuro) to transiently open the blood-brain barrier in glioma, with studies aimed at enhancing drug delivery. Insightec is headquartered in Tirat Carmel, Israel (U.S. HQ in Miami, Florida).

- ***Istari Oncology, Inc.*** Istari Oncology is advancing lerapolturev (PVSRIPO), an intratumoral oncolytic polio/rhinovirus therapy, in recurrent GBM including the LUMINOS-101 Phase 2 study in combination with pembrolizumab. Istari Oncology is headquartered in the Research Triangle area near Durham, North Carolina.

- ***Medicenna Therapeutics Corp***. Medicenna's bizaxofusp (MDNA55), an IL-4R-targeted toxin delivered by convection-enhanced delivery, has shown signals of benefit in recurrent GBM and remains an asset for potential partnering. Medicenna Therapeutics is headquartered in Toronto, Ontario, Canada.

- ***Moleculin Biotech, Inc***. Moleculin is testing the STAT3 inhibitor WP1066 with radiation in newly diagnosed, MGMT-unmethylated GBM in an NIH-funded Phase 2 trial. Moleculin Biotech is headquartered in Houston, Texas.

- ***Northwest Biotherapeutics, Inc***. Northwest Biotherapeutics is developing DCVax-L, an autologous dendritic-cell vaccine for GBM; Phase 3 results were published in *JAMA Oncology* and the company has submitted an MAA to the UK MHRA, which NICE notes remains in process as of April 2, 2025. Northwest Biotherapeutics is headquartered in Bethesda, Maryland.

- ***Novocure Limited***. Novocure develops Tumor Treating Fields therapy delivered via the Optune Gio wearable system, which is FDA-approved for adults with newly diagnosed or recurrent GBM and is now rolling out higher-frequency transducer arrays cleared in late 2024. Novocure is headquartered in Baar, Switzerland.

- ***Plus Therapeutics, Inc.*** Plus Therapeutics is developing rhenium-186 obisbemeda (REYOBIQ) delivered by convection-enhanced delivery for recurrent GBM, with peer-reviewed and company updates reporting safety and signs of efficacy from the ReSPECT-GBM program. Plus Therapeutics is headquartered in Houston, Texas.

- ***TME Pharma N.V.*** TME Pharma targets the tumor microenvironment; in GBM its CXCL12 inhibitor NOX-A12 (olaptesed pegol) produced a final median overall survival of ~19.9 months in the GLORIA Phase 1/2 study and has FDA IND clearance for Phase 2 development. TME Pharma is headquartered in Berlin, Germany (with the parent entity registered in Amsterdam, Netherlands).

Brain Metastases (Solid Tumors)

In brain metastases from solid tumors, treatment typically includes stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT), with systemic therapy guided by the biology of the primary cancer. In biomarker-defined groups, CNS-active TKIs set the bar: tucatinib plus trastuzumab and capecitabine for HER2-positive breast cancer (the FDA label explicitly includes patients with brain metastases), osimertinib for EGFR-mutated NSCLC, and alectinib for ALK-positive NSCLC. By contrast, Kazia is positioning paxalisib for PI3K-altered brain metastases given concurrently with brain radiotherapy; this combination holds FDA Fast Track designation, and a Memorial Sloan Kettering Phase 1 study (NCT04192981) established an MTD of 45 mg once daily with radiotherapy and reported encouraging intracranial responses by RANO-BM to guide the next-study design. Potential competition for this indication may include the following companies:

- ***AstraZeneca plc—osimertinib (Tagrisso) (EGFR-mutant NSCLC brain metastases).*** Osimertinib is a third-generation EGFR inhibitor with robust CNS penetration that improves intracranial outcomes in EGFR-mutant non-small cell lung cancer; randomized data and subsequent analyses show delayed CNS progression versus earlier EGFR TKIs and additional benefit when combined with platinum-pemetrexed. AstraZeneca is headquartered in Cambridge, United Kingdom.

- ***Bristol Myers Squibb—nivolumab (Opdivo) + ipilimumab (Yervoy) (melanoma brain metastases).*** Dual checkpoint blockade with nivolumab plus ipilimumab has produced high intracranial objective response rates and durable disease control in untreated melanoma brain metastases, including in the CheckMate 204 study and subsequent analyses that link intracranial responses to survival. Bristol Myers Squibb is headquartered in New York, New York.

- ***Bristol Myers Squibb—adagrasib (Krazati) (KRAS G12C-mutant NSCLC brain metastases).*** Adagrasib is the first KRAS G12C inhibitor to prospectively demonstrate intracranial activity in patients with untreated CNS metastases from NSCLC, with KRYSTAL-1 analyses reporting intracranial responses and disease control that support its use in this biomarker-defined population.

- ***Daiichi Sankyo Company, Limited & AstraZeneca plc—trastuzumab deruxtecan (Enhertu; T-DXd) (HER2-positive and HER2-low breast cancer brain metastases).*** The antibody-drug conjugate trastuzumab deruxtecan has demonstrated intracranial activity and improved progression-free outcomes in patients with brain metastases across multiple trials and subgroup analyses, including TUXEDO-1 and DESTINY-Breast studies, making it an important CNS-active option in HER2-driven disease. Daiichi Sankyo is headquartered in Tokyo, Japan; AstraZeneca is headquartered in Cambridge, United Kingdom.

- ***F. Hoffmann-La Roche Ltd—alectinib (Alecensa) and entrectinib (Rozlytrek) (ALK-positive and ROS1/NTRK-positive NSCLC brain metastases).*** Alectinib has demonstrated superior intracranial control versus crizotinib in untreated ALK-positive NSCLC, markedly prolonging time to CNS progression, while entrectinib shows meaningful CNS activity in ROS1-positive and NTRK-fusion NSCLC, supporting its use in patients with brain metastases. F. Hoffmann-La Roche Ltd is headquartered in Basel, Switzerland.

- ***Gilead Sciences, Inc.—sacituzumab govitecan (Trodelvy) (Trop-2 ADC; breast cancer brain metastases).*** Sacituzumab govitecan has emerging evidence of CNS penetration and signals of activity in breast cancer brain metastases, including phase 0/real-world datasets and subgroup readouts from ASCENT and other studies that support ongoing use and further evaluation in BCBM. Gilead Sciences is headquartered in Foster City, California.

- ***Novartis AG—dabrafenib (Tafinlar) + trametinib (Mekinist) (BRAF V600-mutant melanoma brain metastases).*** The dabrafenib/trametinib combination yields clinically meaningful intracranial response rates in patients with BRAF V600-mutant melanoma and active brain metastases, as shown in the COMBI-MB program and supportive studies, establishing a targeted standard in this setting. Novartis is headquartered in Basel, Switzerland.

- ***Pfizer Inc.—tucatinib (Tukysa) + trastuzumab + capecitabine (HER2+ breast cancer brain metastases).*** Pfizer markets tucatinib, a selective HER2 TKI, used with trastuzumab and capecitabine and shown in HER2CLIMB to significantly improve intracranial control and overall survival in patients with brain metastases from HER2-positive breast cancer. In the brain-met subgroup, the regimen reduced the risk of intracranial progression or death by ~64% and extended overall survival in later analyses. Pfizer is headquartered in New York, New York.

