ASX and Media release

8 November 2012

Circadian's VGX-100 inhibits colorectal cancer in an animal model when combined with FDA-approved tyrosine kinase inhibitors

Circadian Technologies Limited (ASX:CIR; OTCQX:CKDXY) today released data at the European Organisation for Research and Treatment of Cancer (EORTC-NCI-AACR) annual conference in Dublin, Ireland demonstrating that its lead anti-cancer therapeutic, VGX-100, when combined with three different tyrosine kinase molecules - Sutent®, Nexavar® and Votrient® was able to improve tumour growth reduction in a mouse model of colorectal cancer.

VGX-100 has previously been shown to improve inhibition of tumour growth when combined with the anti-angiogenic agent Avastin®. This data indicates that, if clinically validated, VGX-100 has the potential to improve patient response when combined with other small molecule anti-angiogenic agents.

VGX-100 is a fully human monoclonal antibody targeting the VEGF-C growth factor. VGX-100 inhibits the development of blood vessels that are required for tumour growth. Additionally, VGX-100 may inhibit cancer spread (metastasis) by suppressing the development of both blood and lymphatic vessels.

The poster entitled "Improved inhibition of tumor growth by the novel monoclonal antibody VGX-100 targeting VEGF-C in combination with VEGF-Receptor Tyrosine Kinase Inhibitors" is attached in the Appendix that follows.

"This new data further indicates that VGX-100 can act in combination with a range of anti-angiogenic approved drugs to slow the growth of tumours, opening up possibilities for VGX-100 to be used in a range of new therapeutic combinations across a range of tumour types." commented Dr. Megan Baldwin, Head of Preclinical Research and Development and senior author.

Circadian controls exclusive worldwide rights to an extensive intellectual property portfolio enabling it to commercially develop antibodies targeting VEGF-C.

Circadian is currently undertaking a Phase 1 clinical trial in the USA under an Investigational New Drug (IND) application evaluating the safety and tolerability of ascending doses of VGX-100 alone or when administered in combination with Avastin®. This trial is expected to complete in Q1 2013.

Circadian has recently created a 100% owned subsidiary company, Ceres Oncology Pty Ltd, to specifically focus on the development of VGX-100 as a cancer therapy.

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About Circadian Technologies Limited

Circadian (ASX:CIR; OTCQX:CKDXY)) is a biologics drug developer focusing on cancer and ophthalmological disease therapies. It controls exclusive worldwide rights to a significant intellectual property portfolio around Vascular Endothelial Growth Factor (VEGF)-C and -D. The applications for the VEGF technology, which functions in regulating blood and lymphatic vessel growth, are substantial and broad. Circadian's internal product development programs are primarily focussed on developing VGX-100 (a human antibody against VEGF-C) as a treatment for solid tumours, in particular glioblastoma and colorectal cancer, as well as for ophthalmological diseases such as age-related macular degeneration, corneal neovascularisation and/or dry eye disease applications. Circadian has also licensed rights to some parts of its intellectual property portfolio for the development of other products to ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, including the anti-lymphatic antibody-based drug IMC-3C5 targeting VEGFR-3.

About Circadian's pipeline of treatments for cancer

The clinical and commercial success of Avastin®, an antibody that blocks the activity of VEGF-A, clinically validated anti-angiogenic drugs as an effective means of inhibiting solid tumour growth. By blocking the interaction of VEGF-A with its receptors, primarily VEGFR-2, the multi-billion dollar cancer therapeutic slows tumour growth by inhibiting blood vessel recruitment into the tumour, effectively starving tumours of essential nutrients and oxygen required for growth. However after a short period of time tumours can begin to grow again in the presence of Avastin®. Avastin® is approved by the US FDA in the following indications: metastatic colorectal cancer, non-squamous-cell lung cancer, glioblastoma, and metastatic renal cell carcinoma.

