Kazia Therapeutics

Development update

Multiple paxalisib data points expected in Q4

Pharma & biotech

Kazia expects to release multiple data points from its paxalisib program in Q4 CY21. These include final data from the 30-patient Phase II trial in newly diagnosed glioblastoma multiforme (GBM) patients, as well as initial data for paxalisib in the treatment of brain metastases (BMs). Additionally, the Phase I for EVT801 is expected to begin enrolment by year-end.

Year end	Revenue ($m)	PTP* ($m)	EPADR ($)	DPADR ($)	P/E (x)	Gross yield (%)
6/20	0.8	(8.0)	(1.05)	0.00	N/A	N/A
6/21	11.3	(3.3)	(0.27)	0.00	N/A	N/A
6/22e	1.6	(12.1)	(0.85)	0.00	N/A	N/A
6/23e	1.6	(11.3)	(0.76)	0.00	N/A	N/A

Note: Converted at A$1.35/US$. Dividend yield excludes withholding tax. Investors should consult their tax advisor regarding the application of any domestic and foreign tax laws.

Interim Phase II GBM data very promising

Kazia previously released interim data in 29 patients from its trial in newly diagnosed GBM patients. The data showed progression-free survival (PFS) of 8.4 months and overall survival (OS) of 17.5 months, an improvement over the historical PFS and OS data from temozolomide, a mainstay of GBM treatment. As a reminder, GBM is the most common and aggressive brain tumor and accounts for approximately half of all gliomas. According to the National Cancer Institute, there are approximately 23,820 cases per year of brain and other nervous system cancers in the US and another 64,600 in Europe, according to the International Agency for Research on Cancer.

Initial readouts coming for BM

We consider BMs one of the most interesting indications for which paxalisib could potentially be used and the drug is being investigated for this indication in three clinical studies: one Phase I and two Phase IIs, sponsored by Sloan-Kettering, Alliance Group and Dana-Farber respectively. Some initial data from these studies are expected in Q4 CY21.

EVT801 Phase I expected to start by year-end

EVT801 is an oral small molecule that targets vascular endothelial growth factor receptor 3 (VEGFR3), which Kazia licensed from Evotec in April. Kazia expects to initiate the Phase I program by the end of the year. The Phase I will enroll up to 90 patients with advanced solid tumors that are resistant to existing therapies.

Valuation: US$277m or US$20.92 per basic ADR

We have increased our valuation to US$277m or US$20.92 per basic ADR from US$247m or US$19.14 per basic ADR mainly due to rolling forward our NPV. This was partially offset by lower net cash and slightly higher expenses. Kazia reported net cash of US$20.4m (A$27.6m) at 30 June 2021. Our estimated financing requirement for the company is US$44m (including US$22m in FY23), up from US$36m previously due to increases in R&D spending.

14 October 2021

Price	**$10.96**
Market cap	**$146m**
ADR/Ord conversion ratio	1:10
Net cash (US$m) at 30 June 2021	20.4
ADRs in issue	13.3m
ADR code	KZIA
ADR exchange	NASDAQ
Underlying exchange	ASX
Depository	BNY

ADR share price performance

52-week high/low	1,471c	561c

Business description

Kazia Therapeutics is a pharmaceutical company with lead asset paxalisib, a PI3K inhibitor licensed from Genentech that can cross the blood-brain barrier, which is in a pivotal study for GBM. It also recently in-licensed the Phase I drug EVT801, an inhibitor of lymphangiogenesis in tumors.