- ***Pfizer Inc.—lorlatinib (Lorbrena) (ALK-positive NSCLC brain metastases).*** Lorlatinib is a third-generation ALK inhibitor with best-in-class intracranial efficacy that substantially lowers the risk of CNS progression versus crizotinib and delivers unprecedented long-term progression-free survival in ALK-positive NSCLC, including patients with baseline brain metastases, per CROWN and follow-up reports. Pfizer is headquartered in New York, New York.

Pediatric High-Grade Gliomas (DMG/DIPG; AT/RT)

Radiation remains foundational in DMG/DIPG. On August 6, 2025, the FDA granted accelerated approval to dordaviprone (Modeyso/ONC201) from Jazz Pharmaceuticals for H3 K27M-mutant DMG in adults and children ≥1 year with progressive disease, setting a new benchmark at relapse. Paxalisib holds FDA Orphan Drug and Rare Pediatric Disease designations in DMG/DIPG and AT/RT; in PNOC's DMG study, the post-radiation cohort showed median overall survival above historical benchmarks, and AT/RT is positioned to enter the clinic next, with additional pediatric indications under review. Potential competition for this indication may include the following companies:

- ***AstraZeneca plc—adavosertib (WEE1 inhibitor) with radiotherapy.*** AstraZeneca's WEE1 inhibitor adavosertib has been evaluated with radiotherapy in newly diagnosed pediatric DIPG/DMG based on strong preclinical rationale for radiosensitization; early clinical work shows the combination is feasible and generally tolerated, though survival advantages versus historical controls have not been confirmed. AstraZeneca is headquartered in Cambridge, United Kingdom.

- ***Biodexa Pharmaceuticals plc—MTX110 (aqueous panobinostat) via convection-enhanced delivery (CED).*** Biodexa is developing MTX110, a solubilized panobinostat formulation delivered directly into the tumor or pons using CED to overcome blood-brain barrier limits; pediatric studies in DIPG/DMG (including PNOC015) have shown feasibility and early signals, with additional cohorts running or reported. Biodexa Pharmaceuticals is headquartered in Cardiff, United Kingdom.

- ***Ipsen—tazemetostat (EZH2 inhibitor) in SMARCB1-deficient AT/RT.*** Ipsen (which acquired Epizyme) is developing the EZH2 inhibitor tazemetostat in SMARCB1/INI1-deficient pediatric tumors, including AT/RT, where case series and basket studies from pediatric consortia, such as Pediatric MATCH, support further exploration in relapsed settings. Ipsen is headquartered in Paris, France.

- ***Jazz Pharmaceuticals plc—dordaviprone (Modeyso; ONC201) and ONC206 (imipridones).*** Jazz markets dordaviprone (Modeyso), the first FDA-approved systemic therapy for H3 K27M-mutant diffuse midline glioma (DMG) in patients ≥1 year with progressive disease, establishing a clear benchmark in pediatric DMG; Jazz is also sponsoring ONC206, a next-generation imipridone in an ongoing Phase 1 trial for DMG and related malignant CNS tumors. Jazz Pharmaceuticals is headquartered in Dublin, Ireland.

- ***SonALAsense, Inc.—SONALA-001 + focused ultrasound (sonodynamic therapy, SDT).*** SonALAsense is advancing a drug-device regimen that pairs SONALA-001 (5-ALA derivative) with MRI-guided focused ultrasound to generate tumor-localized oxidative stress, with pediatric DMG/DIPG clinical studies cleared and early data presented from ongoing programs. SonALAsense is headquartered in Oakland, California.

Advanced Breast Cancer

First-line PD-L1-positive TNBC (CPS ≥10) is benchmarked by pembrolizumab plus chemotherapy (KEYNOTE-355), and after progression sacituzumab govitecan (Trodelvy) provides an overall survival benefit. In HR-positive/HER2-negative disease with pathway alterations, key comparators are alpelisib + fulvestrant (PIK3CA-mutated), capivasertib + fulvestrant (PI3K/AKT/PTEN-altered), and everolimus + endocrine therapy after AI failure. Kazia is evaluating paxalisib with pembrolizumab + chemotherapy in TNBC and with olaparib in gBRCA, HER2-negative disease; early translational signals (for example, >50% CTC declines by Day 21) support the approach, but real-world uptake will be judged against KEYNOTE-355 and ADCs like Trodelvy. Potential competition for this indication may include the following companies:

- ***AstraZeneca plc—capivasertib (Truqap) + fulvestrant.*** Capivasertib is an oral AKT inhibitor approved with fulvestrant for HR-positive/HER2-negative metastatic breast cancer harboring PI3K/AKT/PTEN pathway alterations, delivering a significant PFS benefit in CAPItello-291; as an AKT-pathway alternative to PI3K inhibitors, it competes for the same biomarker-defined lines of therapy. AstraZeneca is headquartered in Cambridge, United Kingdom.

- ***AstraZeneca plc & Daiichi Sankyo Co., Ltd.—datopotamab deruxtecan (Datroway/ Dato-DXd).*** Datopotamab deruxtecan is a TROP-2 ADC approved for previously treated HR-positive/HER2-negative metastatic breast cancer, where it is increasingly used before or instead of some targeted combinations, creating competitive pressure on pathway inhibitors for later-line utilization. AstraZeneca is headquartered in Cambridge, United Kingdom, and Daiichi Sankyo is headquartered in Tokyo, Japan.

- ***AstraZeneca plc & Daiichi Sankyo Co., Ltd.—trastuzumab deruxtecan (Enhertu).*** Trastuzumab deruxtecan, an anti-HER2 ADC, is approved in HER2-low and HER2-positive metastatic breast cancer and has documented intracranial activity; as ADCs move earlier in HR-positive disease (particularly HER2-low), they can crowd later lines that might otherwise be addressed by PI3K-pathway drugs. AstraZeneca is headquartered in Cambridge, United Kingdom, and Daiichi Sankyo is headquartered in Tokyo, Japan.

- ***Genentech, Inc. (Roche Group)—inavolisib (Itovebi) + palbociclib + fulvestrant.*** Inavolisib is a next-generation, α-selective PI3K inhibitor approved with palbociclib and fulvestrant for adults with endocrine-resistant, PIK3CA-mutated HR-positive/HER2-negative metastatic breast cancer after recurrence on or after adjuvant endocrine therapy, directly competing for the same PI3K-altered population that paxalisib targets. Genentech is headquartered in South San Francisco, California.

- ***Gilead Sciences, Inc.—sacituzumab govitecan (Trodelvy).*** Sacituzumab govitecan is a TROP-2-directed antibody-drug conjugate with approvals in metastatic TNBC and in previously treated HR-positive/HER2-negative disease; its expanding role in post-endocrine and post-CDK4/6 settings means it competes for the same later-line patients that PI3K-pathway agents aim to treat. Gilead Sciences is headquartered in Foster City, California.