The angiogenic receptor VEGFR-2 can be stimulated by VEGF-A and VEGF-C. As such, VGX-100 has the potential to block blood vessel growth in tumours which grow in the presence of the VEGF-A inhibitor, Avastin® Combined administration of Avastin® and VGX-100 more completely shuts down angiogenesis (the growth of blood vessels) mediated by VEGFR-2.

VEGF-C along with the molecule VEGF-D are also the only known proteins to bind and activate VEGFR-3 which drives lymphatic vessel and tumour-associated blood vessel growth. Inhibitors of VEGF-C thus have therapeutic potential to inhibit not only primary tumour growth through their anti-angiogenic activities, but to also inhibit tumour spread or metastasis via the lymphatic vessels - a mechanism of tumour dissemination that is often the deadliest aspect of many tumour types and a mechanism that is not effectively blocked by anti-VEGF-A or anti-VEGFR-2 therapeutics.

Inherent risks of Investment in Biotechnology Companies

There are a number of inherent risks associated with the development of pharmaceutical products to a marketable stage. The lengthy clinical trial process is designed to assess the safety and efficacy of a drug prior to commercialisation and a significant proportion of drugs fail one or both of these criteria. Other risks include uncertainty of patent protection and proprietary rights, whether patent applications and issued patents will offer adequate protection to enable product development, the obtaining of necessary drug regulatory authority approvals and difficulties caused by the rapid advancements in technology. Companies such as Circadian are dependent on the success of their research and development projects and on the ability to attract funding to support these activities. Investment in research and development projects cannot be assessed on the same fundamentals as trading and manufacturing enterprises. Thus investment in companies specialising in drug development must be regarded as highly speculative. Circadian strongly recommends that professional investment advice be sought prior to such investments.

Forward-looking statements

Certain statements in this ASX announcement may contain forward-looking statements regarding Company business and the therapeutic and commercial potential of its technologies and products in development. Any statement describing Company goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of developing technology and in the process of discovering, developing and commercialising drugs that can be proven to be safe and effective for use as human therapeutics, and in the endeavour of building a business around such products and services. Circadian undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Actual results could differ materially from those discussed in this ASX announcement.

Improved inhibition of tumour growth by the novel monoclonal antibody VGX-100 targeting VEGF-C in combination with VEGF-Receptor Tyrosine Kinase Inhibitors

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Abstract

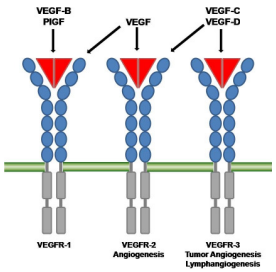
Angiogenesis and lymphangiogenesis are important processes facilitating tumour growth and metastasis. Growth factors that stimulate blood and lymphatic proliferation within tumours are therefore potential targets for anti-cancer therapies. The clinical utility of anti-angiogenic drugs was first established with bevacizumab (Avastin®) which neutralises VEGF-A and subsequently by small molecule tyrosine kinase inhibitors (TKIs) targeting the VEGF-Receptors (VEGFR-1, VEGFR-2 and/or VEGFR-3), including sunitinib (Sutent®), sorafenib (Nexavar®) and pazopanib (Votrient®). However, a significant number of patients may be refractory or develop resistance to bevacizumab or VEGFR-TKIs, suggesting up regulation of alternative pro-angiogenic proteins involved in tumoural escape mechanisms and/or incomplete inhibition of VEGFR-signalling using clinical dosing regimens. VEGF-C is a logical candidate inducing resistance to these therapies since it is a ligand for both VEGFR-2 and VEGFR-3 which is up regulated on tumour-associated vascular endothelium and its activity is not blocked by bevacizumab and may not be fully inhibited by the existing approved VEGFR-TKIs.

VGX-100 is a highly specific, fully human monoclonal antibody targeting VEGF-C and blocks this ligand from binding to both VEGFR-2 and VEGFR-3. A Phase I dose escalation clinical study to evaluate the safety and pharmacokinetics of VGX-100 administered alone or in combination with bevacizumab is currently ongoing in patients with advanced solid tumours (Clintrials.gov identifier NCT01514123).

