EDISON

Kazia Therapeutics

Business update

New asset to target tumor lymphangiogenesis

Pharma & biotech

Kazia announced that it is expanding its pipeline to include EVT801, a novel small molecule inhibitor of VEGFR3. The drug is being licensed from Evotec for €1m upfront, €308m in milestones and tiered single-digit royalties. EVT801 was developed as part of a collaboration between Evotec and Sanofi. Kazia will be responsible for development, but will collaborate with and have access to Evotec resources to support development. The product is currently in preclinical development, but Kazia believes it can launch a Phase I study before the end of CY21.

Year end	Revenue ($m)	PTP* ($m)	EPADR ($)	DPADR ($)	P/E (x)	Gross yield (%)
6/19	1.1	(5.3)	(0.91)	0.00	N/A	N/A
6/20	0.8	(7.7)	(1.01)	0.00	N/A	N/A
6/21e	12.0	1.1	0.09	0.00	N/A	N/A
6/22e	0.9	(13.8)	(0.97)	0.00	N/A	N/A

Source: <Insert>. 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.

A specific inhibitor of VEGFR3

EVT801 is an oral small molecule that targets VEGFR3. The VEGFR family of proteins are receptor tyrosine kinases involved in the formation of the circulatory system, and in cancer they are implicated in angiogenesis. These proteins and their ligand (VEGF) have been a common target for therapeutics, including both targeted angiogenesis inhibitors (eg Avastin) and multi-tyrosine kinase inhibitors (eg Nexavar). However, there have been fewer efforts to specifically target the VEGFR3 isoform, which is important for the formation of lymphatic vessel networks.

Lymphangiogenesis has multiple roles in cancer

Lymphangiogenesis is an important component of tumor biology. An initial metastasis for many tumor types is via the lymphatic system to nearby lymph nodes. The lymphatic system acts as a highway of sorts for immune cells, and EVT801 has also shown capacity in vitro to shift the balance of immune cell subtypes in a tumor. This shift in immune cell populations can potentially sensitize tumors to immunotherapy. We expect this to be the focus of some of the research into this molecule in the coming years.

A good strategic fit while paxalisib is in the clinic

Strategically, this is an important deal for Kazia, because it enables it to expand the pipeline to multiple drugs. Paxalisib will remain the lead asset, but most of the operational burden of that development is borne by the investigators running GBM AGILE. This leaves capacity for the company to expand its offering.

Valuation: Increased on new drug to A$346m

We have increased our valuation to US$247m or US$19.14 per basic ADR from US$215m or US$16.60 per basic ADR due to the new drug (initial valuation of US$33.7m). This has also increased expected R&D spending significantly and our financing requirement for the company to US$36m (including US$21m in FY23) from US$7m, previously.

20 April 2021

Price	**$10.98**
Market cap	**$142m**
	ADR/Ord conversion ratio 1:10
Net cash ($m) at 31 December 2020	13.9
ADRs in issue	12.9
ADR code	KZIA
ADR exchange	NASDAQ
Underlying exchange	ASX
Depository	BNY

ADR share price performance

52-week high/low	$14.71	$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 also recently in-licensed the Phase I drug EVT801, an inhibitor of lymphangiogenesis in tumors.

Next events

Dana-Farber BCBM Phase II	CY21
Sloan-Kettering BM Phase II	CY21
NIH BM Phase II	CY21

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Edison profile page

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Kazia expands its pipeline

Kazia announced on 19 April 2021 that it has licensed the compound EVT801 from Evotec. The deal included €1m upfront for Evotec, €308m in milestones, and tiered single-digit royalties. Kazia will assume all development, regulatory and marketing responsibilities. However, Kazia noted that it would be collaborating with Evotec and will have access to Evotec resources such as clinical trial management and manufacturing as part of a services agreement. The company noted that the initial focus of development will be for renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), and soft tissue sarcoma (STS).

Evotec is a company that is operationally focused on drug discovery, and out-licenses these assets and discovery programs to a range of (typically big pharma) partners. EVT801 in particular was previously discovered in a collaboration agreement between Evotec and Sanofi, but Sanofi decided not to option the program, leaving it open for licensing to Kazia. Sanofi's decision not to exercise the option could have been for any number of strategic reasons, so we do not assume it would have any bearing on the clinical viability of the program.