Next events

Paxalisib Phase II GBM final data	Q4 CY21
Paxalisib initial data from brain metastases trials	Q4 CY21
Initiation of EVT801 Phase I	Q4 CY21

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Edison profile page

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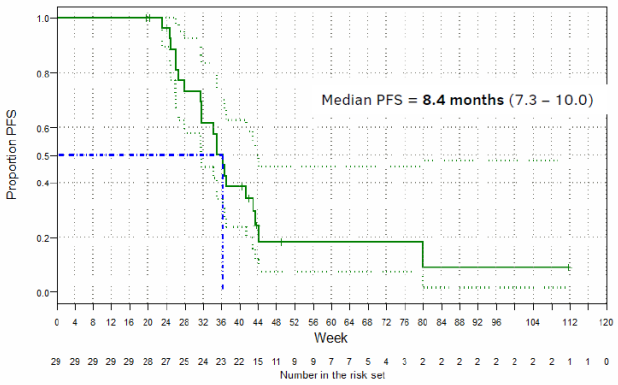
Upcoming data readouts for paxalisib

Paxalisib is a PI3K and mTOR inhibitor being studied in a number of clinical trials involving cancer in the brain. The drug is in a 30-patient Phase II study of patients with newly diagnosed GBM and unmethylated MGMT promotor, with final data expected in Q4 CY21. Paxalisib is being used as an adjuvant following initial resection, radiation treatment and temozolomide.

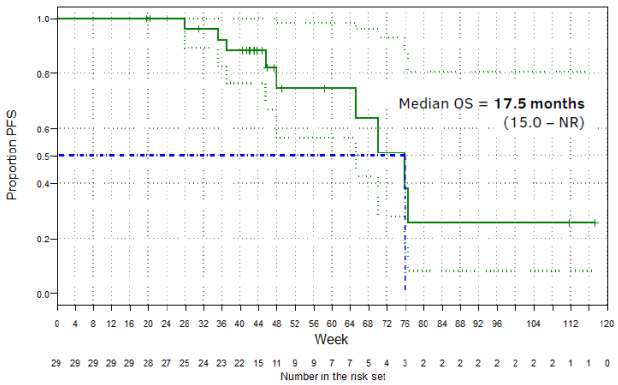
Previously announced interim results have been consistently positive, with the drug demonstrating PFS of 8.4 months and OS of 17.5 months (Exhibits 1 and 2) in 29 patients.

Exhibit 1: PFS of GBM treated with paxalisib



Source: Kazia Therapeutics

Exhibit 2: OS of GBM treated with paxalisib



Source: Kazia Therapeutics

These values compare favorably to historical controls using temozolomide alone in a similar patient population (Exhibit 3). Patients with an unmethylated MGMT promoter are more resistant to temozolomide. It is difficult to draw definitive conclusions using historical controls given the variability between patient populations, so these data should be interpreted with some caution, but they are what is expected with an active drug.

Exhibit 3: OS and PFS in GBM with unmethylated MGMT promoter treated with radiotherapy plus adjuvant temozolomide

	Median overall survival (months)	Median PFS (months)	PFS at six months	Two-year survival rate
Hegi et al, NEJM 2005	12.7	5.3	40%	14%
Nabors et al, Neuro-Oncology 2015	13.4	4.1	N/A	N/A
Gilbert et al, JCO, 2013	14.0	5.7	N/A	N/A
AVAGLIO ASCO, 2013	14.6	5.8	N/A	N/A
RTOG-0825, ASCO, 2013	14.3	N/A	N/A	N/A
Average	**13.8**	**5.2**		

Source: Edison Investment Research; Hegi et al *N Engl J Med* 2005;352(10):997-1003; Nabors et al. *Neuro-Oncology* 2015 17(5):708-717; Gilbert et al. *J Clin Oncol* 2013 31(32):4085-4091. Note: RTOG, Radiation Therapy Oncology Group.

As a reminder, GBM is the most common and aggressive brain tumor and accounts for approximately half of all gliomas.[1] According to the National Cancer Institute, there are approximately 23,820 cases per year of brain and other nervous system cancers in the US, and another 64,600 in Europe according to the International Agency for Research on Cancer. We estimate around 12,000 of these are GBM in the US, with another 32,000 in Europe. The survival

1 Hanif et al., Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. *Asian Pacific Journal of Cancer Prevention*. 18 (1), 3–9

rate of GBM is especially poor with a five-year survival rate of only 5.1% and a median OS of 10 months.[2]

Therapeutic options are limited. Since 2005, only three new treatments have been approved for GBM: temozolomide, bevacizumab and tumor-treating fields. The standard of care for newly diagnosed GBM is a combination of surgery, radiation and temozolomide with recurrence occurring due to resistance to temozolomide.

