

27 May 2011

Circadian Technologies Limited

Year End	Revenue (A\$m)	PBT* (A\$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
06/09	0.7	(8.4)	(20.2)	0.0	N/A	N/A
06/10	0.6	(8.6)	(19.1)	0.0	N/A	N/A
06/11e	0.7	(9.5)	(20.6)	0.0	N/A	N/A
06/12e	0.8	(13.2)	(28.4)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation and exceptional items.

Investment summary: Dawn of VEGF-C therapy

Circadian Technologies is now focused on developing VGX-100, a VEGF-C inhibitory monoclonal antibody. Trials will start in late 2011. If safety studies complete as expected, VGX-100 is scheduled to enter a Phase II trial in glioblastoma as an adjuvant to Avastin. Preclinical data suggests a strong synergistic action. The other lead product, IMC-3C5, is in Phase I licensed to ImClone (Lilly). Circadian has a strong IP position that might be a short-term revenue source if major pharma companies start VEGF-C projects. Two niche diagnostics will start generating sales.

VGX-100: A direct VEGF-C binding antibody

VGX-100 binds VEGF-C, a similar signalling molecule, to the VEGF-A targeted by Avastin. VEGF-C has a specific role in causing new lymphatic vessels to develop. These vessels drain excess tissue fluid and blocking their growth into tumours may slow cancer metastasis. A Phase I dose escalation study is planned to start in Q411 and could take 18-24 months to run. Glioblastoma is a promising initial indication.

IMC-3C5: A VEGFR-3 blocking antibody for solid tumours

The ImClone [trial](#) is an escalating dose study using cohorts of three patients at 5, 10, 20 and 30mg/kg given weekly. Additional patient cohorts will then be treated either at the anticipated 20 or 30mg/kg dose. The study will report in H113. IMC-3C5 targets VEGFR-3, the VEGF-C and D receptor that drives both angiogenesis and lymphangiogenesis. The latter may be important in metastatic spread.

Financials: H111 results

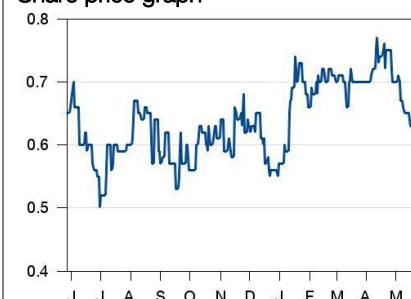
As at December 2010, Circadian had A\$25.8m cash and no debt. H1 cash outflow was A\$5.7m; the FY10 cash outflow was A\$9.2m before interest of A\$1.6m. R&D is expected to rise from A\$4.5m to A\$8.7m as the company gears up for its first independent clinical study in the US, largely in FY13.

Valuation: Long-term Avastin adjuvant upside

The weak clinical results from Avastin (but commercial success), with the strong preclinical models using both Avastin and VGX-100 show that this is a fertile area for development. On a DCF basis, we estimate an indicative value of A\$88m (A\$1.90/share). We expect value to develop strongly as the pipeline develops.

Price A\$0.59
Market Cap A\$27m

Share price graph



Share details

Code CIR
Listing ASX
Sector Pharmaceuticals
Shares in issue 46.4m

Price

52 week High Low
A\$0.76 A\$0.52

Balance Sheet as at 31 December 2010

Debt/Equity (%) N/A
NAV per share (c) 69
Net cash (A\$m) 25.8

Business

Circadian's focus is on its VEGF-C and VEGF-D portfolio, with a receptor blocking antibody (IMC-3C5) in Phase I trials with ImClone (Lilly), and a VEGF-C targeting antibody (VGX-100) due to enter glioblastoma trials in late 2011. The business is a former life sciences investment company.

Valuation

	2010	2011e	2012e
P/E relative	N/A	N/A	N/A
P/CF	N/A	N/A	N/A
EV/Sales	N/A	N/A	N/A
ROE	N/A	N/A	N/A

Revenues by geography

UK	Europe	US	Other
0%	0%	0%	100%

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Investment summary: Dawn of VEGF-C therapy

Company description: Boosting Avastin

Circadian is an Australian biotech company that evolved out of a life sciences investment vehicle with the 2008 acquisition of Vegenics. It still holds low-value stakes in several companies. Vegenics had licensed products in the emerging anti-VEGF-C and D anti-angiogenic and anti-lymph-angiogenesis therapy areas, giving a strong IP position. The focus is on its lead anti-VEGF-C monoclonal, VGX-100, originally developed by Human Genome Science using CAT (now MedImmune (AZ) phage display libraries. There is a residual but material net royalty. VGX-100 is due to enter Phase I glioblastoma trials in late 2011 and its scope will be much greater if it can demonstrate synergistic action with Avastin. VEGF-C and D also target lymphangiogenesis, a process that seems to help cancers spread. A VEGFR-3 receptor blocking antibody licensed to ImClone (IMC-3C5) has started a Phase I clinical trial. Two diagnostics provide near-term revenues.

Sensitivities: The case for VEGF-C and D therapeutics

The investment case rests on anti-VEGF-C agents improving clinical survival in combination with Avastin. Pre-clinical data is strong but solid indicative clinical validation is probably two years away. Any short-term investor upside lies in Circadian's patents as these have already led to one licence (with Ark) and any VEGF-C/D product development would need a deal with Circadian. Strong upfront payments and milestones from FY13 are possible. As the Australian dollar is strong against the US dollar, there is a theoretical currency effect on valuation.

