ASX and Media release
02 June 2014

Circadian's VEGF-C Antibody, VGX-100, Shown to Be Well Tolerated in Phase Ia/b Clinical Trial

Circadian Technologies (ASX: CIR, OTCQX: CKDXY), through its 100% owned subsidiary Ceres Oncology Pty Ltd, is pleased to announce that Phase 1 safety and clinical activity data demonstrating an encouraging clinical profile for VGX-100 in patients with advanced solid tumors was presented over the weekend at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago (USA).

The Phase 1a/b oncology clinical trial, run under an Investigational New Drug (IND) program with the Food and Drug Administration (FDA), enrolled 43 patients and was conducted in the USA at the University of Texas MD Anderson Cancer Center (Houston) and UCLA Hematology-Oncology (Santa Monica) as a dose escalation study of VGX-100 alone or in combination with bevacizimab (Avastin®).

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 "A first-in-human phase I study of VGX-100, a selective anti-VEGF-C antibody, alone and in combination with bevacizumab in patients with advanced solid tumors".

The VGX-100 Phase 1 trial was chosen for presentation as part of a Poster Highlights Session of selected abstracts in the Developmental Therapeutics: Clinical Pharmacology and Experimental Therapeutics Section of the ASCO meeting. The presentation was followed by a discussion session in which clinical oncology experts provided commentary on the research findings.

The presented data demonstrated that weekly intravenous administration of VGX-100 was well tolerated at all of the doses studied alone or in combination with bevacizumab and provided first evidence of anti-tumor activity in patients with refractory or recurrent advanced late stage solid tumors without available therapeutic options. A best response of stable disease was seen in 14 of 39 evaluable subjects (36%) of which five patients (13%) showed durable stable disease for a period ≥ 16 weeks (Tumor types: 2 colon, 1 ovarian, 1 cervical and 1 renal cell carcinoma). In addition, a patient with triple negative breast cancer had a 16% decrease in tumor disease at all sites (bone, lung, lymph nodes and skin) after 8 weeks (2 treatment cycles) with weekly VGX-100 (2.5 mg/kg) + bevacizumab given every 2 weeks (10 mg/kg), before discontinuing the study in cycle 3.

Overall, the most common side effects observed were fatigue, rash, nausea and hypertension which were manageable. The only dose limiting toxicity was a transient Grade 3 hypertension observed in one subject at the lowest dose combination.

Dr Gerald Falchook from MD Anderson commented: "Resistance and tumor escape to currently available anti-cancer drugs such as bevacizumab (Avastin®) remains a major challenge in the treatment of cancer patients. These results with the investigational drug VGX-100 which targets VEGF-C are encouraging, with early evidence of anti-tumor activity in patients who failed to respond to standard treatment. In addition, the observed safety profile of VGX-100 alone or in combination with bevacizumab is promising and warrants further clinical evaluation."

Commercially, Avastin® is approved for a number of solid tumor indications and generates sales in excess of US$6BN a year but is limited by tumor escape and relapse possibly caused by up-regulation of alternate pro-angiogenic factors including vascular endothelial growth factor C (VEGF-C). VGX-100 is a novel fully human monoclonal antibody that selectively inhibits VEGF-C, which is a member of the VEGF family of secreted growth factors that are key mediators of tumor related angiogenesis, lymphangiogenesis and vascular permeability.

A copy of the ASCO poster presentation is attached in the Appendix. In addition, The VGX-100 Phase 1 abstract can be found on the ASCO 2014 Annual Meeting website at: http://abstracts.asco.org/144/AbstView_144_131977.html and more information on the VGX-100 clinical trial (Study ID: NCT01514123) can be found at www.clinicaltrials.gov.

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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 tumor 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 tumors and lymphedema.

About Circadian Technologies Limited

Circadian (ASX:CIR; OTCQX:CKDXY)) is developing cancer and cancer related biologic therapies through its subsidiary Ceres Oncology and ophthalmic disease therapies through its subsidiary Opthea. 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 include VGX-100 (a human antibody against VEGF-C) for cancer therapy and OPT-302 (soluble VEGFR-3) for 'back of the eye' disease including "wet" Age Related Macular Degeneration. 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.

