ASX and Media Release
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Circadian's partner Eli Lilly presents Phase 1 oncology clinical trial of VEGFR-3 antibody IMC-3C5 (LY3022856) at ASCO

Melbourne, Australia – Circadian Technologies Limited (ASX:CIR, OTCQX:CKDXY) is pleased to announce that its partner Eli Lilly has presented clinical data from the Phase 1 oncology clinical trial of the VEGFR-3 antibody IMC-3C5 (LY3022856) at the 2015 Annual Meeting of the American Society of Clinical Oncology (ASCO) in Philadelphia (USA).

IMC-3C5 (LY3022856) is a fully-human IgG1 monoclonal antibody being developed by Eli Lilly as a treatment for cancer. Eli Lilly has an exclusive license to Circadian intellectual property to develop the VEGFR-3 antibody. Eli Lilly pays Circadian an annual license fee and potential royalties on future product sales.

The First-in-Human oncology trial, run under an Investigational New Drug (IND) program with the Food and Drug Administration (FDA), completed enrolment with a total of 44 patients refractory to standard therapy in two parts: Part A dose escalation (dose levels 5, 10, 20 and 30 mg/kg) enrolled 23 patients with advanced solid tumors; Part B was an expansion cohort to evaluate IMC-3C5 (LY3022856) monotherapy at 30 mg/kg in 21 patients with colorectal cancer (CRC).

Weekly intravenous administration of IMC-3C5 (LY3022856) was shown to be well tolerated up to the highest planned dose of 30 mg/kg and a maximum tolerated dose (MTD) was not reached in the study. The pharmacokinetic profile of IMC-3C5 (LY3022856) was favourable with dose-related increases in exposure observed following weekly infusions. Overall, the most common treatment emergent side effects observed were nausea, fatigue, vomiting and anorexia.

In Part A, 4/8 patients with CRC refractory to standard therapy treated at 30 mg/kg had prolonged progression free survival (PFS) (10-39 weeks) while in Part B the median PFS was 6.3 weeks. Interestingly, biomarker analysis revealed an increase in soluble VEGFR-3 levels in patient plasma samples following IMC-3C5 (LY3022856) administration suggesting engagement with the VEGFR-3 target. Plasma VEGF-C and VEGF-D levels were not significantly changed following dosing.

IMC-3C5 (LY3022856) blocks VEGF-C/D activation of VEGFR-3, which inhibits blood and lymphatic vessel growth. IMC-3C5 (LY3022856) does not block VEGFR-2 which VEGF-C and VEGF-D also activate. Eli Lilly will consider future development of IMC-3C5 (LY3022856) in indications in which lymphatic vessel growth plays a prominent role.

A copy of the ASCO poster presentation is attached in the Appendix. In addition, the IMC-3C5 Phase 1 abstract can be found on the ASCO 2015 Annual Meeting website at: http://abstracts.asco.org/156/AbstView_156_143954.html. More information on the IMC-3C5 clinical trial (Study ID: NCT01288989) is available at www.clinicaltrials.gov.

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About Circadian Technologies Limited

Circadian (ASX:CIR; OTCQX:CKDXY) is a biologics drug developer focusing on ophthalmic disease therapies. It controls exclusive worldwide rights to a significant intellectual property portfolio around Vascular Endothelial Growth Factor (VEGF)-C, VEGF-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 OPT-302 (formerly VGX-300, soluble VEGFR-3) for 'back of the eye' disease such as wet age-related macular degeneration (wet AMD). 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 IMC-3C5, a monoclonal antibody 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.

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Phase 1 Study of Anti-VEGF Receptor-3 (VEGFR-3) Monoclonal Antibody (mab) LY3022856/IMC-3C5

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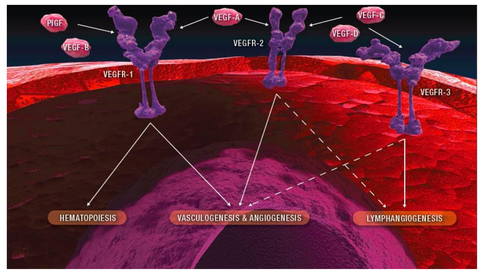
BACKGROUND