- ***Novartis AG—alpelisib (Piqray) + fulvestrant.*** Alpelisib, the first FDA-approved PI3Kα inhibitor in breast cancer, is indicated (with fulvestrant) for postmenopausal patients and men with HR-positive/HER2-negative, PIK3CA-mutated metastatic disease after progression on endocrine therapy, setting a long-standing standard that any PI3K-pathway agent must match or improve upon. Novartis is headquartered in Basel, Switzerland.

- ***Novartis AG—everolimus (Afinitor) + exemestane.*** Everolimus, an mTOR inhibitor, is approved with exemestane for postmenopausal patients with HR-positive/HER2-negative advanced breast cancer after nonsteroidal aromatase inhibitor failure; while older than PI3K/AKT options, it remains a guideline-listed pathway therapy that can displace later-line use of emerging PI3K-pathway drugs. Novartis is headquartered in Basel, Switzerland.

EVT801

Ovarian and Other Solid Tumors

In ovarian cancer, anti-angiogenic therapy commonly uses bevacizumab, and PARP inhibitors are standards in selected BRCA/HRD-positive settings. Across other solid tumors, multi-TKIs like lenvatinib, cabozantinib, and regorafenib are established in specific indications. EVT801 takes a different approach by selectively inhibiting VEGFR3 to target lymphangiogenesis, aiming to limit metastasis and improve the tumor immune environment. In first-in-human testing at Lyon and Toulouse, Stage 1 set the MTD at 500 mg BID and the RP2D at 400 mg BID, with early disease-control signals in high-grade serous ovarian cancer (HGSOC), supporting Phase 2 plans including IO combinations and potential expansion. Potential competition for this indication may include the following companies:

- ***AVEO Oncology (an LG Chem company)/Elevar Therapeutics—tivozanib (FOTIVDA).*** Tivozanib is a potent VEGFR1/2/3 **tyrosine kinase inhibitor** approved for relapsed or refractory renal cell carcinoma, and it remains a recognized anti-angiogenic option in solid tumors that could compete with EVT801 for similar treatment lines in expansion settings. AVEO Oncology is headquartered in Boston, Massachusetts, and Elevar Therapeutics is headquartered in Fort Lee, New Jersey.

- ***AbbVie Inc.—mirvetuximab soravtansine-gynx (Elahere).*** Mirvetuximab soravtansine is a folate receptor-α-directed antibody-drug conjugate with full FDA approval for FRα-positive, platinum-resistant ovarian cancer, and it is increasingly shaping post-platinum sequencing where anti-angiogenic agents might otherwise be used. AbbVie is headquartered in North Chicago, Illinois.

- ***Genentech, Inc. (Roche Group)—bevacizumab (Avastin).*** Bevacizumab is an anti-VEGF-A monoclonal antibody that improves outcomes when added to chemotherapy across multiple ovarian cancer settings, making it the incumbent anti-angiogenic standard most relevant to EVT801 in ovarian disease. Genentech is headquartered in South San Francisco, California.

- ***HUTCHMED (China) Limited & Takeda Pharmaceutical Company Limited—fruquintinib (FRUZAQLA).*** Fruquintinib is an oral VEGFR1/2/3 inhibitor approved in refractory metastatic colorectal cancer and being explored more broadly in solid tumors, making it a mechanism-adjacent comparator to EVT801 given its VEGFR-family profile that includes VEGFR3. HUTCHMED is headquartered in Hong Kong, and Takeda is headquartered in Tokyo, Japan.

Investment Highlights

- *Overview.* Kazia Therapeutics is a clinical-stage oncology company focused on high-need cancers of the central nervous system (CNS) and select hard-to-treat solid tumors. Its portfolio centers on paxalisib, a brain-penetrant PI3K/mTOR inhibitor, and EVT801, a selective VEGFR3 inhibitor.

- *Paxalisib program.* After FDA Type C alignment, Kazia is advancing a single pivotal registrational study in newly diagnosed MGMT-unmethylated glioblastoma (GBM). Paxalisib is also in studies for advanced breast cancer, brain metastases, diffuse midline gliomas, and primary CNS lymphoma, and it holds FDA designations including Orphan Drug and Fast Track in GBM, Fast Track with radiation for PI3K-mutant solid-tumor brain metastases, and Rare Pediatric Disease plus Orphan Drug for DIPG and AT/RT.

- *EVT801 program.* EVT801 is designed to limit lymphangiogenesis and improve the tumor microenvironment. Stage 1 of the first-in-human study is complete, and Phase 2 planning is underway with high-grade serous ovarian cancer (HGSOC) as the initial focus and immunotherapy combinations under evaluation.

- *Near-term catalysts.* Upcoming events include initial efficacy signals from the Phase 1b breast-cancer study, GBM-AGILE-related regulatory updates and pivotal-design milestones, and completion of Stage 1 analyses for EVT801; each could be value-moving and guide the development plan.

- *Validated CNS profile.* Paxalisib originated at Genentech and completed a successful Phase 1 there, supported by extensive preclinical data. Its reliable blood-brain-barrier penetration differentiates it within the PI3K class and supports use in primary CNS tumors and brain metastases.

- *Market opportunity.* GBM is a multi-billion-dollar global market, and broader primary and metastatic brain cancers are often estimated near $10 billion. Expansion into breast cancer could further increase the opportunity.

- *Early breast-cancer signals.* In advanced breast cancer, including triple negative breast cancer (TNBC), early data showed about a 50% reduction in circulating tumor cells by Day 21, supporting combinations such as paxalisib plus olaparib or paxalisib plus pembrolizumab with chemotherapy per study arm.

- *Partnerships.* Simcere holds the exclusive Greater China license for paxalisib with $11 million upfront, up to $281 million in GBM milestones, and mid-teen royalties. Sovargen holds global (ex-Greater China) rights for paxalisib in FCD-T2/TSC epilepsy with $1.5 million upfront, up to $19 million in milestones, royalties, and a share of any sub-licensing revenue.

- *Operating model.* Kazia uses investigator-initiated trials to extend indications, deepen key opinion leader (KOL) engagement, and manage costs; through partnerships and Investigator-Initiated Trials (IITs), more than ten paxalisib trials have advanced while maintaining disciplined spend, with most operating expenses directed to clinical programs.

- *2025 priorities.* In 2025, Kazia's priorities are to finalize the pivotal GBM protocol, assess costs and timelines, and select a strategic clinical research organization (CRO); support PNOC PK/biomarker analyses with a 2Q CY2025 update; close out the Memorial Sloan Kettering Cancer Center (MSKCC) brain-metastasis study; launch the Company-sponsored Phase 1b breast-cancer study and provide QIMR updates; complete EVT801 Stage 1 analysis, plan a Phase 2 in ovarian cancer, and advance global and regional licensing.

- *Focused portfolio and listing.* The Company follows a licensing-driven strategy built on differentiated clinical-stage assets sourced from Genentech (paxalisib) and Sanofi/Evotec (EVT801). Kazia now trades solely on NASDAQ (KZIA) following its ASX delisting in November 2023.