Abstract # 2524

A first-in-human phase I study of VGX-100, a selective anti-VEGF-C antibody, alone and in combination with bevacizumab in patients with advanced solid tumors.

G.S Falchook[1], J.W.Goldman[2], J. Desai[3,4], I.M. Leitch[4], D.S. Hong[1], V. Subbiah[1], R. Kurzrock[1], L.S. Rosen[2]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]UCLA Hematology-Oncology, Santa Monica, CA;

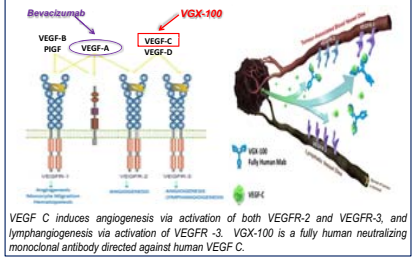
[3]Royal Melbourne Hospital, Melbourne, Australia; [4]Ceres Oncology / Vegenics, Melbourne, Australia;

INTRODUCTION

VGX-100 (anti-VEGF-C)

- VGX-100 is an investigational first-in-class fully human IgG1λ neutralizing monoclonal antibody targeting VEGF-C, inhibiting its receptor activation of VEGFR-2 & VEGFR-3.
- VEGF-C is a pro-angiogenic / lymphangiogenic growth factor that may modulate tumoral escape / resistance to anti-VEGF therapy and allow regrowth of tumor vasculature.[1-2]
- VEGF-C is associated with:
  - Increased vascular density
    - *melanoma, breast, pancreatic, colorectal, lung*
  - Poor outcomes including reduced survival
    - *Gastric, lung, colorectal, lung, breast, pancreatic, ovarian*[3-6]
- In preclinical xenograft models, addition of VGX-100 to bevacizumab +/- chemotherapy or tyrosine kinase inhibitors prolongs tumor regression.[7-9]
- Clinical combination of VGX-100 with bevacizumab (Avastin®) may result in synergistic effects by targeting multiple VEGF signalling pathways that mediate angiogenesis and lymphangiogenesis.

VGX-100 Inhibition of VEGF-C Signaling In Tumors.



VEGF C induces angiogenesis via activation of both VEGFR-2 and VEGFR-3, and lymphangiogenesis via activation of VEGFR -3. VGX-100 is a fully human neutralizing monoclonal antibody directed against human VEGF C.

Targeted CoTherapy

- ***Bevacizumab*** is a humanized monoclonal anti-VEGF-A antibody that binds to and inhibits the biologic activity of human VEGF-A.

OBJECTIVES

Primary Objectives

- To evaluate the safety and establish the recommended dose of VGX 100 alone and co-administered with bevacizumab.

Secondary Objectives

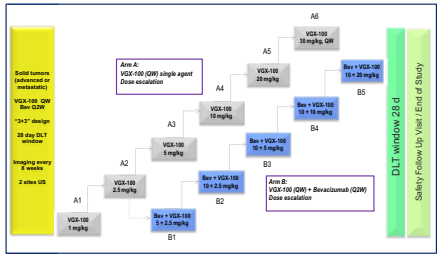
- To assess:
  - the pharmacokinetic profile of VGX-100 alone and co-administered with bevacizumab
  - the incidence of anti-VGX-100 antibody formation
  - potential biomarkers
  - preliminary tumor response

STUDY DESIGN

Study Design

- Open label, phase 1 a / 1b "3+3" dose escalation study (NCT01514123)
- The study has an accelerated two arm design:
  - Arm A: VGX-100 mono-therapy
  - Arm B: VGX-100 in combination with bevacizumab

STUDY DESIGN



VGX-100 +/- bevacizumab administration schedule

- Arm A (VGX 100 mono-therapy)
  - Each 28 day treatment cycle consists of VGX 100 given weekly as an intravenous (IV) infusion at D1, D8, D15 and D22.
- Arm B (VGX 100 plus bevacizumab)
  - Treatment with bevacizumab is given first, followed by VGX-100. For each subject, each 28 day treatment cycle consists of:
    - bevacizumab given as an IV infusion every 2 weeks at D1 and D15.
    - VGX 100 given as an IV infusion weekly at D1, D8, D15 and D22.
- Patients received treatment until disease progression or intolerable toxicity.