Valuation: A\$88m; A\$1.90 per share

We have valued Circadian at A\$1.90 per share using risk-adjusted discounted cash flows to 2030, Exhibit 7. The lead forecast product is VGX-100 for glioblastoma (GBM). In addition to its own value, this is a gatekeeper indication which, by showing proof of principle, could open access to bigger indications alongside VEGF-A inhibitors, for example, in colorectal, lung and maybe breast cancers. We assume a 50% initial deal probability in FY13. By analogy with the Roche-Bioinvent deal on the anti-PIGF antibody, this could be \$75m upfront but we have used only \$12m risk-adjusted in the model as there is a trade-off between upfront and royalties. We cannot properly value IMC-3C5 but assume a 2019 entry and a US\$1bn potential. The royalty is assumed at 15% at a 20% risk. Diagnostics are assumed to build to A\$4.5m revenues. Other VEGF-D products are simply valued at 10% of VGX-100 and IMC-3C5 revenues. This adds 11% to revenues. A 30% tax rate is used.

Financials: Solid financial base

Circadian is entering a relatively high burn period as it moves into the clinical phase of VGX-100. We assume that R&D (inc IP) costs rises from A\$5.7m in FY11 to A\$8.7m in FY12 and to c \$11.3m in 2013. Interim research and development was A\$3.87m and administration costs were A\$2.5m (including IP). Cash as of 31 December 2010 was A\$25.76m after an interim cash burn of A\$5.7m. There are investment assets of A\$1.96m, which may be difficult to realise. An H111 impairment charge of A\$0.61m was required after a FY10 one-off charge of A\$1.2m on impaired assets plus a gain of A\$2.9m on marking equities to market prices. Forecasts are in Exhibit 8.

Outlook: Boosting Avastin

Circadian's investment case rests on its strong position in anti-VEGF-C and D antibodies. Current anti-angiogenic therapy with Avastin is not particularly effective – probably as there are multiple possible mechanisms and escape routes. VEGF-C and D antibodies could block some of these.

The focus is now on its lead anti-VEGF-C monoclonal: VGX-100. This is due to enter Phase I glioblastoma trials in late 2011 but its scope might be much greater if it can demonstrate synergistic action with Avastin. A VEGFR-3 receptor-blocking antibody licensed to ImClone (IMC-3C5) has started a Phase I clinical trial. There is an evolving pre-clinical portfolio. Two niche diagnostics provide near-term revenue opportunities. The portfolio is shown in Exhibit 1.

Exhibit 1: Circadian product portfolio

Product	Indication	Stage	Mechanism
Therapeutics			
VGX-100	Solid cancers	Phase I dose escalation starts in H211	Monoclonal antibody against VEGF-C. Initial indication planned is glioblastoma.
	Eye disease	Late preclinical	Anti-VEGF-C targeting lymphangiogenesis in the cornea.
IMC-3C5	Solid cancers	Phase I dose escalation in 40 patients	Monoclonal against VEGFR-3. This blocks VEGF-C and D. Data should be available in H1 2013 it could then progress to studies in individual cancer types.
VGX-200	Solid cancers	Research	Monoclonal against VEGF-D. Could be a comparable product to VGX-100.
	Lymphangio-leiomyomatosis	Research	A rare respiratory condition whose severity appears to be linked to excess VEGF-D.
VGX-300	Solid cancer	Research	VEGFR-3 receptor – presumably a soluble receptor form. This would absorb circulating VEGF-C and D.
Diagnostics			
Software to type cancers based on genetic analysis	Cancer of Unknown Primary	Clinical validation	Partnered with Healthscope, a leading Australian private hospital; and pathology group. Uses any genetic test data.
Lymphangio-leiomyomatosis	VEGF-D Respiratory	Clinical validation	Licensed to Cincinnati Children's Hospital Medical Center with commercial sales expected from 2011.
VEGF-C	Cancer	Preclinical	Could aid patient selection for VGX-100.

Source: Edison Investment Research

The ABCD of VEGF

All tissues need a supply of oxygen and nutrients delivered by the blood via the circulatory system and a drainage system to remove excess fluids, the lymphatic system. If either one is not functioning, signals are sent out to encourage the development of new vessels.

Angiogenesis – new blood vessels

Cells that have too little oxygen (hypoxia) make a signalling molecule, Vascular-Endothelial Growth Factor (VEGF). Only cells in hypoxic conditions make this protein. The VEGF signal acts on cell lining the nearest blood vessels and causes them to divide and start to make a new artery: angiogenesis. New endothelial cells then line the new vessel. In response to injury or increasing muscle mass, this process is beneficial. However, it is also the mechanism used by cancer masses to get a blood supply. There are other signals, like Fibroblast Growth Factor, but VEGF is most potent.

