Kazia Therapeutics

Clinical update

Phase IIa shows good safety, consistent efficacy

Pharma & biotech

Kazia presented the results from a new interim data analysis of its ongoing Phase IIa study of paxalisib in glioblastoma multiforme (GBM). The data were consistent with previous data and showed progression-free survival (PFS) of 8.4 months and overall survival (OS) of 17.5 months. Importantly, Kazia also published some of the first safety data at the full 60mg dose, which show an attractive profile compared to other members of this class.

Year end	Revenue (US$m)	PTP* (US$m)	EPADR (US$)	DPADR (US$)	P/E (x)	Gross yield (%)
06/19	1.1	(5.3)	(0.91)	0.00	N/A	N/A
06/20	0.8	(7.7)	(1.05)	0.00	N/A	N/A
06/21e	1.0	(8.2)	(0.69)	0.00	N/A	N/A
06/22e	1.1	(8.5)	(0.64)	0.00	N/A	N/A

Note: Converted at A$1.4/US$. Dividend yield excludes withholding tax. Investors should consult their tax advisor regarding the application of any domestic and foreign tax laws.

Pivotal studies here we come

The company presented the data from the study at the Society for Neuro-Oncology (SNO) meeting on 19 November 2020. The study is a dose-escalation/expansion study, which previously established 60mg as the maximum tolerated dose (MTD), and is currently in the Phase IIa expansion portion. A total of 29 patients were included in the analysis, of which 24 received the 60mg dose. The study is expected to continue to follow these patients into H121, but the company is not waiting to progress the program and expects to enroll the first patient into the pivotal GBM AGILE study in early calendar Q121.

Efficacy looks good, safety is key

The PFS and OS currently being reported are very similar to previous reports (8.5 and 17.7 months with n=27), which were promising the first time and it is good to see this consistency. However, the real game changer in this release is the safety data, which give us a much higher degree of confidence in this program. The PI3K class of drugs has historically been difficult to develop without high-risk adverse events such as opportunistic infections or GI complications, but the current profile from the 24 60mg patients presented shows little indication of these problems.

DIPG might need a combination approach

There was also an oral presentation at the meeting on the Phase I investigator-sponsored study of paxalisib in diffuse intrinsic pontine glioma (DIPG), an aggressive childhood brain cancer. Unfortunately, the study did not demonstrate a clear survival benefit for paxalisib, but the study authors believe there is potential in a combination.

Valuation: Increased to US$184m or US$14.55/ADR

We have increased our valuation to US$184m or US$14.55 per ADR from US$104m or US$10.98 per ADR. This is driven by increasing our probability of success for paxalisib in GBM to 35% (US$151.8m) from 20% (US$81.8m) and the October US$18m raise (31.5m shares at A$0.80).

2 December 2020

Price	**US$9.9**
Market cap	**US$125m**
	ADR/Ord conversion ratio 10:1
Net cash (US$m) at 30 September 2020	4.67
ADRs in issue	12.6m
ADR code	KZIA
ADR exchange	NASDAQ
Underlying exchange	ASX
Depository	BNY

ADR share price performance

52-week high/low	US$13.47	US$2.56

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 entering a pivotal study for GBM. It is also being investigated for other brain cancers, and the company has the legacy asset Cantrixil in Phase I for ovarian cancer.

Next events

BCBM Phase II results	H220
First patient in GBM AGILE	Early 2021
GBM Phase IIa complete	H121

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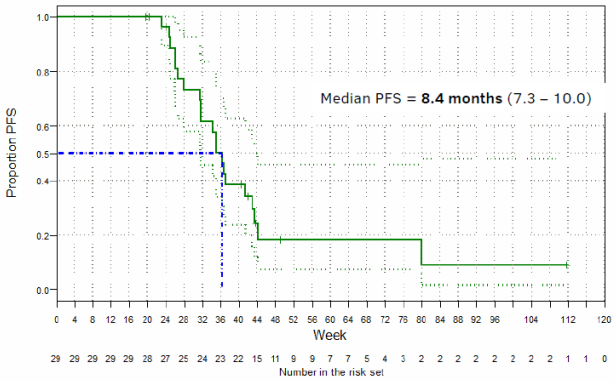
Edison profile page

Phase IIa update: Good news on efficacy and safety

Paxalisib is a PI3K and mTOR inhibitor currently being studied in a Phase I/IIa study of patients with newly diagnosed GBM and unmethylated MGMT promotor. The drug is used as an adjuvant following initial resection, radiation treatment and temozolomide.