Paxalisib for BM

Paxalisib is also the subject of three ongoing investigator-sponsored studies of BMs that are expected to provide readouts in the coming months (although as they are being led by investigators rather than the company, the precise timing of when each study will release data is unclear). BMs are a major cause of mortality in metastatic cancer patients because the blood brain barrier limits the effectiveness of many treatments that work at other metastasis sites. According to the US National Cancer Institute, there are 1.9m new cases of all cancers per year and BM are estimated to present at diagnosis at 2.0% of these.[3] This indicates an incidence of around 38,000 at diagnosis, with a much higher number likely over the course of a patient's battle with cancer.

Paxalisib could be well positioned to provide a benefit to these patients as a targeted cancer treatment designed to cross the blood brain barrier. As a reminder, paxalisib was specifically designed in order to achieve high concentrations in the central nervous system[4] and was shown in preclinical studies to cross the blood-brain barrier freely while demonstrating a pharmacodynamic effect. The earliest-stage program is a Phase I study at Memorial Sloan-Kettering investigating paxalisib in combination with radiotherapy for any primary tumor type as long as it has PI3K pathway mutations. This study has targeted enrolment of 36 and we expect the main readout to be on the safety of the combination treatment. Another program in Phase II sponsored by the Alliance Group is also investigating BMs from any primary solid tumor. This program is also investigating the CDK4/6 inhibitor Verzenio (abemaciclib, Eli Lilly) and the TRK inhibitor Vitrakvi (entrectinib).

Finally, we are expecting a readout from the Phase II BCBM study being performed at Dana-Farber. This study is investigating the drug in combination with Herceptin (trastuzumab) in HER2+ breast cancer patients. One retrospective study of patients in Belgium found that among HER2+ breast cancer patients, 10.8% had BMs at their initial screening and 41.7% developed BMs within their lifetime.[5] Survival of these metastatic breast cancer patients was significantly reduced, from 46.7 months for those with no central nervous system involvement to 20.8 months for those with BMs.

EVT801

In April 2021 Kazia announced that it licensed the compound EVT801 from Evotec. The deal included €1m upfront for Evotec, up to €308m in milestones and tiered single-digit royalties. Kazia expects to initiate the Phase I program by the end of the year. The Phase I will enroll up to 90 patients with advanced solid tumors that are resistant to existing therapies. Expectations are for the focus of development to be renal cell carcinoma (RCC), hepatocellular carcinoma and soft tissue sarcoma.

2 Taylor et al., Glioblastoma Multiforme: An Overview of Emerging Therapeutic Targets. *Frontiers in Oncology*. September 2019, Volume 9, Article 963