- *Leadership and governance.* Kazia's leadership and governance team includes experienced management, an active Board, and a strong Scientific Advisory Board.

    - In FY2024, John Friend, MD, moved from chief medical officer (CMO) to CEO and Managing Director; after Iain Ross resigned on August 11, 2023, Dr. Friend served as Interim Chairman until January 18, 2024, when longtime board member Bryce Carmine became Chairman.

    - Kazia's Scientific Advisory Board member, Dr. Olivero, is an expert on intracellular signaling pathways and was the team leader for Genentech's PI3K franchise. He has a specialist interest in brain cancer and is a coinventor of paxalisib (formally GDC-0084). He led the early development of paxalisib and was responsible for bringing the drug into human trials.

- *Access to capital.* As of December 31, 2024, cash and equivalents were about A$3.06 million. Subsequent activity included a $2.0 million registered direct offering (January 2025), $1.0 million from the Cantrixil IP sale (March 2025), and a $2.0 million premium private placement (August 2025), providing flexibility to use both dilutive and non-dilutive sources as late-stage studies progress.

Historical Financial Results

Figure's 24, 25, and 26 (pages 45-47) provide a summary of Kazia Therapeutics' most recent key financial statements for the most recently released half year ended 2024.

Figure 24
KAZIA THERAPEUTICS LIMITED
STATEMENT OF PROFIT OR LOSS AND OTHER COMPREHENSIVE INCOME
FOR THE HALF-YEAR ENDED 31 DECEMBER 2024 (in Australian Dollars)

	Note	Consolidated December 2024 $	Consolidated December 2023 $
Revenue and other income			
Other income		22,290	5
Finance Income		28,667	6,453
Expenses			
Research and development expense		(4,282,101)	(4,327,717)
General and administrative expense		(5,108,573)	(4,555,691)
Fair value (loss)/gain on financial liabilities		(1,999,648)	84,587
Gain/(loss) on revaluation of contingent consideration		750,008	(166,696)
Loss before income tax benefit		(10,589,357)	(8,959,059)
Income tax benefit		135,546	135,546
Loss after income tax benefit for the half-year attributable to the owners of Kazia Therapeutics Limited		(10,453,811)	(8,823,513)
Other comprehensive income			
Items that may be reclassified subsequently to profit or loss			
Net exchange difference on translation of financial statements of foreign controlled entities, net of tax		174,335	(103,687)
Other comprehensive income for the half-year, net of tax		174,335	(103,687)
Total comprehensive income for the half-year attributable to the owners of Kazia Therapeutics Limited		(10,279,476)	(8,927,200)
		Cents	**Cents**
Basic earnings per share	18	(2.459)	(3.680)
Diluted earnings per share	18	(2.459)	(3.680)

Source: Kazia Therapeutics Limited.

Figure 25
KAZIA THERAPEUTICS LIMITED
STATEMENT OF FINANCIAL POSITION
AS AT 31 DECEMBER 2024 (IN AUSTRALIAN DOLLARS)

	Note	Consolidated December 2024 $	June 2024 $
Assets			
Current assets			
Cash and cash equivalents	4	3,064,308	1,657,478
Trade and other receivables	5	96,132	3,896,729
Other assets	6	246,248	591,162
Total current assets		3,406,688	6,145,369
Non-current assets			
Intangibles	7	14,465,312	15,400,023
R&D rebate due		40,000	40,000
Total non-current assets		14,505,312	15,440,023
Total assets		17,912,000	21,585,392
Liabilities			
Current liabilities			
Trade and other payables	8	10,459,756	15,067,945
Other financial liabilities	9	2,017,878	6,478,060
Borrowings	10	140,737	634,191
Employee benefits	11	378,841	364,933
Contingent consideration	12	3,515,233	3,252,904
Total current liabilities		16,512,445	25,798,033
Non-current liabilities			
Deferred tax	13	1,882,634	2,018,180
Employee benefits	11	35,800	35,219
Contingent consideration	12	3,288,664	3,751,717
Total non-current liabilities		5,207,098	5,805,116
Total liabilities		21,719,543	31,603,149
Net liabilities		(3,807,543)	(10,017,757)
Equity			
Contributed equity	14	117,457,171	101,637,758
Unissued equity	15	380,224	-
Reserves	16	3,443,243	3,474,755
Accumulated losses		(125,088,181)	(115,130,270)
Total deficiency in equity		(3,807,543)	(10,017,757)

Source: Kazia Therapeutics Limited.

Figure 26
KAZIA THERAPEUTICS LIMITED
STATEMENT OF CASH FLOWS
FOR THE HALF-YEAR ENDED 31 DECEMBER 2024 (IN AUSTRALIAN DOLLARS)

	Note	Consolidated December 2024 $	Consolidated December 2023 $
Cash flows from operating activities			
Payments to suppliers (inclusive of GST)		(8,420,244)	(6,295,615)
Interest paid		-	(39,257)
Net cash used in operating activities	19	(8,420,244)	(6,334,872)
Cash flows from financing activities			
Proceeds from issue of shares (net of costs)	14	8,561,589	1,327,468
Proceeds from promissory note	15	-	776,670
Repayment of promissory note	15	-	(371,802)
Proceeds from issue of equity and pre-funded warrants	9	1,178,106	3,020,315
Net cash from financing activities		9,739,695	4,752,651
Net increase/(decrease) in cash and cash equivalents		1,319,451	(1,582,221)
Cash and cash equivalents at the beginning of the financial half-year		1,657,478	5,241,197
Effects of exchange rate changes on cash and cash equivalents		87,379	(96,374)
Cash and cash equivalents at the end of the financial half-year	4	3,064,308	3,562,602

Source: Kazia Therapeutics Limited.

Recent Events

October 7, 2025—Kazia Therapeutics Limited ("Kazia" or "the Company") in-licensed NDL2 from QIMR Berghofer, a first-in-class PD-L1 degrader that targets resistant, post-translationally modified PD-L1 across the cell surface, cytoplasm, and nucleus to restore T-cell activity. In preclinical TNBC models, NDL2 reduced tumor growth as monotherapy and with anti-PD-1, with no observed toxicity; initial indications are advanced breast cancer and NSCLC, with IND-enabling studies expected in about six months and first-in-human in roughly 15 months. Financial terms include about $1.39 million upfront, Kazia funding development, and shared revenue from future commercialization or out-licensing.

September 11, 2025—Reported that paxalisib monotherapy achieved 100% disruption of circulating tumor cell (CTC) clusters in Stage IV HER2-positive breast cancer blood samples in an ex vivo study led by Professor Sudha Rao. These clusters are known biomarkers of metastasis and poor prognosis. The findings highlight paxalisib's potential beyond triple-negative breast cancer (TNBC), addressing an unmet need in HER2-positive cases resistant to current therapies. The study supports the use of biomarker-driven precision medicine and complements Kazia's ongoing trials in metastatic breast cancer.