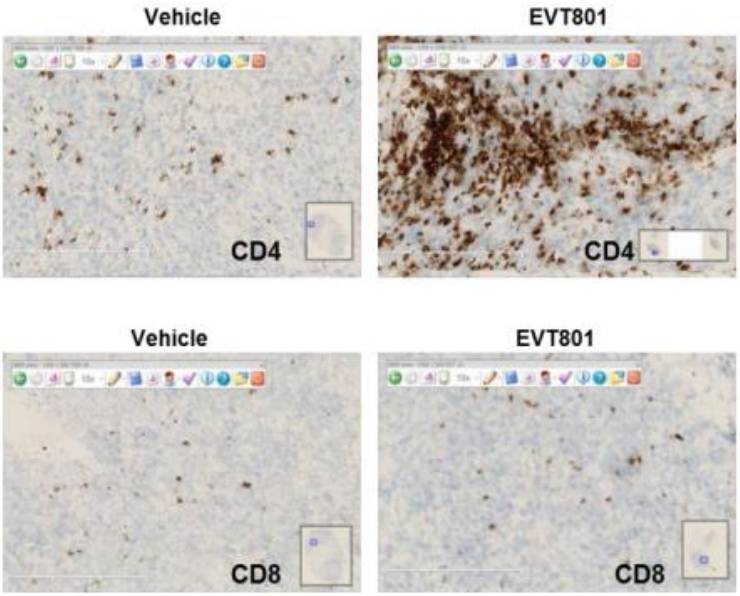
EVT801 is an inhibitor of vascular endothelial growth factor receptor 3 (VEGFR3). Many readers are likely to be familiar with this family of proteins (VEGFR) and their ligand (VEGF) because they have been successfully targeted by a number of anti-cancer therapeutics. Avastin (bevacizumab, Genentech) was the first drug approved to specifically target this signalling 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 like Nexavar (sorafenib, Bayer) inhibit a wide number of these receptors to varying degrees, and achieve their efficacy by this combined effect.

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 featured highlighted by Evotec is that EVT801 can shift the balance of immune cells in a tumor including the proliferation of CD4+ (helper) T-cells among others (Exhibit 1). This may be an advantage if EVT801 is combined with immunotherapy such as checkpoint inhibitors. Most of the research into tumor-infiltrating lymphocytes has been into the role of CD8+ (killer) T-cells, but CD4+ cells are important for driving a sustained immune response.[1]

1 Tay RE, et al. (2021) Revisiting the role of CD4+ T cells in cancer immunotherapy—new insights into old paradigms. *Cancer Gene Ther.* 28, 5-17.

Exhibit 1: EVT801 induces CD4+ T-cells



Source: Evotec

Relatively few programs in which VEGFR3 was specifically targeted have reached the clinic. IMC-3C5, originally developed by ImClone (now owned by Eli Lilly), was an anti-VEGFR3 monoclonal antibody that was abandoned after it failed to show activity in Phase I. VGX-100 (Ceres Oncology) is a VEGF-C ligand trap (and this is a ligand primarily associated with VEGFR3 activation) that was tested in Phase I, but never further developed. Most other drugs that have had activity against VEGFR3 have been multi-tyrosine kinase inhibitors, with a range of other activities, so it is difficult to draw conclusions from these programs. However, the aim is that by using a more targeted approach this can improve the tolerability of EVT801 compared to tyrosine kinase inhibitors.

Much of Kazia's operational capacity has opened up with the inclusion of paxalisib in the GBM AGILE study, and the company believes that it can dedicate significant resources to the EVT801 program. It has the drug on an accelerated track to the clinic and is targeting initiation of Phase I in CY21.

Valuation

We have increased our valuation to US$247m or US$19.14 per basic ADR from US$215m or US$16.60 per basic ADR. This increase is due to the Evotec transaction, and we have added EVT801 to our models with an initial valuation of US$33.7m. We model initial commercialization of the drug for RCC, and assume it will be used in the second line after progression on checkpoint inhibitors. We estimate a total addressable market of approximately 70,000 in the US and Europe. We assume an initial launch price of US$120,000 per course. This is a discount from the pricing of checkpoint inhibitors (~$150,000 per course in current day pricing) because we model it being used primarily as an adjunct to these treatments. Our peak penetration is 15%, and we expect initial commercialization in 2028. The company noted in the press release that patents on the compound extend to 2031/32 in most jurisdictions and we assume a five-year patent term extension to this. We model royalties of 4–8% payable to Evotec as well as €158m in milestones (out of €308m in total), of which €18m are clinical and regulatory and €140m are commercial. Our probability of success is 10%, which we view as average for a drug at this stage. Many of these details are subject to change based on the performance of the drug and its particular qualities in the clinic, which are not clearly understood at this point. For instance, RCC is one of several potential target

indications for this treatment, and this may change in the future. We have adjusted our net cash line to reflect the €1m upfront payment for the program.

Exhibit 2: Valuation of Kazia

Development Program	Indication	Clinical stage	Prob. of success	Launch year	Patent/Exclusivity Protection	Launch Pricing ($/course)	Peak sales (US$m)	rNPV (US$m)
Paxalisib	GBM	Phase II	35%	2025	2037	169,000	450	173.66
	BCBMs	Phase II	5%	2029	2037	183,000	249	6.15
Cantrixil	OC	Phsae I complete	15%	2027	2040	124,000	174	6.05
EVT801	RCC	Phase I ready	10%	2028	2037	120,000	807	33.74
Total								219.60
Net cash and equivalents (FQ221 + Oasmia + Simcere - Evotec) (A$m)								27.72
Total firm value (US$m)								247.32
Total basic ADRs (m)								12.9
Value per basic ADR (US$)								19.14
Dilutive options (as ADRs, m)								0.45
Total diluted ADRs								13.4
Value per diluted ADR								18.69

Source: Kazia reports, Edison Investment Research.