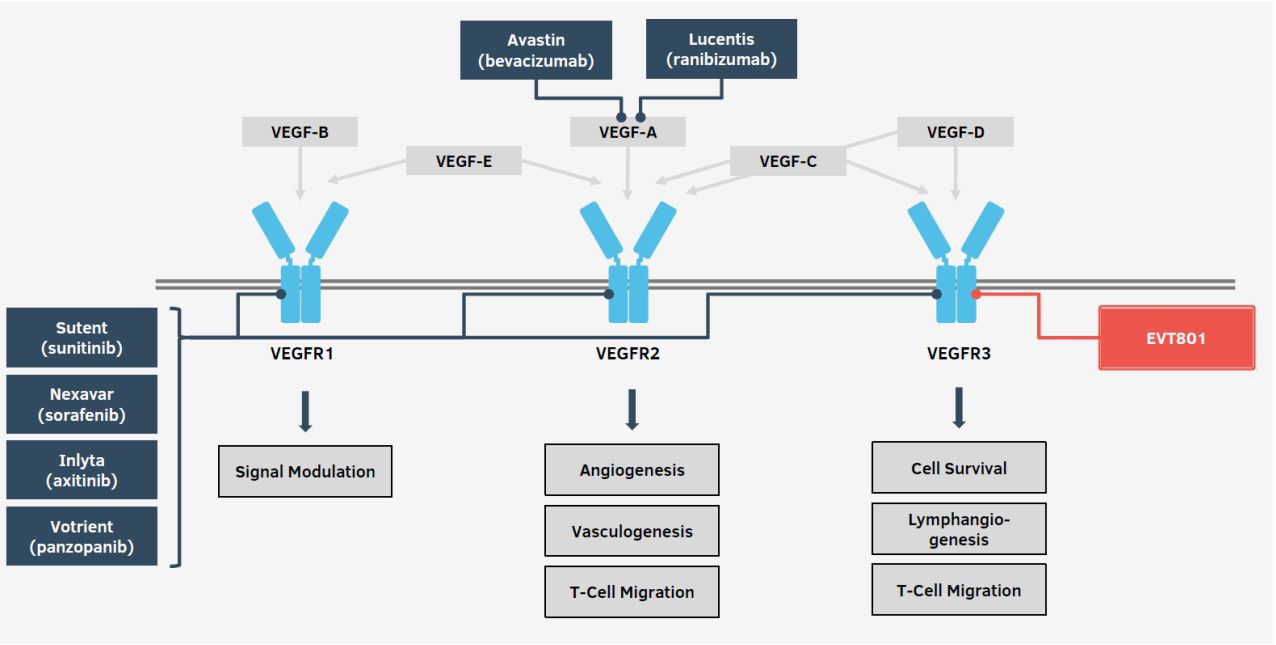
3 Cagney et al., Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro-Oncology* 2017 Oct; 19(11): 1511–1521.

4 Heffron TP, et al. (2016) Discovery of Clinical Development Candidate GDC-0084, a Brain Penetrant Inhibitor of PI3K and mTOR. *ACS Med Chem Let* 7, 351-356.

5 Maurer et al. Risk factors for the development of brain metastases in patients with HER2-positive breast cancer. *ESMO Open* 3,(2018) e000440.

EVT801 is an inhibitor of VEGFR3. This family of proteins (VEGFR) and their ligands (VEGF) have been successfully targeted by a number of anti-cancer therapeutics. Avastin (bevacizumab, Genentech) was the first drug approved to specifically target this signaling pathway. It is a ligand trap for VEGF-A that depletes this growth factor from the blood and prevents activation of the VEGFR family of receptors. Additionally, proteins of the VEGFR family are frequent targets for so-called multi-tyrosine kinase inhibitors. VEGFR proteins are members of the receptor tyrosine kinase class along with other growth factor receptors such as EGFR and FLT3. These other growth factors are also important for tumorigenesis and multi-tyrosine kinase inhibitors such as Nexavar (sorafenib, Bayer) inhibit a wide number of these receptors to varying degrees and achieve their efficacy by this combined effect.

Exhibit 4: The VEGF landscape



Source: Kazia Therapeutics

Historically, the VEGFR family has been targeted to prevent the formation of new blood vessel (angiogenesis) in a tumor. By preventing the generation of new blood vessels, the tumors can be starved of nutrients and oxygen. Avastin is a so-called angiogenesis inhibitor. However, the specific isoform VEGFR3 is associated with the formation of lymphatic vessels (as opposed to blood vessels). Therefore, the specific inhibition of this protein may have a different activity profile from other drugs that target this VEGFR class. The lymphatic system is the primary route of metastasis for many tumor types.

One feature highlighted by Evotec is that EVT801 can shift the balance of immune cells in a tumor, which may be an advantage if EVT801 is combined with immunotherapy such as checkpoint inhibitors.