August 1, 2025—Raised $2 million via a private placement (PIPE) with institutional investors, priced at a 5% premium to market. The financing includes ordinary shares and prefunded warrants, without common warrant coverage, and is expected to close on August 4, 2025. Proceeds will support ongoing clinical development of paxalisib and EVT801, as well as general corporate purposes. CEO Dr. John Friend highlighted the funding's role in advancing near-term catalysts, particularly in advanced breast cancer.

July 10, 2025—Reported encouraging early efficacy data from the first patient in its Phase 1b trial combining paxalisib, pembrolizumab (Keytruda®), and chemotherapy for metastatic TNBC. After 21 days, the patient showed a >50% reduction in circulating tumor cells (CTCs) and significant disruption of CTC clusters, key markers of metastatic potential. These findings mirror Kazia's preclinical models and suggest a synergistic anti-metastatic effect from the combination therapy. Enrollment continues with further analyses planned to evaluate safety, immune response, and long-term outcomes.

June 12, 2025—A QIMR Berghofer-led study with Kazia Therapeutics found that paxalisib combined with immunotherapy triggered a novel epigenetic mechanism that blocked cancer spread and overcame resistance in preclinical TNBC models. The dual inhibition of PI3K and mTOR pathways disrupted EZH2, a key metastasis driver, while enhancing tumor immune visibility. These findings support an ongoing Phase 1b trial of paxalisib in combination with chemo-immunotherapy or olaparib in metastatic breast cancer patients. The study was published in *Molecular Cancer Therapeutics*.

June 5, 2025—Dosed the first patient in its Phase 1b trial of paxalisib in advanced breast cancer, evaluating combinations with olaparib or pembrolizumab plus chemotherapy. The trial aims to assess safety, efficacy, and biomarker responses, including circulating tumor cells and immune signatures. It marks paxalisib's expansion beyond brain cancer into broader solid tumors. This study may unlock new combination strategies for treatment-resistant breast cancers, particularly triple-negative and BRCA-mutated subtypes.

May 15, 2025—Announced key advancements in Q1 2025, including a $3 million capital raise and a research grant from The Michael J. Fox Foundation to explore paxalisib for Parkinson's disease. The Company also launched a new Phase 1b trial in advanced breast cancer, and reached FDA alignment on the design for a pivotal Phase 3 glioblastoma study. Additionally, final follow-up was completed in the Phase 1 trial of EVT801 for solid tumors, and Kazia is actively addressing NASDAQ compliance following a notification regarding market value.

March 10, 2025—Postponed its Annual General Meeting (AGM) to Thursday, May 22, 2025 at 10:00am AEST, to be held virtually. No changes were made to the original Notice of Meeting or Proxy Form, and previously submitted proxies remain valid. Shareholders can join the meeting via Zoom and vote live through the provided online platform.

February 20, 2025—Kazia and the Hebrew University of Jerusalem have received a research grant from The Michael J. Fox Foundation to explore paxalisib as a potential treatment for Parkinson's disease. The study will assess paxalisib's effects on motor function and disease biomarkers in preclinical models. This collaboration aims to establish mechanistic links and therapeutic relevance for future development.

January 30, 2025—Launched the ABC-Pax Phase 1b trial combining paxalisib with either Keytruda® or Lynparza® in women with advanced TNBC. The study will enroll 24 patients in Australia and builds on preclinical research showing that the combination reprograms dormant cancer cells and boosts immune response. It is the first clinical trial to test these combinations in TNBC. The trial also integrates a novel liquid biopsy platform for real-time treatment monitoring.

January 14, 2025—Closed a $2 million registered direct offering with Alumni Capital LP, issuing 1.33 million ADSs at $1.50 each, alongside a private placement of warrants exercisable at the same price. The warrants are valid for 5.5 years. Maxim Group LLC acted as the placement agent. Proceeds will support general corporate purposes, including clinical development and operational expenses

January 10, 2025—Announced a $2 million registered direct offering, selling 1.33 million ADSs at $1.50 each, alongside a private placement of equal-numbered warrants with the same exercise price. The warrants are immediately exercisable and expire in 5.5 years. Maxim Group LLC is acting as the exclusive placement agent. Proceeds will fund research, clinical development, and general corporate purposes.

December 31, 2024—Shared a regulatory update on paxalisib for glioblastoma following a Type C meeting with the FDA. The agency indicated that overall survival data from the GBM-AGILE study could support a traditional (not accelerated) approval. Kazia and the FDA reached alignment on key design elements for a pivotal Phase 3 trial. The Company also noted ongoing trials in pediatric brain cancer and brain metastases, with additional potential in breast cancers with PI3K mutations.

November 4, 2024—Announced it has been granted a Type C meeting with the FDA in December 2024 to discuss registration pathways for paxalisib in newly diagnosed GBM. The meeting follows promising overall survival data from the GBM-AGILE Phase 2/3 trial. Paxalisib has orphan and fast track designations for GBM. Kazia also released an updated corporate presentation and will present at key medical meetings including SNO and SABCS later in 2024.

October 2, 2024—Presented promising Phase 1 data at ASTRO 2024 showing that paxalisib combined with radiation therapy achieved a 67% partial response rate in patients with PI3K-mutant brain or leptomeningeal metastases. Over two-thirds of patients at the maximum tolerated dose (45 mg/day) showed intracranial response, exceeding historical WBRT response rates. The regimen was well-tolerated, and further data, including ctDNA analysis, will be presented at future conferences. Discussions for a pivotal registration study are underway.

September 23, 2024—Presented encouraging Phase 1 clinical data for EVT801 at the 15th Biennial Ovarian Cancer Research Symposium. In heavily pretreated patients with high-grade serous ovarian cancer, 46% achieved stable disease, and one patient had a partial response (-39% decrease). The study met its safety goals, establishing a recommended Phase 2 dose of 400 mg BID, with good tolerability across all dose levels. These results support EVT801's potential as a first-in-class VEGFR3-targeted therapy.

July 10, 2024—Announced results from the GBM-AGILE Phase 2/3 trial, showing a 3.8-month improvement in overall survival in newly diagnosed unmethylated GBM patients treated with paxalisib, compared to standard of care in a prespecified secondary analysis. Median overall survival reached 15.54 months vs. 11.89 months in the concurrent control arm. Paxalisib was well tolerated, with no new safety issues. Kazia plans to discuss a potential accelerated approval pathway with the FDA based on these findings.

June 27, 2024—Announced new paxalisib data presentations at ISPNO 2024 and a related publication in the *European Journal of Cancer* emphasizing the need for CNS-penetrant PI3K inhibitors in pediatric brain cancers. Highlights include survival data from 132 DMG patients in the PNOC022 Phase 2 trial, with median overall survival of 13.2-15.8 months in newly diagnosed cohorts. Additional preclinical data on paxalisib combinations in DMG and AT/RT models will also be presented, with plans to advance these findings into future clinical trials.

Risks and Disclosures

This Executive Informational Overview® (EIO) has been prepared by Crystal Research Associates, LLC ("CRA") with the assistance of Kazia Therapeutics Limited ("Kazia" or "the Company") based upon information provided by the Company. CRA has not independently verified such information. Some of the information in this EIO relates to future events or future business and financial performance. Such statements constitute forward-looking information within the meaning of the Private Securities Litigation Act of 1995. Such statements can only be predictions and the actual events or results may differ from those discussed due to the risks described in Kazia's SEC statements on forms filed from time to time.