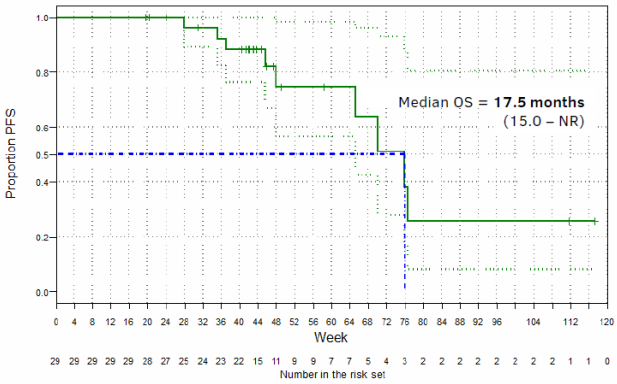
Throughout the course of the study, the efficacy results presented by the company have been very consistent, showing survival data in the same range as the current results: PFS of 8.4 months and an OS of 17.5 months (Exhibits 1 and 2). Only two additional patients have been included in the most recent survival analysis (n=29 vs n=27 in the AACR update), but the new data also include six more months of data on previously enrolled patients. It is not necessarily surprising that the previous results were replicated, but this is not something that was guaranteed, even if the drug is active.

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 you would expect with an active drug.

Exhibit 3: Overall survival 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 encouraging as the efficacy data are from this presentation, the key insight from this release is in the safety data. PI3K inhibitors as a class have generally shown anti-cancer activity, but their utility has been severely limited by safety issues. Three of the four drugs approved from this class have documented fatal side effects, with opportunistic infections being the most common, but including fatal GI, lung and liver complications. Countless other PI3K programs in development have been terminated following the discovery of similar problems. By comparison, paxalisib shows a profile much more similar to Piqray (alpelisib, Novartis), where hyperglycemia and rash are the

most common grade 3-4 adverse events (AEs). We should note that neither paxalisib nor Piqray has a fully benign profile by any means. However, safety is one of the key hurdles for this drug, and this is the first definitive bit of data showing that the drug has to potential to clear it.

Previous safety data largely come from the Genentech Phase I study, which only examined six patients at this approximate dosing level.[1] Moreover, the dose used was poorly tolerated in that much more heavily treated population. However, the general profile is consistent. A key aspect of Kazia's strategy is to improve on these earlier results by finding a higher MTD in earlier-stage patients, and the current research establishes the safety profile at this higher dose.

Exhibit 4: Adverse events in two or more patients, 60mg paxalisib (n=24)

Term	Gr 1	Gr 2	Gr 3	Gr 4	Total (%)
Rash	4	6	7		17 (71%)
Fatigue	2	10	2		14 (58%)
Stomatitis	4	6	1		11 (46%)
Decr. appetite	5	5	1		11 (46%)
Nausea	3	5	1		9 (38%)
Hyperglycemia	1	2	5		8 (33%)
Diarrhea	5	1			6 (25%)
Decr. neutrophils	2	3		1	6 (25%)
Vomiting	3	2	1		6 (25%)
Decr. weight	3	2			5 (21%)
Decr. platelets	4	1			5 (21%)
Dehydration		4	1		5 (21%)
Dysgeusia		4			4 (17%)
Decr. lymphocytes	1	2			3 (13%)
Drug reaction			3		3 (13%)
Malaise	2	1			3 (18%)
Incr. cholesterol	2				2 (8%)
Pruritis	1		1		2 (8%)

Source: Kazia Therapeutics, taken from SNO 2020 poster

This trial is slated to continue into H121, but we believe we have gained the bulk of the information we can get from the study already. Kazia is also not waiting for the final readout and is progressing directly to pivotal studies. The drug is to be included in the GBM AGILE study, a Phase II/III study examining multiple drugs from multiple institutions in GBM. The company has officially started its participation in the study (at least on paper, which triggered a A$5m fee) and expects to enroll its first patient in early CY21.