Valuation

We have increased our valuation to US$277m or US$20.92 per basic ADR from US$247m or US$19.14 per basic ADR mainly due to rolling forward our NPV. This was partially offset by lower net cash and slightly higher expense expectations.

Exhibit 5: Kazia valuation table

Development Program	Indication	Clinical stage	Prob. of success	Launch year	Patent/Exclusivity Protection	Launch Pricing ($/course)	Peak sales (US$m)	rNPV (US$m)
Paxalisib	GBM	Phase II	35%	2025	2037	169,000	450	203.87
	BCBMs	Phase II	5%	2029	2037	183,000	249	7.17
Cantrixil	OC	Phsae I complete	15%	2027	2040	124,000	174	7.05
EVT801	RCC	Phase I ready	10%	2028	2037	120,000	807	38.78
Total								256.88
Net cash and equivalents (FY21) (US$m)								20.41
Total firm value (US$m)								277.29
Total basic ADRs (m)								13.3
Value per basic ADR (US$)								20.92
Dilutive options (as ADRs, m)								0.61
Total diluted ADRs								13.9
Value per diluted ADR								20.19

Source: Edison Investment Research

Financials

Kazia reported revenue for FY21 (ending 30 June 2021) of US$11.3m (A$15.2m), stemming from licensing agreements such as the Oasmia deal for cantrixil and the Simcere licensing of the Greater China rights for paxalisib. R&D increased to US$10.8m (A$14.5m) from US$7.0m (A$9.5m) the year before due to the advancement of the clinical trial programs. G&A also increased from US$2.7m (A$3.7m) to US$5.2m (A$7.0m). The net loss for the year was US$6.2m (A$8.4m) compared to US$9.2m (A$12.5m) in FY20. Based on these results, we have increased our FY22 revenue estimate by US$0.4m (A$0.6m) due to a higher expected R&D rebate (due to higher R&D spending). We have also increased our R&D estimate for FY22 by US$0.3m (A$0.4m), although we have decreased our G&A estimate by US$1.6m (A$2.2m) as much of the spending in FY21 was transaction related and one-time (non-recurring). Additionally, we are introducing our FY23 estimates, which feature R&D spending of US$9.7m (A$13.2m), down from the current level as we believe much of the pivotal trial spending is front-end loaded, and G&A of US$4.5m (A$6.1m).

The company reported net cash of US$20.4m (A$27.6m) at 30 June 2021. Our estimated financing requirement for the company is US$44m (including US$22m in FY23), up from US$36m due to higher R&D spending as well as to provide a higher cushion for working capital needs.