- The vascular endothelial growth factor receptor-3 (VEGFR-3) and its ligands, VEGF-C and VEGF-D, control tumor lymphangiogenesis by enhancing proliferation and survival of lymphatic endothelial cells. The VEGFR-3 pathway is also active in blood vessel endothelial cells at the sprouting tips of tumor capillaries; therefore, it may also promote tumor angiogenesis.[1]
- The level of VEGFR-3 expression is higher in the majority of tumor blood vessels and lymphatics than in surrounding normal vessels.[2]
- LY3022856 is a fully human IgG1 monoclonal antibody (Mab) designed to bind VEGFR-3 and block the binding of VEGF-C[3] and VEGF-D* ligands to the receptor, thereby inhibiting subsequent signaling.

* Marc Achen and Steve Stacker, personal communication, March 2005.

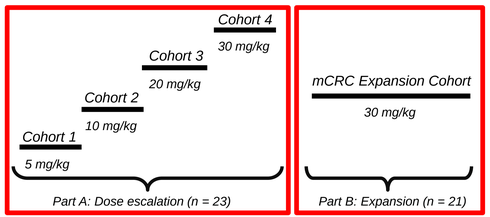
Figure 1. VEGFR Signaling Pathways



METHODS

Figure 2. Study Design

- LY3022856 was investigated as monotherapy in a multicenter, open-label, Phase 1 dose-escalation clinical trial (3+3)
- Dosing once weekly, treatment cycle 4 weeks, 90-minute IV infusion
- Cycle 1 of PART A only: 4 weeks treatment + 2 weeks DLT observation period



mCRC: advanced/metastatic colorectal cancer

Study I5G-IE-JBCA; NCT01288989

Study Objectives

Primary Objectives

- To establish the safety profile and maximum tolerated dose (MTD) in patients with advanced solid tumors (Part A)
- To gain additional safety, tolerability, and dose confirmation in patients with advanced/metastatic colorectal cancer (Part B)

Secondary Objectives

- To describe the pharmacokinetics (PK) of LY3022856
- To assess the antitumor activity of single-agent LY3022856
- To assess the immunogenicity of LY3022856

Exploratory Objectives

- To determine the pharmacodynamic (PD) effect of LY3022856 based on plasma proteins
- To investigate potential biomarkers for the safety and efficacy of LY3022856

Patient Eligibility (Parts A and B)

Key inclusion criteria

- Advanced solid tumors refractory to standard therapy or for which no standard therapy is available (Part A)
- Advanced mCRC refractory to standard therapy or for which no standard therapy is available (Part B)
- Measurable (Parts A and B) or non-measurable (Part A) disease according to RECIST version 1.1
- No prior chemotherapy or treatment with investigational agent within 28 days prior to enrollment
- Adequate hematologic, hepatic and renal function
- Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0, 1, or 2
- 18 years of age or older, and life expectancy > 3 months

Key exclusion criteria

- Patient has received treatment with any Mab within 6 weeks prior to enrollment
- Major surgical procedure or radiation therapy within 28 days of enrollment
- Concurrent active malignancy
- Uncontrolled hypertension (> 150/90 mm Hg)
- Arterial thromboembolic or deep venous thrombotic event within 6 months prior to enrollment

PK Methods

In Part A, intensive PK samples were collected up to 168 hours following the first infusion and up to 504 hours following the fourth infusion for all 4 cohorts. Part A PK data were analyzed by standard noncompartmental analysis.
In Part B, trough concentrations were collected up to 16 infusions.

PD Methods

VEGF-C/D and soluble VEGFR-3 (sVEGFR-3) were measured in plasma by immunoassays using MSD Electrochemiluminescence (ECL) assay.