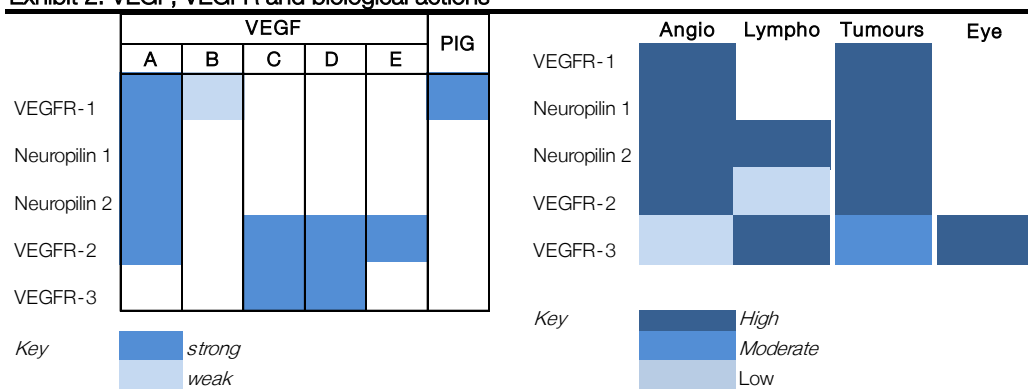
Lymphangiogenesis – new lymphatic vessel growth

A different combination of signalling factors is responsible for growth of the tissue drainage system, the lymphatic system. Fluid enters tissues from the blood as arterial pressure is high. The excess fluid drains out by the lymphatic vessels. This is a low pressure system that collects fluid from all over the body and drains into the blood in the upper chest. The lymph system has nodes that are immune system checkpoints. These swell with immune cells if infectious agents (bacteria, viruses) are detected in lymph. Cancer cells also use the lymphatic system as a metastatic highway and lodge in the nodes. For example, in breast cancer, the armpit nodes are checked to see if the tumour is localised or might have spread via the lymph.

Signaling

VEGF comes in six forms (inc. PlGF) derived by gene evolution, Exhibit 2.¹ These bind to three types of VEGF receptors (VEGFR-1, 2, and 3) to have an effect. VEGFR-1 and 2 are associated with new blood vessels. VEGFR-3 is found on lymphatic vessels. Finally, the receptors, Neuropilin-1 and 2, can bind with VEGF-A, with Neuropilin-2 being associated with lymphatic tissue as well. It may be that VEGF-A is associated with hypoxia whereas VEGF-C and D may have an inflammatory role.

Exhibit 2: VEGF, VEGFR and biological actions



Source: Cardiovascular Research 2005²

Even this picture is over-simplified as each VEGF type can have variations.³ It is also known that there are anti-angiogenic signals.⁴ As this biological system is very complex, evidence from clinical trials is the only effective way of assessing efficacy.⁵

¹ The types are:

- A – is major driver of angiogenesis and is targeted by Avastin (bevacizumab, Roche).
- PlGF (Placenta Growth Factor) is closely related to A but triggers different responses.
- B – has a poorly defined role in angiogenesis; it is weakly related to other VEGF types.
- C – drives both angiogenesis and lymphangiogenesis, VGX-100 targets this molecule.
- D – has a similar profile and molecular shape to C but with an ill-defined clinical role.
- E – is similar to A but with a restricted receptor specificity, it is poorly studied.

² Tammela, T. *et al.* The Biology of Vascular Endothelial Growth Factors. [Cardiovascular Research 2005: 65: 550-565.](#)

³ For VEGF-A these are splice variants, the most common being VEGF₁₆₅. Splice variants are when the gene coding for the protein can be being processed in different ways to make alternative hormone forms. For C and D, different forms are made by enzymes altering the nascent protein in different ways.

⁴ One well known one is the protein angiostatin. This proved commercially unviable but did show efficacy in clinical trials; it has been commercialised in China. Nucleolin, a protein normally found in the cell nucleus, is linked to angiogenesis and cell survival; Antisoma had a blocking peptide (AS1411) that failed to show superior efficacy over conventional therapy in a Phase II AML study. ImmuPharma has a different molecule which binds and naturalises nucleolin, now in Phase I which will target solid tumours, including glioblastoma in its planned Phase II trials from 2012.

⁵ Ellis LM, and Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. [Nat Rev Cancer.2008 Aug;8:579-91.](#)

Small-molecule angiogenesis inhibitors have had limited success only in a few indications.⁶

A complication in anti-angiogenesis therapy is that tumour capillaries are normally narrow and very convoluted. Anti-angiogenic agents can reduce the VEGF “noise” in the tumour, allowing a better functioning blood supply. This gives fewer larger blood vessels allowing faster tumour growth.⁷

VEGF-C and D in cancer

Exhibit 3 summarised some clinical studies looking at VEGF-C and D. VEGF-A (targeted by Avastin), is better studied but does not seem to correlate to disease progression.

Exhibit 3: Some literature studies of CEGF –C, VEGF-D and VEGFR-3 expression in cancer

Note: We have focused on clinical data, there are also extensive experimental model studies. Just because VEGF-C or D are elevated does not mean necessarily that they are driving the disease. Most studies are small and use retrospective data sets. However, a direct role seems likely given this evidence. VEGF-D is associated with cancer lymphatic spread; VEGF-C shows a mixed response pattern.