We have previously demonstrated that VGX-100 has an additive effect in combination with docetaxel and/or anti-VEGF-A (bevacizumab) in several preclinical tumour models, suggesting that VEGF-C may be an important mediator of the resistance to this therapy. Here we demonstrate that VGX-100 also exhibits additive activity in a mouse tumour xenograft model of human colorectal cancer (Colo205) when co-administered with the VEGFR-TKIs sunitinib, sorafenib and pazopanib. The increased inhibition of tumour growth by co-administration of VGX-100 and the VEGFR-TKIs is associated with reduced tumoural angiogenesis and lymphangiogenesis. These data indicate that VGX-100 has great potential as a cancer therapeutic, with potential clinical utility in combination with existing therapies to allow greater flexibility in dosing regimens and improved tumour response.

Introduction

The various VEGF ligands have distinct receptor binding specificities which contribute to their diversity of function, as summarised below. VEGF-C and VEGF-D are ligands for VEGFR-2, which signals for angiogenesis, and VEGFR-3 which mediates lymphangiogenesis and tumour-associated angiogenesis. The receptor binding specificity of VEGF-C and VEGF-D is distinct to that of VEGF-A, which binds VEGFR-2 but not VEGFR-3.



VEGF-C and VEGF-D, the alternative ligands to VEGF-A for VEGFR-2, can be up-regulated during VEGF-A blockade[1,2,3,4,5]. Furthermore, in some mouse tumor models, administration of small molecule inhibitors of the VEGFR tyrosine kinase activity can increase subsequent tumor invasion and metastasis[6,7,8]. VEGF-C and VEGF-D up-regulation during VEGF-A/VEGFR suppression may be a key driver of resistance to anti-VEGF-A/VEGFR therapies. Expression of VEGF-C is elevated in a diverse range of tumors, including cancers of the colon, stomach, breast, ovary and prostate. Elevated levels of intra-tumoural and circulating VEGF-C frequently correlate with poor prognosis and features associated with tumor aggression (e.g. tumor depth, size, lymphatic invasion and lymph node metastasis).

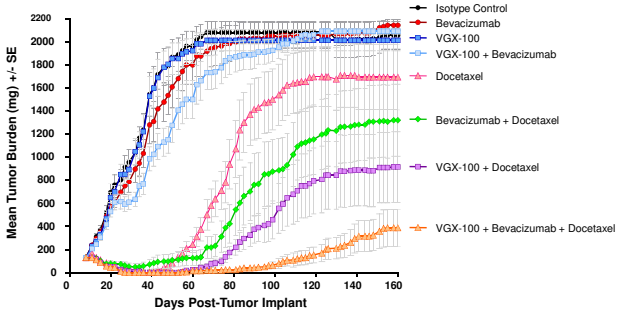
VGX-100 is a highly specific, fully human monoclonal antibody that neutralises binding of VEGF-C to VEGFR-2 and VEGFR-3. Therefore, VGX-100 has the potential to inhibit not only primary tumor growth through its anti-angiogenic and anti-lymphangiogenic activities, but to also inhibit metastasis via the lymphatic vessels. Lymphatic metastasis is associated with poor prognosis that is not effectively blocked by anti-VEGF-A or anti-VEGFR-2 therapeutics. VGX-100 is currently being evaluated in a Phase I clinical study in patients with advanced solid tumors.

We have previously reported that VGX-100 inhibits the primary tumour growth and incidence of metastasis to local lymph nodes in an orthotopic prostate tumour model. Furthermore VGX-100 has an additive anti-tumor effect in combination with docetaxel and/or anti-VEGF-A (bevacizumab) in several preclinical tumor models, suggesting that VEGF-C may be an important mediator of the resistance to this therapy. Here we demonstrate that VGX-100 also exhibits additive activity in a mouse tumor xenograft model of human colorectal cancer (Colo205) when co-administered with the VEGFR-TKIs sunitinib, sorafenib or pazopanib.