Key Eligibility Criteria

- Adult patients (≥ 18 years) with advanced solid tumors.
- Adequate hematologic, renal and hepatic function.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1
- Evaluable OR measurable disease by RECIST 1.1 criteria.
- Patients excluded with CNS / cerebrovascular haemorrhage, myocardial infarction or reversible posterior leukoencephalopathy syndrome associated with prior anti-VEGF/anti-VEGFR therapy.

DLT Criteria

- A DLT is defined as any AE of ≥ grade 3 up to day 28 despite optimal supportive care, unless there is a clear alternative explanation that the AE was not caused by either VGX-100 or bevacizumab, except for the following:
  - alopecia; fatigue; or grade 3 hypertension controlled within 72 hrs.
- The maximum tolerated dose (MTD) is defined as the highest dose level with an observed incidence of DLT in < 33% of subjects enrolled in a cohort dose level.

RESULTS

Patient Disposition and Dose Limiting Toxicities

Cohort`	VGX-100 (mg/kg, QW)	Bevacizumab (mg/kg, Q2W)	Patients N	Patients with DLT N (%)	DLT's in 28 day Cycle 1
Arm A: VGX-100					
A1	1	-	4[a]	0	
A2	2.5	-	3	0	
A3	5	-	3	0	
A4	10	-	3	0	
A5	20	-	3	0	
A6	30	-	3	0	
Arm B: Bevacizumab + VGX-100					
B1	2.5	5	6	1	G3 hypertension
B2	2.5	10	3	0	
B3	5	10	6*	0	
B4	10	10	3	0	
B5	20	10	6*	0	

[a]*One pt in cohort A1 withdrew consent @ D18 after 2 doses of VGX-100 and was replaced per protocol*

**Enrollment into cohorts was expanded to gain additional safety experience with VGX-100*

RESULTS (*continued*)

Demographics and Patient Characteristics

	Arm A: VGX-100 (N=19)	Arm B: Bevacizumab + VGX-100 (N=24)
Females, n (%)	10 (53)	12 (46)
Males, n (%)	9 (47)	12 (54)
Age, mean years (SD)	59.6 (14)	57.2 (13)
Min, Max	20, 76	28, 85
Race, n (%)		
White	12 (63)	19 (79)
African American	2 (10.5)	2 (8)
Latino	3 (16)	3 (13)
Asian	2 (10.5)	0 (0)
ECOG score, n (%)		
0	2 (11)	7 (29)
1	17 (89)	17 (71)
Prior Therapy, n (%)		
≥ 1 line of Chemotherapy	17 (90)	24 (100)
Bevacizumab	9 (47)	9 (38)
Radiotherapy	8 (42)	17 (71)
Primary Tumor Type, n (%)		
Breast	0 (0)	2 (8)
Cervical	0 (0)	2 (8)
Colon	5 (26)	4 (17)
Pancreatic	2 (11)	1 (4)
Renal cell carcinoma	0 (0)	2 (8)
Urothelial	0 (0)	2 (8)
Other	12 (63)	11 (46)
Arm A (all other tumor types n=1 [5%]): *Adnexal, Aveolar soft tissue sarcoma, Cholangiocarcinoma, Endometrial, Gastroesophageal junction, Lacrymal duct carcinoma, Melanoma, Ovarian, Pancreatic neuroendocrine Tumor, Prostate (Undifferentiated), Rectal, Submandibular salivary gland.*		
Arm B (all other tumor types n=1 [4%]): *Adrenal, Appendiceal, Gastric, Inflammatory breast cancer, Lung, Melanoma, Mixed Mullerian, Neuroendocrine Tumor of cervix, Sarcoma, Thymic, Uterine.*		