Cancer	Size	Finding	Ref
GI cancers	Review of 11 studies	VEGF-C expression correlates with poor survival in gastric cancer. The roles of VEGF-C and D in colorectal cancer are less clear.	Duff 2003
Multiple invasive	218 samples	Lung, colorectal, cervical, breast and prostate cancers were studied. Metastasis was associated with either VEGFR-3 or VEGF-C; the outcome was worse if both were present.	Su, J-L 2006
Gastric	91 patients	VEGF-C and D expression was seen in increased lymph node metastatic spread and decreased survival.	Juttnerl 2006
Gastric	69 surgical patients	VEGF-D correlated with metastatic disease but not survival	Schimanski 2011
Oesophageal	106 patients	Compared to normal matched samples, cancer patients had higher VEGF-C levels. When separated into above and below median VEGF-C levels, those patients with above median VEGF-C had worse survival: median c 16 months as opposed to c 37 months with below average levels.	Tanaka 2007
Colorectal	20 biopsy samples	High levels of VEGF-C and D RNA found in cancer biopsy samples. Higher levels correlated significantly with poor outcomes. Interestingly, VEGF-C did not correlate with VEGF-D indicating different expression patterns.	Onogawal 2004
Colorectal	81 histology samples	VEGF-C expression regulated by the gene regulator Metastasis Associated Protein 1 and acts as a marker of poor prognosis and late stage cancer progression.	Bin 2011
Colorectal	69 patients with tested histology samples	Increased VEGF-C correlated with progressive stage of cancer. VEGF-D correlated with lymphatic spread. High levels of both C and D gave the shortest survival.	Hu 2007
Colorectal	108 histology samples	Found that patients with increasing numbers of metastatic lymph nodes tended to have VEGF-D expression. High VEGF-D expression gave a 30% worse survival chance.	Moehlerl 2008
Colorectal	42 CRC patients plus 405 database samples	Patients followed over the time course of disease showed a 72% rise in VEGF-C if disease progressed (p=0.004). PiGF also rose. A large, diverse data set was ambiguous due to the spread of data.	Lieu 2011 (ASCO abstract)
Breast	462 patients	Low VEGF-C might be a marker for greater progression-free survival advantage in breast cancer when Avastin is used with Capecitabine, a 5-fluoro-uracil pro drug sold as Xeloda	Jubb 2011
Non-small cell lung cancer	180 patients of whom 73% were VEGF-C positive and 22% VEGFR-3 positive	VEGF-C and VEGFR-3 each indicated a worse prognosis. If both were present, patients had a very poor prognosis. VEGFR-3 was a stronger prognostic indicator than VEGF-D, perhaps as it is also triggered by VEGF-D or because it is found on lymph.	Arunagal 2003

Sources: Edison Investment Research

Glioblastoma (GBM)

The brain has no lymphatic system.⁸ It is therefore not likely that normal brain tissue would express VEGF-C or VEGFR-3. Hence, any VEGF-C should be associated with tumour angiogenesis. This

⁶ Examples of successes in specific cancers only are Nexavar (sorafenib, Bayer) in renal and hepatocellular cancer and Sutnet (sunitinib, Pfizer). These are multi-functional kinase inhibitors that target receptors like VEGFR. A recent overview is El Zouhairi M *et al.* Molecularly targeted therapy for metastatic colon cancer: proven treatments and promising new agents. [Gastrointest Cancer Res. 2011;4:15-21.](#)

⁷ Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. [Science 2005; 307: 58-62.](#)

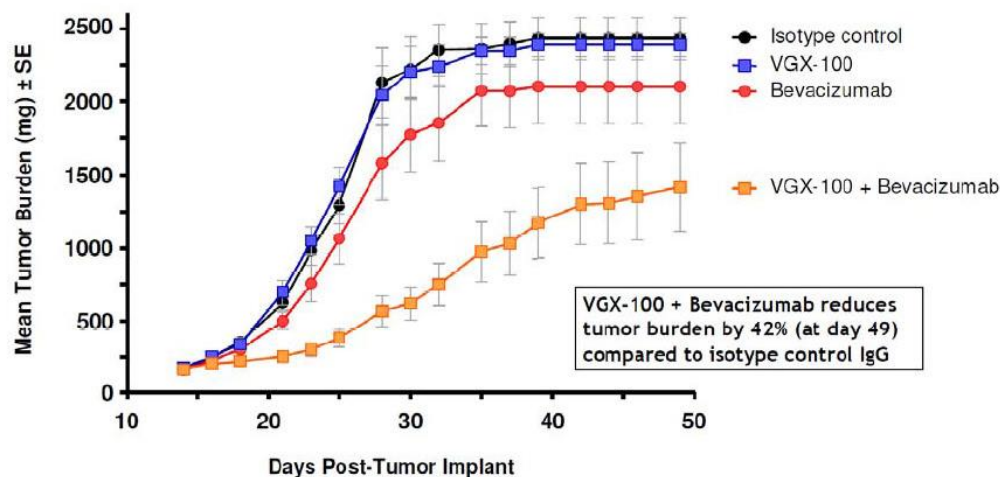
⁸ The brain is bathed in cerebro-spinal fluid which drains through specialist membranes at the base of the skull and through the ends of nerves which connect to other organs.

should be a clean system to show VGX-100 efficacy against angiogenesis. Experiments⁹ have shown that neuronal epithelial cells do not respond to VEGF-C or D or express these proteins. After 14 days' exposure to Avastin, they started to respond to VEGF-C and D.

There is molecular evidence that a switch to VEGF-C or D might enable GBM to resist Avastin therapy. Hence, adding a specific VEGF-C agent should give efficacy but using it on its own as first-line therapy would have no effect, as VEGF-C will not be an early disease driver. Circadian has now confirmed this hypothesis in a very convincing preclinical GBM model, Exhibit 4.

Exhibit 4: Preclinical glioblastoma model

Note: These preclinical models are of fast growing tumours. Glioblastomas are particularly well vascularised so have been a consistent target for anti-angiogenic therapy. A critique of these models is that because the tumours grow so fast, the vascular systems may be very responsive whereas in the clinical situation, tumours are slower growing and hence may be less susceptible to therapy. In the model shown, VGX-100 as a sole agent has no effect and Avastin was poorly effective. By blocking both VEGF-A and VEGF-C, a 42% tumour burden reduction was seen. The VGX-100 dose was 40mg/kg, which is twice the expected human dose.