Financials

With the new development program, we expect an increased R&D expenditure going forward. We have increased our expected R&D spending for FY21 to US$7.6m (from US$5.8m) and to US$10.0m (from US$4.7m) in FY22. We may adjust this spending schedule in the future once we have a more concrete timeline for development. This has also increased our expected financing requirement for the company to US$36mm (A$21m in FY23, A$15m in FY25) from US$7m previously (which had been modelled in FY24). Otherwise, our forecasts remain unchanged.

Exhibit 3: Financial summary

$'k	2019	2020	2021e	2022e
30-June	IFRS	IFRS	IFRS	IFRS
INCOME STATEMENT				
Revenue	1,117.9	757.8	12,003.4	1,124.0
Cost of Sales	0.0	0.0	0.0	0.0
Gross Profit	1,117.9	757.8	12,003.4	1,124.0
R&D	4,625.4	6,781.7	7,596.4	9,996.4
SG&A	2,704.0	2,635.6	4,285.6	5,871.3
EBITDA	(5,260.9)	(7,697.7)	1,083.1	(13,782.0)
Normalised operating profit	(5,261.0)	(7,697.7)	1,083.1	(13,782.0)
Amortisation of acquired intangibles	(774.5)	(774.5)	(774.5)	(774.5)
Exceptionals	(1,337.4)	(458.8)	0.0	0.0
Share-based payments	(176.0)	(187.2)	(187.2)	(187.2)
Reported operating profit	(7,548.9)	(9,118.3)	121.4	(14,743.8)
Net Interest	0.0	0.0	0.0	0.0
Joint ventures & associates (post tax)	0.0	0.0	0.0	0.0
Exceptionals	0.0	0.0	0.0	0.0
Profit Before Tax (norm)	(5,261.0)	(7,697.7)	1,083.1	(13,782.0)
Profit Before Tax (reported)	(7,548.9)	(9,118.3)	121.4	(14,743.8)
Reported tax	213.0	213.0	(4.6)	562.7
Profit After Tax (norm)	(5,261.0)	(7,404.0)	1,041.8	(13,256.1)
Profit After Tax (reported)	(7,335.9)	(8,905.3)	116.7	(14,181.1)
Minority interests	0.0	0.0	0.0	0.0
Discontinued operations	0.0	0.0	0.0	0.0
Net income (normalised)	(5,261.0)	(7,404.0)	1,041.8	(13,256.1)
Net income (reported)	(7,335.9)	(8,905.3)	116.7	(14,181.1)
Basic average number of ADRs outstanding (m)	5.8	7.3	11.9	13.6
EPADR - basic normalised ($)	(0.91)	(1.01)	0.09	(0.97)
EPADR - diluted normalised ($)	(0.91)	(1.01)	0.09	(0.97)
EPADR - basic reported ($)	(1.28)	(1.22)	0.01	(1.04)
Dividend (A$)	0.00	0.00	0.00	0.00
BALANCE SHEET				
Fixed Assets	9,758.8	8,864.4	12,497.4	10,294.3
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	4,407.5	2,979.0
Current Assets	5,367.3	7,609.7	24,411.6	13,040.9
Stocks	0.0	0.0	0.0	0.0
Debtors	1,221.9	965.9	1,093.9	739.1
Cash & cash equivalents	3,881.3	6,260.0	22,933.9	11,918.0
Other	264.0	383.8	383.8	383.8
Current Liabilities	(1,357.4)	(3,619.6)	(2,927.4)	(3,910.1)
Creditors	(1,260.0)	(2,492.1)	(2,692.7)	(3,675.5)
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)	(3,838.4)	(3,275.7)
Long term borrowings	0.0	0.0	0.0	0.0
Other long term liabilities	(3,629.6)	(2,764.8)	(3,838.4)	(3,275.7)
Net Assets	10,139.1	10,089.7	30,143.2	16,149.3
Minority interests	0.0	0.0	0.0	0.0
Shareholders' equity	10,139.1	10,089.7	30,143.2	16,149.3
CASH FLOW				
Op Cash Flow before WC and tax	(5,260.9)	(7,697.7)	1,083.1	(13,782.0)
Working capital	252.1	1,192.2	(4,154.2)	2,203.5
Exceptional & other	213.0	213.0	(4.6)	562.7
Tax	0.0	0.0	0.0	0.0
Net operating cash flow	(4,795.9)	(6,292.5)	(3,075.7)	(11,015.8)
Capex	0.0	0.0	0.0	0.0
Acquisitions/disposals	0.0	0.0	(1,114.3)	0.0
Net interest	0.0	0.0	0.0	0.0
Equity financing	2,725.5	8,671.2	20,863.8	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	16,673.8	(11,015.8)
Opening net debt/(cash)	(4,254.4)	(3,881.3)	(6,260.0)	(22,933.9)
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)	(22,933.9)	(11,918.0)

Source: Kazia reports, Edison Investment Research.

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