ECOG, Eastern Cooperative Oncology Group

RESULTS – SAFETY AND TOLERABILITY

Treatment-Related Adverse Events

	VGX-100 (N =19)	Bevacizumab + VGX-100 (N = 22)
Patients with any treatment related AE, n (%)	9 (47)	17 (77)
Worst grade of 1	7 (37)	8 (33)
Worst grade of 2	7 (37)	12 (55)
Anorexia	0 (0)	2 (9)
Anemia	1 (5)[b]	1 (5)
Back pain	0 (0)	1 (5)[d]
Chills	0 (0)	1 (5)
Deep vein thrombosis	0 (0)	1 (5)
Dermatitis allergic	2 (11)[b]	0 (0)
Fatigue	1 (11)[a]	0 (0)
Headache	0 (0)	1 (5)
Hypersensitivity	2 (11)	2 (9)[c]
Hypertension	0 (0)	4 (18)[d]
Infusion related reaction	1 (5)	0 (0)
Infusion site reaction	1 (5)[a]	0 (0)
Thrombosis	0 (0)	1 (5)[c]
Worst grade of 3	0 (0)	2 (9)
Cardiac failure congestive*	0 (0)	1 (4)
Hypertension#	0 (0)	1 (4)
Worst grade of 4	0 (0)	0 (0)
Worst grade of 5	0 (0)	0 (0)

At the time of the data cut-off, safety data was available for 22 subjects enrolled in Arm B cohorts

[a,b,c,d]*Occurred in the same patient*

**Observed in Cycle 3 for Cohort B2 (VGX-100 2.5 mg/kg, QW + bevacizumab 10 mg/kg, Q2W)*

#*Observed in Cycle 1 for Cohort B1 (VGX-100 2.5 mg/kg, QW + bevacizumab 5 mg/kg, Q2W)*

AE, Adverse event

RESULTS – SAFETY AND TOLERABILITY

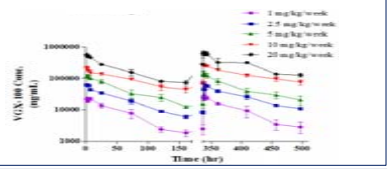
Treatment-emergent Adverse Events

- All patients had treatment emergent adverse events of ≥ Grade 1.
- Grade 3 treatment emergent adverse events occurred in 1 patient each with either hyperbilirubinemia, hypophosphatemia, dyspnoea, lipase increased, intestinal obstruction, syncope, or abdominal cramps; and 1 patient with abdominal pain, syncope vasovagal and pleural effusion
- 1 patient had a treatment-emergent grade 4 adverse event: visual disturbance (Cohort B5: VGX-100 20 mg/kg, QW + bevacizumab 10 mg/kg, QW)
- 2 patients had treatment-emergent grade 5 events: of progressive disease (Cohort A5: VGX-100 20 mg/kg, QW) and aspiration (Cohort B3: VGX-100 5 mg/kg, QW + bevacizumab 10 mg/kg, Q2W).
- None of these AEs were considered related to VGX-100 or bevacizumab.

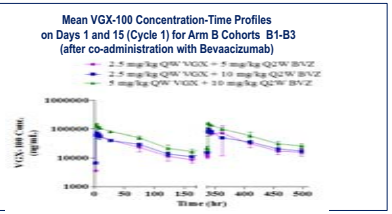
RESULTS - PHARMACOKINETICS

Serum Concentration versus Time Profiles

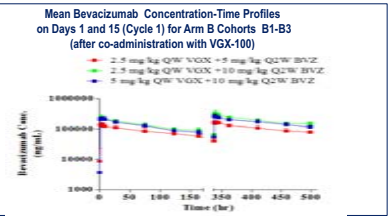
Mean VGX-100 Concentration-Time Profiles on Days 1 and 15 (Cycle 1) for Arm A Cohorts A1-A5



Mean VGX-100 Concentration-Time Profiles on Days 1 and 15 (Cycle 1) for Arm B Cohorts B1-B3 (after co-administration with Bevacizumab)



Mean Bevacizumab Concentration-Time Profiles on Days 1 and 15 (Cycle 1) for Arm B Cohorts B1-B3 (after co-administration with VGX-100)