Source: Circadian Technologies, AACR Poster April 2010

In support of the Avastin adjuvant theory, there is some biomarker data; more is expected at ASCO in June 2011.

Clinical development of VGX-100

Circadian aims to start a Phase I/II safety study later in 2011. This will progress in cohorts of three patients with a single rising dose format. The patients will have advanced solid tumours of all types. The starting dose is likely to be low, maybe 0.5mg/kg and could rise to 20mg/kg depending on tolerability, as being the maximum economically viable dose. In some animal models, a 40mg/kg dose equalled 10mg/kg of Avastin but animal models often use more drug than is needed, which overstates human dosing.

Once a tolerable dose has been found, an extension study will be run to test multiple doses. When completed, Circadian wishes to move directly to a Phase II in GBM in which VGX-100 will be given with Avastin. It is possible this Phase II could be powered to be pivotal in this second-line indication, although this will need to be agreed with the FDA once Phase I data is available.

GBM is a difficult indication. The brain is isolated from blood and the rest of the body by the blood-brain barrier. This would normally prevent antibodies from crossing into the brain itself but in

⁹ Grau S, et al. Bevacizumab can induce reactivity to VEGF-C and -D in human brain and tumour derived endothelial cells. [J Neurooncol. 2011 Feb 11.](#)

glioma, the barrier is often disrupted. Avastin clearly penetrates to some extent. This variability could affect the effectiveness of the VGX-100 dose in a random way between patients and at different disease time points.

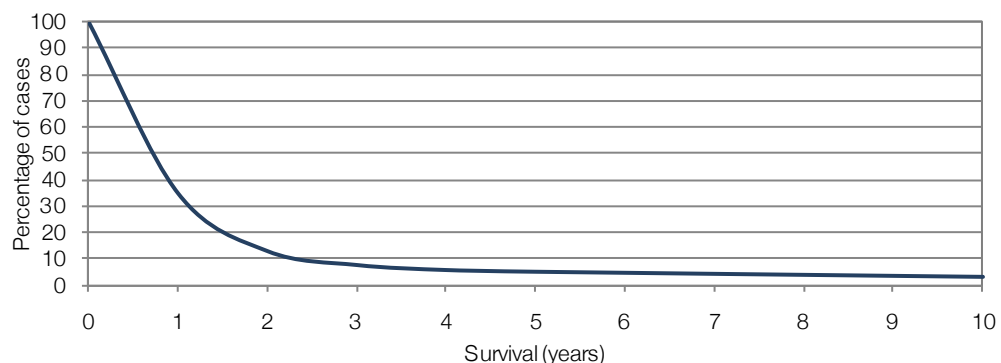
Resistance mechanisms are poorly understood.¹⁰ Gliomas can rebound if Avastin therapy is stopped.¹¹ Some reports suggest that Avastin encourages invasive tumour spread; VEGF-C agents might retard this, depending on mechanism.¹²

Glioblastoma market

The standard rate of new malignant central nervous system tumours is around 6.5 per 100,000 of the adult population: c 17-20,000 cases per year in the USA (incidence varies by state). GBM accounts for 54% of all malignant tumours with c 9,500 new cases per year in the US.¹³ It is caused by proliferation of glial cells, which are a cell type that normally aids the function of nerve cells. The other major glioma category consists of various forms of astrocytoma (22%).

Survival of GBM patients is low. Exhibit 5 shows the 1995-2007 10-year survival curve; survival may now be slightly better. Some 65% of patients die within a year and nearly 90% die within two years. By contrast, astrocytomas have a 27-94% five-year survival, depending on subtype. GBM is the commonest and most deadly brain tumour.

Exhibit 5: Survival curve for glioblastoma in the US



Source: SEER data 1995-2007 based on 19,979 cases

The main treatment for GBM is radiotherapy in with [Temodar](#) (temozolomide, Merck & Co) following maximum surgical resection. In a Phase III trial in newly-diagnosed GBM, Temodar showed an increase in median survival from 12.1 to 14.6 months: a 2.5-month survival benefit over radiation alone. Sales were US\$1.07bn in 2010. Other GBM therapies have a more modest survival impact, eg Eisai's [Gliadel](#) (carmustine wafer – implanted into the surgical resection cavity) demonstrated a 2.2-month survival benefit in primary patients; it also can be used for recurrent disease.

Possible competition in GBM

At least 20 products for GBM are in clinical trials. As a high-risk area, we expect a high attrition rate. The two candidates in Phase III are trabedersen [SAPPHIRE](#) from AntiSense Pharma and

¹⁰ Loges, S et al Mechanisms of resistance to anti-angiogenic therapy and development of third generation anti-angiogenic drugs. [Genes & Cancer 2010; 1: 12-24.](#)

¹¹ Zuniga RM *et al.* Rebound tumour progression after the cessation of bevacizumab therapy in patients with recurrent high-grade glioma. [J Neurooncol. 2010;99:237-42.](#)

¹² Keunen O *et al.* Anti-VEGF treatment reduces blood supply and increases tumor cell invasion in glioblastoma. [Proc Natl Acad Sci U S A. 2011;108:3749-54.](#)

¹³ Central Brain Tumor Registry of the United States Statistical Report February 2011

cilengitide from Merck KGaA in [CENTRIC](#) and [CORE](#). Cilengitide results are due 2012-13. A new antibody, anti-PIGF (BioInvent/ThromboGenics), has just entered Phase I trials with Roche in a \$765m upfront deal; we are uncertain if this is a true benchmark but the magnitude should entice investors as a validated Phase II Circadian product could command similar or greater fees.