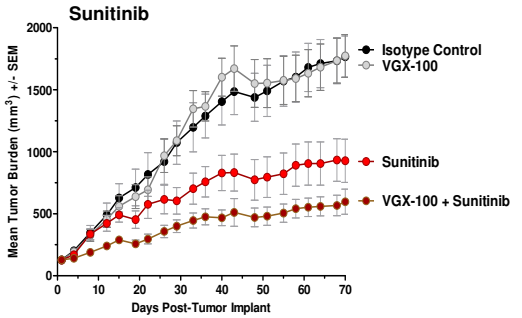
Materials and Methods

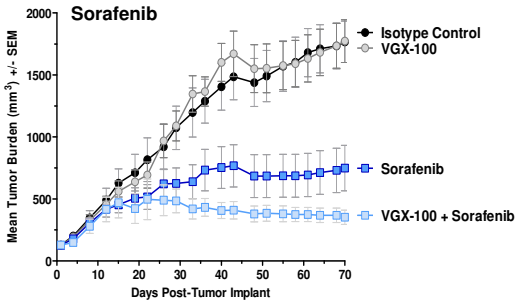
Colo205 and PC-3 xenograft tumour models: Colo205 (1 x 10^6) or PC-3 (5 x 10^6) cells were implanted subcutaneously in the flank of nu/nu mice. Mice were triaged into treatment groups (n=10/group) when the mean tumour burden was 100-150 mg. Tumour burden was estimated from calliper measurements by the formula: Tumour burden = (L x W^2)/2, where L and W are the respective orthogonal tumour length and width measurements (mm). Antibodies were administered twice per week via intraperitoneal injection (isotype control and VGX-100, 40 mg/kg; bevacizumab, 10 mg/kg). The TKI's were administered daily via oral delivery (sunitinib 20 mg/kg; sorafenib 15 mg/kg and pazopanib 30 mg/kg). Docetaxel (10 mg/kg) was administered intravenously weekly for three weeks. Tumour growth curves are plotted with last observation carried forward.

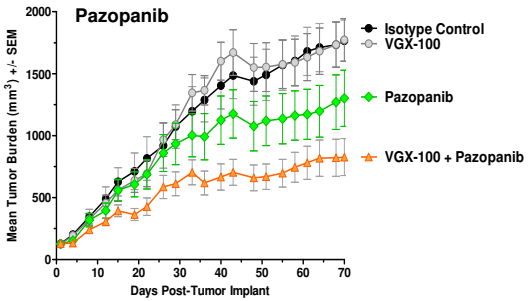
Prostate Carcinoma Model (PC-3)



Colorectal Carcinoma Model (Colo205)







Tumor Analysis at Day 70

Treatment Group	% TGI
Isotype Control	0
VGX-100	-0.37
Sunitinib	47.51
VGX-100 + Sunitinib	66.22
Sorafenib	57.61
VGX-100 + Sorafenib	80.08
Pazopanib	26.33
VGX-100 + Pazopanib	53.17

%TGI - percentage of tumor growth inhibition

Conclusions

- VGX-100 enhances the efficacy of docetaxel and bevacizumab combination therapy in xenograft cancer models.
- VGX-100 enhances the efficacy of sunitinib, sorafenib or pazopanib when co-administered in a colorectal cancer model.
- The combination of VGX-100 with sunitinib, sorafenib, pazopanib, bevacizumab or docetaxel showed no evidence of increased toxicity or antagonism of single-agent efficacy.
- Combination of VGX-100 with existing anti-angiogenic strategies can simultaneously inhibit multiple VEGF pathways and improve anti-cancer therapy. This may reduce redundant signalling that drives tumour resistance and limits the efficacy of currently available therapies.

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