Paxalisib for DIPG

Additionally, at the SNO conference, the physician from St Jude running the study gave a presentation on the results from the Phase I investigator-sponsored trial of paxalisib for DIPG (n=27). The investigator stated that the study did not show a clear survival benefit compared to historical controls. DIPG is one of the hardest cancers to treat, and single agent activity has never been seen for the disease. The possibility of seeing activity as a monotherapy was therefore a longshot, but the study fulfilled its primary purpose, because it helped to establish the safety profile of the drug in pediatrics. Kazia stated that the profile was similar to that seen in other paxalisib studies, although the MTD of 27mg/m^2 in children is a bit lower than for adults (35mg/m^2, assuming 1.7m^2 for an adult). We expect any future investigations in this indication to examine the drug as a combination therapy. The study remains ongoing and final data will be released in calendar 2021.

[1] Wen PY, et al. (2020) First-in-Human Phase I Study to Evaluate the Brain-Penetrant PI3K/mTOR Inhibitor GDC-0084 in Patients with Progressive or Recurrent High-Grade Glioma. *Clin Cancer Res* 26, 1820-1828.

Valuation

We have increased our valuation to US$184m or US$14.55 per ADR from US$104m or US$10.98 per ADR. This is driven by increasing our probability of success for paxalisib in GBM to 35% from 20%. We are increasing this on the basis of the interim safety and efficacy results from the Phase IIa study. The study is not complete, but we do not expect to see any more definitive data than we have already seen. The company highlights the fact that the current study stage is relatively mature, which suggests the final results will be very similar to the interim analyses. We believe the reported data reduces some of the risk surrounding safety for the molecule. Conversely, we are removing DIPG from our models. We do not necessarily believe the drug cannot work in this indication, but new studies will need to be undertaken and we are unaware of any plans to finance this program internally. Moreover, more preclinical research may be needed on paxalisib in DIPG.

Additionally, we have rolled forward our NPVs and adjusted for the new cash balance, which includes US$4.67m reported at the end of September 2020 and the US$18m offering (estimated US$17m net) announced (for approximately 31.5m shares at A$0.80) in October 2020. Additionally, we have deducted US$5m to reflect the milestone fees associated with starting the GBM AGILE study.

Exhibit 5: Valuation of Kazia

Development program	Indication	Clinical stage	Prob. of success	Launch year	Patent/ exclusivity protection	Launch pricing (US$/course)	Peak sales (US$m)	rNPV (US$m)
Paxalisib	GBM	Phase II	35%	2025	2037	169,000	450	151.80
	BCBMs	Phase II	5%	2029	2037	183,000	249	5.97
Cantrixil	OC	Phase I	10%	2027	2040	124,000	174	9.27
Total								167.04
Net cash and equivalents (Q121 + subsequent transactions) (US$m)								16.59
Total firm value (US$m)								183.63
Total basic ADRs (m)								12.6
Value per basic ADR (US$)								14.55
Dilutive options (as ADRs, m)								0.45
Total diluted ADRs								13.1
Value per diluted ADR (US$)								14.05

Source: Kazia Therapeutics reports, Edison Investment Research

Financials

We have not changed our financial forecasts at this time, save for the addition of the October offering. This offering has reduced our expected financing requirement to US$14m (from US$32m previously), which we include in our forecasts as illustrative debt in FY23.