A class of drugs targeting tumour vascular systems are the vascular disruptive agents. Two are focused on GBM: Azixa (Verubulin) from Myrexis and CYT997, from YM Biosciences. The lead vascular disruptive agent is ombrabulin from Sanofi, targeting soft tissue sarcoma. Other anti-angiogenic therapies are constantly being developed, for example N6L from ImmuPharma.

Avastin efficacy

Avastin is approved as a single agent for relapsed GBM based on limited data from the two registration studies in Exhibit 6. A clinical benefit¹⁴ was seen in 25.9% of relapsed patients treated with Avastin as monotherapy. Median survival increased by 4.1 months. However, the pack leaflet notes: *“The effectiveness of Avastin in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.”* Combination chemotherapy and Avastin is not approved.

Exhibit 6: Avastin glioblastoma response data

Note: An objective response means stable disease or signs of a reduction in tumour mass of less than 50%.

Design	Size	Outcome
Infusion at 10mg/kg every two weeks until disease progression therapy with irinotecan every two weeks.	85 patients in Avastin-only arm used for registration 82 patients in combination arm	A 25.9% objective response with a 4.2 month average duration of response
Infusion at 10mg/kg every two weeks until disease progression	56 patients	A 19.6% objective response with a 3.9 month duration

Source: FDA approved [Avastin prescribing information](#)

Avastin has a number of side effects. The most serious are perforation of the intestine (seen in 0.3-2.4% of patients), bleeding and cardiovascular problems and slow wound healing. The discontinuation rate range is 8.4-21%. The side effects from adding a second anti-VEGF antibody are unknown and will need to be determined in the clinical context.

VGX-100 in other cancers

The likely second indication will be with Avastin in refractory colorectal cancer with chemotherapy. The chemotherapy used will depend on whether it is first or second line. A more difficult indication would be lung cancer. The US breast cancer situation is not clear but trials could be run.

Corneal grafts

The cornea is the only tissue that does not have blood vessels. Oxygen diffuses directly into the tissue from the atmosphere. It is thought that VEGFR-3 acts as a sink for anti-VEGF-C and D produced, preventing any inflammatory response and production of VEGF-A, which could trigger corneal vascularisation.¹⁵

The potential indication is improving the survival of corneal grafts. About 20% have rejection problems and 10% are lost. Injury to the cornea can cause vascularisation. The market is c 40,000 per year in the US and maybe 20-30,000 in the EU. There is no systematic registry of corneal grafts

¹⁴ It should be noted that the responses seen were objective, that is stable disease or some shrinkage of the tumour plus reduced steroid use, corticosteroids being used to moderate the disease effects.

¹⁵ Cursiefen C *et al.* Nonvascular VEGF receptor 3 expression by corneal epithelium maintains avascularity and vision. [Proc Natl Acad Sci U S A. 2006;103:11405-10.](#)

in many countries including the US. The numbers imply a market of c 8,000 US and maybe 4,000 EU patients for an anti-rejection treatment. Assuming a 50% share and \$7,500 cost, the value is \$45m. Circadian could maybe address this market directly to ophthalmic surgeons with a specially formulated product.

In a model, VGX-100 reduced the number of blood vessels in an inflamed transplant by 44% and doubled graft survival rates.¹⁶ VGX-100 will probably be given as a sub-conjunctival depot injection.

IMC-3C5 – solid refractory cancers of any type

This product is an antibody that blocks the VEGFR-3 receptor. It is in a dose escalation study ([NCT01288989](#)) in c 40 patients. The study should report in H113. Circadian will receive milestones and a double-digit royalty. We have no information about milestone structure or magnitude. We have given this product a nominal US\$1bn market potential on the basis that Lilly will seek that level of sales. Currently, there is no real data on which to assess the product.

Diagnostic products

These are near-term products serving niche diagnostic markets. One is for a rare lung condition and the other is a genetic test for cancer.

Circadian has released data on the [lymphangioma](#) (LAM) lung cancer test. LAM is a rare disease of child-bearing women with a general population incidence of one per million, c 300 new US cases per year.¹⁷ The condition is caused by muscle cells migrating into lung tissue and forming cysts. Over a long period, this degrades lung function. There is no effective. The disease is associated with the genetic condition [tuberous sclerosis complex](#) (TSC).¹⁸

It has been shown that VEGF-D levels are elevated in LAM but this alone is not diagnostic since there is a high range overlap between normal and disease patients.¹⁹ High VEGF-D levels can identify patients with strong lymphatic involvement in LAM. The tests help with diagnosis and could be used for disease progression monitoring. It could broaden to a biannual year screen for women with confirmed TSC who have a high risk of developing LAM. LAM is currently screened by expensive CT scanning so a reliable diagnostic screen could be widely used. Long term, the test could be used in diagnosing lung diseases and in cancer monitoring. Circadian estimates that up to 25,000 tests could be run in the next few years priced at an average \$300 per test; 75% of this would be laboratory cost. We have assumed Circadian sales increase up to A\$1m. This could be much greater if the tests show strong utility.

The genetic test is an algorithm to analyse the results of gene array data to identify the original cancer type in patients diagnosed with Cancer of Unknown Provenance (CUP). Finding the original

¹⁶ Funaki T et al. Concomitant Blockade of Lymphatic and Blood Vessel Growth Into the Corneal Graft Improves Corneal Transplant Survival. [ARVO Meeting Session 234 2010 Poster 1554/D9995](#).

