VGX-100 Phase 1 oncology clinical trial in progress presented at ASCO 2013 Annual Meeting

Circadian Technologies Limited (ASX: CIR, OTCQX:CKDXY), through its 100% owned subsidiary Ceres Oncology Pty Ltd, reported overnight the study design and progress of the phase 1 clinical trial in advanced cancer patients of its anti-VEGF-C monoclonal antibody, VGX-100 at the 49th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago.

Gerald Falchook, M.D., Assistant Professor, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, and a principal investigator on the study presented "Phase I study of VGX-100, an anti-VEGF-C monoclonal antibody, with or without bevacizumab, in patients with advanced solid tumours." in the “Trials in Progress” Developmental Therapeutics - Clinical Pharmacology and Experimental Therapeutics Poster Session (Abstract TPS2619, Monday, June 3).

The Trials in Progress Session at ASCO highlights the transition of emerging biologic pathways and new agents into the clinic - providing "coming attractions" for oncologists in clinical practice.

Dr Falchook presented a scientific background / rationale for VGX-100 in oncology together with an overview of the accelerated Phase 1a / 1b trial design and an interim clinical update. The Phase 1 clinical trial is being conducted under an Investigational New Drug (IND) application (ClinTrials.gov study # NCT01514123) at two clinical sites in the USA in patients with advanced or metastatic solid tumours. The study has an accelerated two arm dose escalation design consisting of Arm A: VGX-100 mono-therapy and Arm B: VGX-100 in combination with bevacizumab (Avastin®). The objectives of the clinical trial are to establish the safety and toxicity, pharmacokinetic and biomarker profiles, as well as preliminary anti-tumour activity of VGX-100 in refractory patients. To date more than 35 patients have received weekly VGX-100 at doses ranging from 1 to 30 mg/kg.

Key updates presented included the following:

- Arm A cohorts A1 to A5, of single agent VGX-100 at weekly doses up to 20 mg/kg have completed accrual without any investigator reported Dose Limiting Toxicities (DLTs). In addition, Arm B cohorts B1 to B4, of VGX-100 at weekly doses of 2.5, 5 or 10 mg/kg in combination with bevacizumab given every 2 weeks at doses of 5 or 10 mg/kg have completed accrual with one reported protocol specified DLT in the lowest dose level cohort B1.
- The combination of inhibiting the VEGF-A and VEGF-C signalling pathways with VGX-100 + bevacizumab appears promising.
- Patient accrual for remaining cohorts A6 (single agent VGX-100 at weekly doses of 30 mg/kg) and B5 (combination of VGX-100 at weekly doses of 20 mg/kg + bevacizumab 10 mg/kg every 2 weeks) are near completion.

A copy of the ASCO poster presentation is attached in the Appendix.

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About Ceres Oncology Pty Ltd

Ceres Oncology Pty Ltd is a 100% owned subsidiary of Circadian Technologies Limited based in Melbourne, Australia. Ceres is developing VGX-100, which is a fully human monoclonal antibody that specifically and potently blocks the activity of vascular endothelial growth factor C (VEGF-C) which is involved in tumour angiogenesis (blood vessel growth), lymphangiogenesis (lymphatic vessel growth) and vascular leakage. By targeting and inhibiting the effects of VEGF-C, VGX-100 may have a broad utility in a range of oncology related disease states characterised by aberrant blood and/or lymphatic vessel growth, vascular leakage or edema, and/or inflammation, including solid tumours and lymphedema.

About Circadian Technologies Limited

Circadian (ASX:CIR; OTCQX:CKDXY)) is a biologics drug developer focusing on cancer, cancer related and ophthalmic disease therapies. It controls exclusive worldwide rights to a significant intellectual property portfolio around Vascular Endothelial Growth Factor (VEGF)-C and –D and VEGFR-3. 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 focused on developing VGX-100 (a human antibody against VEGF-C) as a treatment for lymphedema resulting from breast cancer treatment and solid tumours, in particular glioblastoma and colorectal cancer through its subsidiary Ceres Oncology, as well as developing VGX-300 (soluble VEGFR-3) for ‘back of the eye’ disease such as “wet” Age Related Macular Degeneration through its subsidiary Opthea. 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.

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.
Phase 1 Study of VGX-100, an anti-VEGF-C monoclonal antibody, with or without Bevacizumab in Patients with Advanced Solid Tumors

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Abstract #TPS2619

INTRODUCTION / BACKGROUND

- VGX-100 is an investigational, novel fully human IgG1k neutralizing monoclonal antibody that selectively targets vascular endothelial growth factor C (VEGF-C), inhibiting its signaling through VEGF-R2 & VEGF-R3 receptor pathways.
- 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-VEGF-R2 therapeutics.

PHASE 1 STUDY OBJECTIVES

Primary Objectives
- To evaluate the safety and establish the recommended dose of VGX-100 alone and in combination with bevacizumab.
- To assess: o the pharmacokinetic profile of VGX-100 alone and co-administered with bevacizumab o the incidence of anti-VGX-100 antibody formation o potential biomarkers of VGX-100 alone and co-administered with bevacizumab o preliminary tumor response to VGX-100 alone and co-administered with bevacizumab

Secondary Objectives
- To describe, using routine clinical laboratory parameters, safety endpoints, and tumor response, the efficacy of VGX-100 alone and in combination with bevacizumab.

- The combination of VGX-100 with bevacizumab may result in synergistic antitumor effects by targeting multiple VEGF signaling pathways that mediate tumor angiogenesis and lymphangiogenesis.

- Here we describe the ongoing first-in-human, Phase 1 clinical study design of the anti-VEGF-C human monoclonal antibody VGX-100 administered alone and in combination with bevacizumab in adult patients with advanced or metastatic solid tumors.

- Over-expression of VEGF-C has been shown in human tumors, including cancers of the colon, stomach, breast, ovary and prostate. Elevated levels of intratumoral and circulating VEGF-C often correlate with poor outcomes and features associated with tumor agression (e.g. tumor depth, size, lymphatic invasion and lymph node metastasis).

- Tumoral escape and relapse following VEGF-A inhibition with bevacizumab (a humanized monoclonal antibody that binds to and inhibits the biologic activity of human VEGF-A), may in part be due to increased VEGF-C that signals through VEGF-R2 and VEGF-R3.1,2

- Previous published results in several mouse xenograft models of human cancer with VGX-100 have demonstrated efficacy when used as a monotherapy and in combination with approved cancer therapies.

- In an orthotopic PC3 prostate cancer model, single agent VGX-100 effectively reduced lymph node metastasis.3

- In addition, enhanced efficacy has been demonstrated pre-clinically in models of human xenograft tumor growth using:
  o VGX-100 in combination with bevacizumab (Avastin®) and/or standard chemotherapy.4
  o VGX-100 in combination with pazopanib, sorafenib or sunitinib which are small molecule tyrosine kinase inhibitors (TKIs) of the receptors for VEGF ligands.