Exhibit 6: Financial summary

$'k	2020	2021	2022e	2023e
30-June	IFRS	IFRS	IFRS	IFRS
INCOME STATEMENT				
Revenue	785.1	11,268.1	1,592.2	1,570.7
Cost of Sales	0.0	0.0	0.0	0.0
Gross Profit	785.1	11,268.1	1,592.2	1,570.7
R&D	7,025.8	10,760.6	10,615.3	9,738.4
SG&A	2,730.5	5,196.1	4,468.5	4,513.2
EBITDA	(7,974.9)	(3,281.4)	(12,084.4)	(11,273.7)
Normalized operating profit	(7,974.9)	(3,281.4)	(12,084.4)	(11,273.7)
Amortization of acquired intangibles	(802.4)	(936.3)	(936.3)	(936.3)
Exceptionals	(475.4)	(1,902.0)	0.0	0.0
Share-based payments	(194.0)	(470.9)	(470.9)	(470.9)
Reported operating profit	(9,446.6)	(6,590.7)	(13,491.6)	(12,680.9)
Net Interest	0.0	0.0	0.0	0.0
Joint ventures & associates (post tax)	0.0	0.0	0.0	0.0
Exceptionals	0.0	0.0	0.0	0.0
Profit Before Tax (norm)	(7,974.9)	(3,281.4)	(12,084.4)	(11,273.7)
Profit Before Tax (reported)	(9,446.6)	(6,590.7)	(13,491.6)	(12,680.9)
Reported tax	220.7	358.4	514.9	484.0
Profit After Tax (norm)	(7,670.5)	(3,156.2)	(11,623.2)	(10,843.4)
Profit After Tax (reported)	(9,225.9)	(6,232.3)	(12,976.7)	(12,197.0)
Minority interests	0.0	0.0	0.0	0.0
Discontinued operations	0.0	0.0	0.0	0.0
Net income (normalized)	(7,670.5)	(3,156.2)	(11,623.2)	(10,843.4)
Net income (reported)	(9,225.9)	(6,232.3)	(12,976.7)	(12,197.0)
Basic average number of ADRs outstanding (m)	7.3	11.8	13.6	14.3
EPADR - basic normalized ($)	(1.05)	(0.27)	(0.85)	(0.76)
EPADR - diluted normalized ($)	(1.05)	(0.27)	(0.85)	(0.76)
EPADR - basic reported ($)	(1.26)	(0.53)	(0.95)	(0.85)
Dividend (A$)	0.00	0.00	0.00	0.00
BALANCE SHEET				
Fixed Assets	9,183.5	21,235.2	18,818.9	16,402.5
Intangible Assets	9,183.5	16,281.9	15,345.6	14,409.3
Tangible Assets	0.0	0.0	0.0	0.0
Investments & other	0.0	4,953.3	3,473.3	1,993.3
Current Assets	7,883.7	21,749.2	10,867.0	23,068.1
Stocks	0.0	0.0	0.0	0.0
Debtors	1,000.7	62.4	1,046.9	1,032.8
Cash & cash equivalents	6,485.4	20,414.2	8,547.5	20,762.7
Other	397.6	1,272.6	1,272.6	1,272.6
Current Liabilities	(3,749.9)	(6,161.6)	(5,883.8)	(5,678.6)
Creditors	(2,581.8)	(3,650.2)	(3,372.3)	(3,167.1)
Tax and social security	0.0	0.0	0.0	0.0
Short term borrowings	0.0	0.0	0.0	0.0
Other	(1,168.1)	(2,511.5)	(2,511.5)	(2,511.5)
Long Term Liabilities	(2,864.3)	(8,813.2)	(8,298.3)	(30,014.4)
Long term borrowings	0.0	0.0	0.0	(22,200.0)
Other long term liabilities	(2,864.3)	(8,813.2)	(8,298.3)	(7,814.4)
Net Assets	10,452.9	28,009.5	15,503.7	3,777.7
Minority interests	0.0	0.0	0.0	0.0
Shareholders' equity	10,452.9	28,009.5	15,503.7	3,777.7
CASH FLOW				
Op Cash Flow before WC and tax	(7,974.9)	(3,281.4)	(12,084.4)	(11,273.7)
Working capital	1,235.2	(4,137.2)	(297.2)	805.0
Exceptional & other	220.7	676.8	514.9	484.0
Tax	0.0	0.0	0.0	0.0
Net operating cash flow	(6,519.0)	(6,741.8)	(11,866.7)	(9,984.7)
Capex	0.0	0.0	0.0	0.0
Acquisitions/disposals	0.0	0.0	0.0	0.0
Net interest	0.0	0.0	0.0	0.0
Equity financing	8,983.4	20,800.5	0.0	0.0
Dividends	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0
Net Cash Flow	2,464.3	14,058.8	(11,866.7)	(9,984.7)
Opening net debt/(cash)	(4,021.1)	(6,485.4)	(20,414.2)	(8,547.5)
FX	0.0	(130.0)	0.0	0.0
Other non-cash movements	0.0	0.0	0.0	0.0
Closing net debt/(cash)	(6,485.4)	(20,414.2)	(8,547.5)	1,437.3

Source: Company reports, Edison Investment Research

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