¹⁷ Johnson, S et al Lymphangioma [Ophanet 2004](#).

¹⁸ TSC in severe forms leads to benign brain tumours in childhood resulting in mental retardation. Mostly cases are mild and maybe half are never diagnosed. The US prevalence is perhaps c 25,000 based on modern genetic surveys. About 40% of adult pre-menopausal women with TSC develop Lymphangioma. On a US population incidence of 1:12,500, there are c 25,000 TSC cases alive. Assuming 50% female and with 34% of adult women showing the disease ([Moss, J et al 2001](#)), the prevalence might be c 4,000. This is c 50 new TSC associated cases per year in the US plus presumably c 250 spontaneous mutation cases. A therapy, (everolimus) for TSC has now been approved in the USA.

¹⁹ Glasgow, CG *et al*. Serum Vascular Endothelial Growth Factor-D Levels in Patients With Lymphangioma Reflect Lymphatic Involvement. [Chest. 2009; 135: 1293–1300](#).

cancer is necessary to prescribe the correct chemotherapy. The software would need a 510(k) FDA approval. It is currently in *Beta* testing. It can be sold in Asian markets once validated.

Valuation: A\$88m; A\$1.90 per share

We have valued Circadian at A\$88m using risk-adjusted discounted cash flows to 2030, Exhibit 7. The lead forecast product is VGX-100 for GBM. In addition to its own value, this is a gatekeeper indication which, by showing proof of principle, could open access to bigger indications alongside VEGF-A inhibitors, for example, in colorectal, lung and maybe breast cancers. We assume a 50% initial deal probability in FY13. By analogy with the Roche-Bioinvent deal on the anti- PIGF antibody, this could be \$75m upfront but we have used only \$12m risk-adjusted in the model as there is a trade-off between upfront and royalties. We cannot properly value IMC-3C5 but assume a 2019 entry and a US\$1bn potential. The royalty is assumed at 15% at a 20% risk. Diagnostics are assumed to build to A\$4.5m revenues. VEGF-D therapeutics are simply valued at 10% of VGX-100 and IMC-3C5 revenues. This adds 11% to revenues. A 30% tax rate is used.

Exhibit 7: Valuation model

Indication	Probability	Royalty	NPV (AU\$m)	% Total
Milestones	50-11%	NA	22.61	11.9%
VGX-100 Glioblastoma	20%	25%	12.47	6.5%
VGX-100 with Avastin	15%	25%	101.86	53.4%
IMC-3C5	20%	5%	27.00	14.2%
Corneal grafts	10%	25%	3.65	1.9%
Diagnostics	NA	NA	9.68	5.1%
Other	NA	NA	13.52	7.1%
Total risk-adjusted revenues			190.79	
Royalties to third parties			(27)	
Costs (inc tax)			(168)	
Continuing value			92.44	
Total value			88.35	
Value per share (46.2m)			1.90	

Source: Edison

Sensitivities: The case for VEGF-C and D therapeutics

The investment case rests on anti-VEGF-C agent improving clinical survival in combination with Avastin. Pre-clinical data is strong but solid indicative clinical validation is probably two years away. Any short-term investor upside lies in Circadian's patents as these have already lead to one licence (with Ark) and any VEGF-C/D product development would need a deal with Circadian. Strong upfront payments and milestones from FY13 are possible. As the Australian dollar is strong against the US dollar, there is a theoretical currency effect on valuation.

Financials: Solid financial base

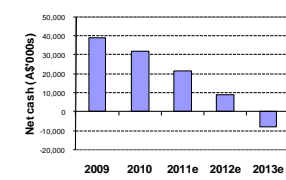
Circadian is entering a relatively high burn period as it moves into the clinical phase of VGX-100. We assume that R&D (inc IP) costs rises from A\$5.7m in FY11 to A\$8.7m in FY12 and to c \$11.3m in 2013. Interim research and development was A\$3.87m and administration costs were A\$2.5m (including IP). Cash as of 31 December 2010 was A\$25.76m after an interim cash burn of A\$5.7m. There are investment assets of A\$1.96m, which may be difficult to realise. An H111 impairment charge of A\$0.61m was required after a FY10 one-off charge of A\$1.2m on impaired assets plus a gain of A\$2.9m on marking equities to market prices. Forecasts are shown in Exhibit 8.

Exhibit 8: Financials

Note: Interest is charged after operating profit as is normal in the US and EU markets. The Australian treatment is to class interest as top-line income but we have put this below operating expenses in lien with US practice. In 2013, Circadian will require either milestone payments from a deal (A\$12m risk-adjusted is assumed but not in financial forecast) or a fund raising in FY13. A loan of A\$16.75m has been assumed in FY13 as a surrogate. This figure is speculative as it depends on clinical trial expenditure and the progress of other projects. Edison does not include deal upfront or milestones unless the deal has been announced.