- The increases in C_{max} and AUC_{0-168} for VGX-100 appear to be dose proportional over the available dose range and support weekly dosing
- Preliminary PK for VGX-100 appears to be similar alone and when co-administered with bevacizumab.
- Bevacizumab PK appears to be comparable to historical data.
- Weekly i.v doses of VGX-100 ≥ 20 mg/kg, had C_{min} values at Day 15 (Mean 128000 ng/mL, SD 27495 ng/mL) that exceeded:
  - maximal serum VEGF-C levels (6 - 32 ng/mL) reported in cancer patients[10]
  - *In vivo* PK exposures of VGX-100 (~≥100000 ng/mL) associated with efficacy in xenograft tumor models in mice (data on file).
  - *In vitro* VGX-100 IC50 values of (26 ng/mL and 19 ng/mL) to inhibit VEGF-C binding to VEGFR-2 and VEGFR-3 receptors respectively in BAF/3 cell assays (data on file).

RESULTS - IMMUNOGENICITY

Anti-VGX-100 Antibodies

	Patients N	Binding Antibodies N	Neutralizing Antibodies N
Arm A: VGX-100 single agent	19	0	0
Arm B: Bevacizumab + VGX-100	24	1*	0
Overall incidence rate		2% (1/43)	0% (0/43)

**One patient had a "low positive" for pre-existing binding antibodies to VGX-100 at baseline prior to receiving VGX-100 and tested negative at subsequent post-dose timepoints.*

RESULTS – TUMOR RESPONSE

Best Post Dose Tumor Response by RECIST[a]

	VGX-100 (N=19)	Bevacizumab + VGX-100 (N=24)
Evaluable Patients	17	22
Stable Disease, n (%)	6 (35)	8 (36)
Progressive Disease, n (%)	11 (65)	14 (64)

[a]*In patients with measurable disease at baseline and one follow-up assessment who received at least one dose of VGX-100 (Arm A cohorts n=17; Arm B cohorts n=22).*

- A best response of stable disease was seen in 14 of 39 (36%) evaluable patients.
- Five patients (13%) had durable stable disease ≥ 16 weeks as follows:
  - 2 patients with colon cancer
    - Cohort A3: VGX-100 monotherapy 5 mg/kg, QW
    - Cohort B1: VGX-100 2.5 mg/kg, QW + Bevacizumab 5 mg/kg, Q2W
  - 1 patient with ovarian cancer
    - Cohort A5: VGX-100 monotherapy 20 mg/kg, QW
  - 1 patient with renal cell carcinoma (RCC)
    - Cohort B2: VGX-100 2.5 mg/kg, QW + Bevacizumab 10 mg/kg, Q2W
  - 1 patient with cervical cancer
    - Cohort B5: VGX-100 20 mg/kg, QW + Bevacizumab 10 mg/kg, Q2W
- A patient with triple negative breast cancer had a 16% decrease in disease at all sites (bone, lung, LN and skin) at the end of cycle 2 (Cohort B2:VGX-100 2.5 mg/kg, QW + bevacizumab 10 mg/kg, Q2W) but discontinued in cycle 3 (SAE).
- Four patients discontinued prior to post-dose tumor assessment (1 clinical progression, 1 withdrawal of consent and 2 SAE's).

CONCLUSIONS

- VGX-100 at weekly doses up to 30 mg/kg alone or up to 20 mg/kg in combination with bevacizumab 5 or 10 mg/kg, Q2W was safe and tolerable in patients with advanced solid tumors. No MTD was reached.
- Preliminary PK data for VGX-100 support weekly dosing and combining treatments did not markedly affect the profiles of VGX-100 or bevacizumab.
- Weekly dosing with VGX-100 ≥20 mg/kg exceeded predicted human circulating VEGF-C levels and efficacy exposures in xenograft models.
- There were no findings of altered safety or pharmacokinetic profiles due to development of anti-VGX-100 binding or neutralizing antibodies.
- Five patients had durable stable disease ≥ 16 weeks (2 colon, 1 ovarian, 1 RCC and 1 cervical).
- The combination of inhibiting both VEGF-C and VEGF-A ligand signaling pathways with VGX-100 and bevacizumab appears promising.
- Further clinical evaluation of VGX-100 in combination with VEGF-A inhibitors, chemotherapy and other targeted agents is warranted.

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