The content of this report concerning Kazia has been compiled primarily from information available to the public released by the Company through news releases and other filings. Kazia is solely responsible for the accuracy of this information. Information as to other companies has been prepared from publicly available information and has not been independently verified by Kazia or CRA. Certain summaries of activities and outcomes have been condensed to aid the reader in gaining a general understanding. CRA assumes no responsibility to update the information contained in this report. In addition, for year one of its agreement, CRA has been compensated by the Company in cash of forty five thousand dollars for its services in creating this report and for quarterly updates.

Investors should carefully consider the risks and information about Kazia's business, as described below and more fully detailed in the Company's recent filings. Investors should not interpret the order in which considerations are presented in this document or other filings as an indication of their relative importance. In addition, the risks and uncertainties covered in the accompanying sections are not the only risks the Company faces. Additional risks and uncertainties not presently known to Kazia or that it currently believes to be immaterial may also adversely affect the Company's business and are outlined in the Company's recent filings. If any such risks and uncertainties develop into an actual event, Kazia's business, financial condition, and results of operations could be materially and adversely affected.

This report is published solely for information purposes and is not to be construed as an offer to sell or the solicitation of an offer to buy any security in any state. Past performance does not guarantee future performance. For more complete information about the risks involved in investing in the Company, as well as for copies of this report, please contact Kazia by calling +61 2 9472 4101.

Risk Factors

Financial Condition and Capital Requirements

Continuing losses and limited revenue

Kazia has not generated significant product revenue and has incurred net losses of A$25.0 million, A$20.5 million, and A$26.48 million for fiscal years ended June 30, 2022 (restated), 2023, and 2024, respectively. FY2024 revenue of A$2.3 million came from licensing, which is irregular and milestone-dependent. As of 30 June 2024, accumulated losses were A$115.1 million. Given ongoing R&D, clinical, and regulatory activities, the Company expects substantial operating losses for the foreseeable future and may never achieve or maintain profitability.

Funding needs and dilution

The Company has financed operations primarily through equity issuance, Australian R&D grants, and collaboration payments. It expects to seek additional capital via public or private financings, debt, licensing, and alliances. There is no assurance of availability or acceptable terms. Any equity financing will dilute existing holders; dilution could be significant if the share price is low at the time of financing. Debt financing could impose restrictive covenants or require asset pledges.

Runway, going concern, and "baby shelf" limits

As of December 31, 2024, cash was A$3.06 million. Management expects existing cash, together with December 2024 capital raised and access to the ATM and Alumni Capital equity line, to fund R&D activities until approximately March 2026. Financial statements are prepared on a going concern basis, but continuation depends on new capital, licensing, and other revenue.

Macroeconomic and geopolitical conditions

Inflation, capital-markets volatility, and geopolitical conflicts may disrupt funding markets, supply chains, and commodity prices. Sanctions and broader market instability could reduce liquidity and increase financing costs, adversely affecting operations and the ability to raise capital or partner programs.

Foreign exchange exposure

As an Australian issuer with significant USD-denominated operations and costs, results are exposed to AUD-USD exchange-rate movements, which can affect reported expenses, cash runway, and funding needs.

Product Development and Regulatory Risks

Pipeline concentration and clinical risk

Kazia's clinical programs are paxalisib (**PI3K/AKT/mTOR inhibitor**) and EVT801 (selective VEGFR3 inhibitor). Despite target validation, either or both candidates may fail to demonstrate sufficient safety and efficacy to support approval or commercial viability, which would materially harm operations and financial condition.

Explicit GBM-AGILE outcome

In glioblastoma, paxalisib did not achieve statistical significance on the GBM-AGILE primary analysis versus the cumulative control arm. This increases the risk that subsequent studies may fail to meet endpoints and may affect timelines, cost, and probability of success.

FDA pathway status

Following FDA interactions, accelerated approval is not currently available for paxalisib. A traditional, adequately powered Phase 3 registration study is required for standard approval, which adds time and capital requirements and increases execution risk.

Unexpected safety events

Human studies carry the risk of adverse events, including unanticipated toxicities despite preclinical characterization. Significant safety concerns could force trial halts or program discontinuation and damage reputation.

Dependence on successful trials and timely data

Prospects depend on initiating and completing preclinical and clinical studies on schedule, enrolling and dosing patients, generating interpretable data, and achieving endpoints. Negative or ambiguous results, delays, or changes in regulatory expectations would impair approval timelines and value.

Regulatory designations and limits

Paxalisib holds U.S. Orphan designations in glioblastoma, malignant glioma (including DIPG), and AT/RT. Orphan exclusivity, if obtained, can be lost or bypassed if a competitor demonstrates clinical superiority. Designations do not guarantee approval or commercial success.

Market acceptance post-approval

If approved, uptake will depend on comparative efficacy and safety, clinical practice trends, competing therapies, exclusivity, launch timing, pricing, reimbursement, and commercial execution.

Commercialization and Competitive Landscape

Commercial infrastructure and partnerships

Kazia will need agreements for packaging, branding, market access, distribution, and potentially sales and marketing. Negotiations can be lengthy and uncertain, and counterparties may be deterred by limited operating history. Inability to secure or maintain agreements could delay launches and reduce revenue potential.

Intense competition

Biotech and pharmaceutical companies, universities, and research institutions are developing treatments for the same indications, many with greater capital, experience, and infrastructure. Competitors may secure earlier approvals, superior efficacy, better safety, or lower prices, limiting market share. Competition also extends to recruiting key personnel, CRO capacity, trial sites, and partners.

Strategic Transactions and Collaborations

Execution and integration risk

The Company evaluates collaborations, licensing, acquisitions, and asset sales. Any transaction may carry integration challenges, unknown liabilities, higher-than-expected costs, impairment charges, or management distraction. Terms may be suboptimal. Failure to secure beneficial transactions could slow development, increase cost, and weaken competitive position.

Reliance on external experts

Kazia engages outside scientists, clinicians, and consultants who are not employees and may have competing commitments and interests. Conflicts or availability constraints could limit access to expertise or continuity of clinical leadership.

Reliance on Third Parties and Manufacturing

CROs and vendors

Kazia depends on third parties for preclinical studies, clinical trials, and manufacturing. Performance shortfalls, noncompliance, or scheduling constraints can delay or derail programs and may necessitate vendor changes. Collaborator-run activities are outside the Company's direct control.

Manufacturing capacity, quality, and cost

The Company outsources API and drug product manufacturing to FDA-registered facilities. Pharmaceutical manufacturing is complex and capacity-constrained; processes are not readily portable. Vendor deficiencies, quality issues, or limited capacity could disrupt supply. Cost increases in materials or services would raise trial expenses and could pressure future margins. Loss, damage, or theft of intermediates or finished product, including during transit or storage, could cause significant setbacks.