Year end 30 June	A\$ '000s	2009	2010	2011e	2012e	2013e
		IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue		722	622	656	756	1,056
Cost of Sales		0	0	0	0	0
Gross Profit		722	622	656	756	1,056
EBITDA		(10,716)	(10,180)	(10,699)	(13,932)	(17,107)
Operating Profit (before amort. and except.)		(10,750)	(10,209)	(10,717)	(13,950)	(17,125)
Intangible Amortisation		0	0	0	0	0
Exceptionals		(891)	1,676	0	0	0
Other		61	14	0	0	0
Operating Profit		(11,641)	(8,533)	(10,717)	(13,950)	(17,125)
Net Interest		2,309	1,630	1,174	770	262
Profit Before Tax (norm)		(8,380)	(8,566)	(9,543)	(13,180)	(16,862)
Profit Before Tax (FRS 3)		(9,271)	(6,890)	(9,543)	(13,180)	(16,862)
Tax		(46)	(110)	0	0	0
Profit After Tax (norm)		(8,380)	(8,566)	(9,543)	(13,180)	(16,862)
Profit After Tax (FRS 3)		(9,922)	(6,948)	(9,543)	(13,180)	(16,862)
Average Number of Shares Outstanding (m)		44.6	45.2	46.4	46.4	46.4
EPS - normalised (c)		(20.2)	(19.1)	(20.6)	(28.4)	(36.3)
EPS - normalised and fully diluted (c)		(20.2)	(19.1)	(20.6)	(28.4)	(36.3)
EPS - (IFRS) (c)		(22.2)	(15.4)	(20.6)	(28.4)	(36.3)
Dividend per share (c)		0.0	0.0	0.0	0.0	0.0
Gross Margin (%)		100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)		N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)		N/A	N/A	N/A	N/A	N/A
BALANCE SHEET						
Fixed Assets		1,856	2,384	2,384	2,384	2,384
Intangible Assets		153	46	46	46	46
Tangible Assets		67	54	54	54	54
Investments		1,636	2,284	2,284	2,284	2,284
Current Assets		39,424	32,285	22,256	9,562	4,449
Stocks		0	0	0	0	0
Debtors		587	430	500	500	500
Cash		38,837	31,855	21,756	9,062	3,949
Other		0	0	0	0	0
Current Liabilities		(2,331)	(2,659)	(2,173)	(2,659)	(2,659)
Creditors		(2,331)	(2,659)	(2,173)	(2,659)	(2,659)
Short term borrowings		0	0	0	0	0
Long Term Liabilities		(174)	(190)	(190)	(190)	(11,940)
Long term borrowings		0	0	0	0	(11,750)
Other long term liabilities		(174)	(190)	(190)	(190)	(190)
Net Assets		38,774	31,820	22,277	9,097	(7,765)
CASH FLOW						
Operating Cash Flow		(8,898)	(9,173)	(11,256)	(13,447)	(22,107)
Net Interest		2,309	1,630	1,174	770	262
Tax		0	0	0	0	0
Capex		(15)	(23)	(18)	(18)	(18)
Acquisitions/disposals		(680)	0	0	0	0
Financing		(45)	630	0	0	0
Dividends		0	0	0	0	0
Net Cash Flow		(7,329)	(6,936)	(10,099)	(12,694)	(21,862)
Opening net debt/(cash)		(46,217)	(38,837)	(31,855)	(21,756)	(9,062)
HP finance leases initiated		0	0	0	0	0
Other		(51)	(45)	(0)	0	0
Closing net debt/(cash)		(38,837)	(31,855)	(21,756)	(9,062)	12,801

Source: Edison Investment Research

Growth	Profitability	Balance sheet strength	Sensitivities evaluation	
NA	NA		Litigation/regulatory	○
			Pensions	○
			Currency	◐
			Stock overhang	○
			Interest rates	○
			Oil/commodity prices	○

Growth metrics	%	Profitability metrics	%	Balance sheet metrics	Company details
EPS CAGR 08-12e	N/A	ROCE 11e	N/A	Gearing 11e	N/A
EPS CAGR 10-12e	N/A	Avg ROCE 08-12e	N/A	Interest cover 11e	N/A
EBITDA CAGR 08-12e	N/A	ROE 11e	N/A	CA/CL 11e	N/A
EBITDA CAGR 10-12e	N/A	Gross margin 11e	N/A	Stock turn 11e	N/A
Sales CAGR 08-12e	N/A	Operating margin 11e	N/A	Debtor days 11e	N/A
Sales CAGR 10-12e	N/A	Gr mgn / Op mgn 11e	N/A	Creditor days 11e	N/A
				Address:	
				Level 1, 10 Wallace Avenue Toorak, Victoria 3142 Australia	
				Phone	+61 3 9826 0399
				Fax	+61 3 9824 0083
				www.circadian.com.au	

Principal shareholders	%	Management team
Packer & Co Limited	16.6	MD: Robert Klupacs
Licentia Ltd	6.8	Robert Klupacs joined Circadian in 2005, becoming managing director in 2008. Before 2005, he was CEO of ES Cell International, a human stem cell company and was COO of the Monash Institute of Reproduction and Development. He has a BSc in Pharmacology and is a registered patent attorney
Ludwig Institute for Cancer Research	6.7	
Select Asset Management Limited	5.1	
		Finance manager: Susan Madden
		Susan Madden has been the company secretary since May 2010 and finance manager since 2009. Ms Madden is the company secretary for Vegenics and other Circadian subsidiary companies. She has held senior positions at Shell.
Forthcoming announcements/catalysts	Date *	Chairman: Dominique Fisher
Investor day	June 2011	Dominique Fisher was appointed a non-executive director and chairman of Circadian in 2005. Ms Fisher is executive director of EC Strategies Pty, chairman of Sky Technologies Pty, managing director of Helix Digital Pty and is a member of the Prostate Cancer Foundation, Victoria.
Final Results	August 2011	
AGM	November 2011	
Interim results	February 2012	
<i>Note: * = estimated</i>		
Companies named in this report		
Roche, Ark Therapeutics, Imclone (Eli Lilly), Merck & Co		

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