Exhibit 6: Financial summary

$'k	2019	2020	2021e	2022e
Year end 30 June	IFRS	IFRS	IFRS	IFRS
INCOME STATEMENT				
Revenue	1,117.9	757.8	1,003.4	1,087.0
Cost of Sales	0.0	0.0	0.0	0.0
Gross Profit	1,117.9	757.8	1,003.4	1,087.0
R&D	4,625.4	6,781.7	7,346.4	7,746.4
SG&A	2,704.0	2,635.6	2,785.6	2,841.3
EBITDA	(5,260.9)	(7,697.7)	(8,166.9)	(8,539.0)
Normalised operating profit	(5,261.0)	(7,697.7)	(8,166.9)	(8,539.0)
Amortization of acquired intangibles	(774.5)	(774.5)	(774.5)	(774.5)
Exceptionals	(1,337.4)	(458.8)	0.0	0.0
Share-based payments	(176.0)	(187.2)	(187.2)	(187.2)
Reported operating profit	(7,548.9)	(9,118.3)	(9,128.6)	(9,500.8)
Net Interest	0.0	0.0	0.0	0.0
Joint ventures & associates (post tax)	0.0	0.0	0.0	0.0
Exceptionals	0.0	0.0	0.0	0.0
Profit Before Tax (norm)	(5,261.0)	(7,697.7)	(8,166.9)	(8,539.0)
Profit Before Tax (reported)	(7,548.9)	(9,118.3)	(9,128.6)	(9,500.8)
Reported tax	213.0	213.0	348.4	362.6
Profit After Tax (norm)	(5,261.0)	(7,697.7)	(8,166.9)	(8,539.0)
Profit After Tax (reported)	(7,335.9)	(8,905.3)	(8,780.2)	(9,138.2)
Minority interests	0.0	0.0	0.0	0.0
Discontinued operations	0.0	0.0	0.0	0.0
Net income (normalised)	(5,261.0)	(7,697.7)	(8,166.9)	(8,539.0)
Net income (reported)	(7,335.9)	(8,905.3)	(8,780.2)	(9,138.2)
Basic average number of ADRs outstanding (m)	5.8	7.3	11.8	13.3
EPADR - basic normalised (US$)	(0.91)	(1.05)	(0.69)	(0.64)
EPADR - diluted normalised (US$)	(0.91)	(1.05)	(0.69)	(0.64)
EPADR - basic reported (US$)	(1.28)	(1.22)	(0.74)	(0.69)
Dividend (A$)	0.00	0.00	0.00	0.00
BALANCE SHEET				
Fixed Assets	9,758.8	8,864.4	8,089.9	7,315.3
Intangible Assets	9,638.9	8,864.4	8,089.9	7,315.3
Tangible Assets	0.0	0.0	0.0	0.0
Investments & other	119.9	0.0	0.0	0.0
Current Assets	5,367.3	7,609.7	15,239.0	6,812.4
Stocks	0.0	0.0	0.0	0.0
Debtors	1,221.9	965.9	659.8	714.7
Cash & cash equivalents	3,881.3	6,260.0	14,195.5	5,713.9
Other	264.0	383.8	383.8	383.8
Current Liabilities	(1,357.4)	(3,619.6)	(2,495.8)	(2,608.2)
Creditors	(1,260.0)	(2,492.1)	(2,261.2)	(2,373.5)
Tax and social security	0.0	0.0	0.0	0.0
Short term borrowings	0.0	0.0	0.0	0.0
Other	(97.4)	(1,127.5)	(234.7)	(234.7)
Long Term Liabilities	(3,629.6)	(2,764.8)	(2,416.4)	(2,053.8)
Long term borrowings	0.0	0.0	0.0	0.0
Other long term liabilities	(3,629.6)	(2,764.8)	(2,416.4)	(2,053.8)
Net Assets	10,139.1	10,089.7	18,416.7	9,465.7
Minority interests	0.0	0.0	0.0	0.0
Shareholders' equity	10,139.1	10,089.7	18,416.7	9,465.7
CASH FLOW				
Op Cash Flow before WC and tax	(5,260.9)	(7,697.7)	(8,166.9)	(8,539.0)
Working capital	252.1	1,192.2	(1,166.1)	(305.2)
Exceptional & other	213.0	213.0	348.4	362.6
Tax	0.0	0.0	0.0	0.0
Net operating cash flow	(4,795.9)	(6,292.5)	(8,984.6)	(8,481.6)
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	2,725.5	8,671.2	16,920.0	0.0
Dividends	0.0	0.0	0.0	0.0
Other	1,685.1	0.0	0.0	0.0
Net Cash Flow	(385.3)	2,378.7	7,935.4	(8,481.6)
Opening net debt/(cash)	(4,254.4)	(3,881.3)	(6,260.0)	(14,195.5)
FX	12.2	0.0	0.0	0.0
Other non-cash movements	0.0	0.0	0.0	0.0
Closing net debt/(cash)	(3,881.3)	(6,260.0)	(14,195.5)	(5,713.9)

Source: Kazia Therapeutics reports, Edison Investment Research

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