Intellectual Property

Patent uncertainty and challenges

The Company relies on patents, trade secrets, and know-how. Patent prosecution outcomes are uncertain; applications may not issue or may issue with limited scope. Patents can be opposed, re-examined, or invalidated, and competitors may design around claims or assert prior commercial use. Patent terms are finite, and delays to approval can erode effective exclusivity.

Trade secret risks

Protecting confidential information is challenging. Breaches, inadequate agreements, or independent discovery by others could weaken protection. Enforcement in some jurisdictions is difficult and costly, with uncertain outcomes.

Administrative compliance

Patent rights can lapse for failure to meet procedural or fee requirements across jurisdictions. Global filing, prosecution, and defense are costly, and protection gaps may permit competitors to exploit Kazia technologies in certain markets.

Information Technology and Data Security

Cybersecurity and system failures

Internal systems and those of CROs, manufacturers, and other partners are vulnerable to cyberattacks, unauthorized access, and infrastructure failures. Data loss or exposure, including clinical or preclinical data, could delay development, increase costs, create liability, and damage reputation.

Tax Matters

Utilization of tax losses

Kazia has significant carried-forward tax losses that may be unavailable depending on Australian continuity of ownership or same/similar business tests. Future ownership changes could further limit usage.

PFIC status

For U.S. federal income tax purposes, the Company believes it was a Passive Foreign Investment Company (PFIC) for 2023 and believes it was not a PFIC for 2024, but there is no assurance regarding current or future years. PFIC status can adversely affect U.S. investors' after-tax returns and reduce the value of ordinary shares or ADSs.

Securities, Listing, and Corporate Status

NASDAQ listing risk and volatility

The ADSs trade on NASDAQ. Failure to meet continued listing requirements, including minimum bid price, could result in delisting, reducing liquidity and access to capital and potentially triggering further share-price pressure. On November 20, 2023, Kazia received a NASDAQ notice for bid-price deficiency, received an extension to November 18, 2024, and implemented an ADS ratio change effective October 28, 2024 (one ADS now representing one hundred ordinary shares), which functions like a one-for-ten reverse ADS split. There is no assurance the Company will maintain compliance. The ADS price is highly volatile and can be affected by clinical news, regulatory developments, analyst estimates, financings, and broader biotech sentiment. Volatility may increase litigation risk and can limit use of ADSs as margin collateral if priced below US$5.00.

NASDAQ MVLS deficiency

On May 12, 2025, Kazia received a NASDAQ notice that its Market Value of Listed Securities (MVLS) was below the US$35 million minimum from March 28 to May 9, 2025. Under Listing Rule 5810(c)(3)(C), the Company has until November 10, 2025 to regain compliance by maintaining MVLS at or above US$35 million for at least ten consecutive business days. While management is evaluating options, such as capital raising and potential M&A, there is no assurance Kazia will regain or maintain compliance. Failure to do so could lead to delisting from the Nasdaq Capital Market, which would likely reduce liquidity, increase volatility, and impair the Company's ability to access capital on favorable terms.

ASX delisting

The Company delisted from the ASX effective November 15, 2023. Ordinary shares are no longer quoted on ASX and trade only as ADSs on NASDAQ. This may reduce liquidity and require holders to convert ordinary shares to ADSs or transact privately.

Foreign private issuer and governance

Kazia is an Australian company and a foreign private issuer. Loss of this status would increase reporting and compliance costs under the U.S. domestic issuer regime and could complicate insurance and director recruitment. Australian takeover laws restrict acquisitions above certain thresholds, which could discourage takeover offers and limit shareholders' ability to obtain a control premium.

Depositary structure and ADS holder rights

ADS holders rely on the depositary to exercise voting rights and to receive distributions. Timing, procedural limitations, and legal constraints may prevent ADS holders from voting or receiving distributions on a comparable basis to ordinary shareholders. The depositary may restrict transfers or distributions under certain circumstances.

Civil liabilities and enforceability

With many assets and officers outside the U.S., service of process and enforcement of U.S. judgments may be difficult in Australia. This may limit investor remedies under U.S. securities laws.

Internal control over financial reporting

The Company previously identified a material weakness related to accounting for the EVT801 intangible and contingent consideration; this has been remediated. Ongoing compliance with Section 404 of the Sarbanes-Oxley Act is resource-intensive, and future deficiencies or weaknesses could occur, affecting reporting reliability, investor confidence, and share price.

Human Capital

Attracting and retaining key personnel

Success depends on continued service from management and specialized technical staff. Competition for talent is intense, and the Company does not maintain key person life insurance. Loss of personnel or inability to recruit could delay programs, increase cost, and weaken execution.

Strategic Focus and Resource Allocation

Portfolio prioritization risk

With limited resources, the Company may delay or forgo opportunities that later prove more valuable, misjudge target markets, or out-license assets on terms that, in hindsight, are less favorable than retaining rights. R&D spending may not yield commercially viable products.

Glossary

Atypical Teratoid/Rhabdoid Tumor (AT/RT)—A rare, fast-growing embryonal tumor of the central nervous system (CNS), most common in children under 3 but can occur in older kids. Frequently driven by loss of the SMARCB1 (INI1) tumor suppressor (less commonly SMARCA4). It is treated with combinations of surgery (when possible), intensive chemotherapy, and radiation; prognosis remains poor though outcomes are improving at specialized centers.

Basket studies—Clinical trials that test a single investigational therapy across multiple cancer types that share a common biomarker or pathway (e.g., PI3K/mTOR activation). Each cancer type is a separate cohort ("basket") analyzed independently, allowing cohorts to open, expand, or close based on their own signals under one master protocol. (Contrast: an "umbrella" trial tests multiple therapies within one cancer type).

Blood-brain barrier—Tight junctions in brain capillary endothelium that restrict and actively efflux substances into the CNS, limiting drug entry.

BRCA mutations—BRCA mutations are harmful changes in the BRCA1 or BRCA2 genes that impair DNA repair by homologous recombination and raise the risk of certain cancers, especially breast and ovarian cancer.

Cox models—Cox models are survival-analysis methods (Cox proportional hazards models) that estimate the effect of variables on the hazard of an event over time, assuming proportional hazards.

Diffuse Intrinsic Pontine Glioma (DIPG)—A highly aggressive pediatric brain tumor that forms in the pons (brainstem). It is infiltrative and not surgically resectable. Mostly affects children ages 5-10. Symptoms include cranial nerve problems, balance issues, and weakness. Standard care is focal radiation, which can temporarily improve symptoms; median survival is typically 9-11 months. Paxalisib holds FDA Rare Pediatric Disease and Orphan Drug designations.

Diffuse midline glioma (DMG)—Diffuse midline glioma is a high-grade glioma arising in midline CNS structures (e.g., pons, thalamus, spinal cord), often with H3 K27-altered biology and a dismal prognosis.

Fast Track—A designation to speed the development and review of drugs for serious conditions with unmet medical need. It provides earlier and more frequent FDA meetings, rolling review of sections of the NDA/BLA as they are completed, and eligibility for Priority Review and Accelerated Approval if criteria are met.

Focal cortical dysplasia, type II (FCD-T2)—A malformation of brain cortical development that features disorganized cortex with dysmorphic neurons (type IIA) and often balloon cells (type IIB), typically causing focal, medication-resistant seizures beginning in childhood; mTOR-pathway dysregulation is common, which makes it a target for pathway-directed therapies.

Glioblastoma (GBM)—The most common and aggressive primary malignant brain tumor in adults, marked by rapid growth, diffuse invasion, and poor median survival despite standard therapy.

Glioblastoma Adaptive Global Innovative Learning Environment (GBM-AGILE)—An international, seamless Phase 2/3 adaptive platform trial run under a single master protocol to test multiple therapies for newly diagnosed and recurrent GBM against a common control, adding or dropping arms over time based on performance (Bayesian response-adaptive randomization). It is sponsored by the Global Coalition for Adaptive Research (GCAR), is designed with registrational intent, and data from successful arms can support regulatory filings.

Glioma—A primary tumor that arises from glial cells in the central nervous system. In this report, "glioma" most often refers to high-grade forms like glioblastoma and diffuse midline glioma, which are key targets for paxalisib.

HER2-negative—Breast cancer that does not overexpress or amplify the HER2 (ERBB2) gene on standard pathology testing. These tumors are not candidates for traditional anti-HER2 monoclonal antibodies; most are managed as hormone receptor-positive disease or triple-negative breast cancer.

High-grade serous ovarian cancer (HGSOC)—The most common and aggressive epithelial ovarian cancer, usually arising from the fallopian tube, with near-universal TP53 mutations and frequent BRCA/HRD. It typically presents at an advanced stage and is treated with surgery and platinum-taxane chemotherapy, with bevacizumab and PARP-inhibitor maintenance in selected BRCA/HRD-positive disease.

IDH-mutant glioma—A brain tumor whose cells carry a mutation in the IDH1 or IDH2 gene. These mutations create an "oncometabolite" (2-hydroxyglutarate) that rewires cell metabolism and epigenetics. Clinically, IDH mutations are common in lower-grade diffuse gliomas and in many gliomas that progress from lower to higher grade ("secondary" GBM).

Kaplan-Meier—A nonparametric method that estimates the survival function from time-to-event data while appropriately handling censored observations.

Lymphangiogenesis—The formation of new lymphatic vessels, a process that can facilitate tumor fluid drainage and the spread of cancer cells to lymph nodes.

MGMT-unmethylated glioblastoma (GBM)—Glioblastoma with an unmethylated MGMT promoter, typically indicating active DNA repair and reduced benefit from temozolomide chemotherapy.

Myeloid-derived suppressor cells (MDSCs)—Tumor-induced myeloid cells that blunt T-cell/NK activity and drive immune evasion; their abundance predicts poor response to immunotherapy and they are an active target for combinations that inhibit recruitment, function, or survival.

Orphan Drug—A therapy intended to treat a rare disease affecting fewer than 200,000 people in the United States (or one that would not be profitable without incentives), eligible for FDA benefits such as tax credits, user-fee waivers, FDA guidance, and seven years of marketing exclusivity upon approval.

Pacific Pediatric Neuro-Oncology Consortium (PNOC)—An international clinical-trial network focused on bringing new therapies to children and young adults with brain tumors. PNOC designs and runs biology-driven studies across member hospitals in the U.S. and abroad (Europe, Asia/Australia, and more), aiming to translate the latest tumor-biology insights into personalized treatments and better outcomes. UCSF is the lead institution, and PNOC often partners with groups like the Children's Brain Tumor Network to accelerate research and data sharing.

Poly (ADP-ribose) polymerase (PARP) inhibitors—Oral cancer drugs that block the DNA-repair enzymes PARP1/2 (poly[ADP-ribose] polymerases). By disabling repair of single-strand DNA breaks, they push tumor cells—especially those already deficient in homologous recombination (e.g., BRCA1/2 mutations)—over the edge, causing cell death via "synthetic lethality." They are used in ovarian, breast, prostate, and pancreatic cancers; examples include olaparib, niraparib, rucaparib, and talazoparib. Common side effects include fatigue, nausea, and low blood counts.

PI3K/AKT/mTOR inhibitor—A drug that blocks signaling in the PI3K/AKT/mTOR pathway to reduce tumor cell growth, survival, and metabolism.

PI3K/AKT/mTOR pathway—A core cell-signaling cascade that carries growth and survival signals from activated cell-surface receptors through PI3K-generated PIP3 to AKT, which then controls metabolism, proliferation, and protein synthesis via downstream targets that include the mTOR complexes. The pathway is commonly dysregulated in cancer through PI3K or AKT mutations, loss of PTEN, or aberrant mTOR activation, which is why inhibitors of these nodes are used therapeutically; in brain tumors, effective drugs must also cross the blood-brain barrier.

Priority Review Voucher—An FDA incentive awarded with certain drug approvals (e.g., for rare pediatric diseases) that grants priority review to another application and may be sold or transferred.

Rare Pediatric Disease—An FDA designation for drugs targeting serious or life threatening diseases primarily affecting patients under 18 years with a U.S. prevalence under 200,000, potentially making the sponsor eligible for a Priority Review Voucher upon approval.

Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM)—An MRI-based response system for brain metastases that sums the longest diameters of up to five contrast-enhancing target lesions (each typically ≥10 mm on axial T1 post-contrast and meeting slice-thickness rules) to define CR (disappearance), PR (≥30% decrease), SD (between PR and PD), or PD (≥20% increase or any new brain lesion/unequivocal CNS worsening), with CR/PR/SD requiring stable or decreasing corticosteroids and stable or improved neurologic status, and with non-target brain disease and leptomeningeal spread documented separately.

Triple negative breast cancer (TNBC)—A breast cancer subtype lacking estrogen and progesterone receptors and without HER2 overexpression or amplification, often associated with aggressive behavior and limited targeted therapy options.

Tuberous sclerosis complex (TSC)—A multisystem genetic disorder caused by pathogenic variants in *TSC1* or *TSC2* that hyperactivate the mTOR pathway, leading to cortical tubers, subependymal tumors, skin findings, kidney angiomyolipomas, and a high rate of drug-resistant seizures and neurodevelopmental symptoms. It is usually inherited in an autosomal-dominant pattern but often arises from a new mutation.

Tyrosine kinase inhibitor (TKI)—A small-molecule drug that blocks specific signaling proteins (kinases) driving a cancer (e.g., HER2, EGFR, ALK). Tucatinib (HER2), osimertinib (EGFR), and alectinib (ALK) are CNS-active TKIs: they cross the blood-brain barrier and have proven intracranial efficacy in brain metastases.

Vascular endothelial growth factor receptor 3 (VEGFR3)—A receptor tyrosine kinase primarily expressed on lymphatic endothelial cells that is activated by VEGF-C and VEGF-D to drive lymphangiogenesis; in cancer, VEGFR3 signaling supports tumor-associated lymphatic remodeling and lymphatic metastasis, making it a therapeutic target (e.g., EVT801) for limiting metastatic spread and improving the tumor immune microenvironment.

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