RESULTS

Table 1. Baseline Characteristics

	PART A								PART B		TOTAL	
	Cohort 1 5 mg/kg (N = 6)		Cohort 2 10 mg/kg (N = 3)		Cohort 3 20 mg/kg (N = 3)		Cohort 4 30 mg/kg (N = 11)		30 mg/kg (N = 21)		(N = 44)	
	Med	Range	Med	Range	Med	Range	Med	Range	Med	Range	Med	Range
Age	61	41-79	65	44-68	64	58-79	58	33-67	55	37-74	58	33-79
Weight (kg)	79	52-117	95	69-114	77	57-92	77	54-132	77	54-119	77	52-132
	n	%	n	%	n	%	n	%	n	%	n	%
Male	5	83	1	33	3	100	5	45	12	57	26	59
White	6	100	3	100	2	67	10	91	15	71	36	82
Age ≥ 65	2	33	2	67	1	33	3	27	8	38	16	36
ECOG PS 0	3	50	3	100	0	0	6	55	10	48	22	50
ECOG PS 1	2	33	0	0	2	67	5	45	11	52	20	45
ECOG PS 2	1	17	0	0	1	33	0	0	0	0	2	5

Abbreviations: Med, Median; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

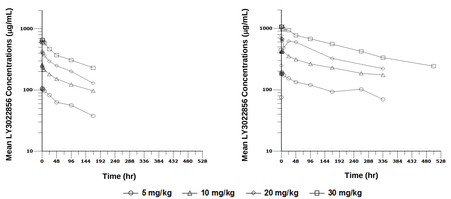
Table 2. PK Parameters Following Weekly IV Infusions (Part A)

	Pharmacokinetic Parameter	Geometric Mean (CV%)[a] Cohort 1 5 mg/kg (N = 6)	Cohort 2 10 mg/kg (N = 3)	Cohort 3 20 mg/kg (N = 3)	Cohort 4 30 mg/kg (N = 11)
First Infusion	C_{max} (μg/mL)	110 (21)	259 (26)	435 (15)	689 (18)
	t_{max}[b] (h)	2.61 (1.55-5.60)	2.00 (1.55-2.00)	1.67 (1.50-2.00)	3.55 (1.52-6.38)
	$AUC_{0-t(last)}$ (μg·h/mL)	9550 (28)	22400 (24)	37100 (12)	59900[c] (30)
Fourth Infusion	C_{max} (μg/mL)	198[d] (13)	456 (22)	754 (17)	1150[e] (16)
	t_{max}[b] (h)	2.00[f] (1.62-5.55)	2.08 (2.00-5.63)	1.75 (1.63-2.58)	2.55[e] (1.50-9.92)
	$AUC_{τ}$ (μg·h/mL)	20400[g] (24)	47300 (28)	81800 (22)	122000[e] (18)
	$t_{1/2}$[g] (days)	11.7[h] (10.4-13.7)	8.45[i]	8.97 (8.81-9.22)	10.4[j] (8.79-12.1)
	CL_{ss} (L/h)	0.0198[d] (39)	0.0192 (29)	0.0181 (27)	0.0191[e] (19)
	Vss(L)	NP	NP	NP	6.67 (8)[k]
	$R_{A,Cmax}$	1.68[d] (7)	1.76 (6)	1.73 (13)	1.69[e] (10)
	$R_{A,AUC}$	1.88[d] (10)	1.98; 2.08[a]	2.26 (7)	2.16[j] (15)

Abbreviations: $AUC_{0-t(last)}$ = area under the concentration-time curve from time 0 to t_{last}; $AUC_{τ}$ = area under the concentration-time curve during 1 dose interval (168 hours); CL_{ss} = clearance at steady state (after intravenous administration); C_{max} = maximum observed drug concentration; CV = coefficient of variation; N = number of patients dosed; n = number of observations; NP= Not presented (extrapolated AUC was more than 30% and estimated V_{ss} values may not be reliable); $R_{A,AUC}$ = accumulation ratio calculated using AUC; $R_{A,Cmax}$ = accumulation ratio calculated using C_{max}; $t_{1/2}$ = terminal elimination half-life; t_{max} = time of maximum observed drug concentration; V_{ss} = volume of distribution at steady state.

Footnotes: a) Geometric mean and geometric CV% are provided for n ≥ 3; otherwise, actual values are provided. b) Median and range are provided for n ≥ 3; otherwise actual values are provided for t_{max}. c) n=5. d) n=8. f) n=4. g) Geometric mean and range are provided for n ≥ 3; otherwise actual values are provided for $t_{1/2}$. h) n=3. i) n=1. j) n=6. k) n=2.

Figure 3. Serum Concentrations Grouped by Dose (Part A)



Note: Mean values were presented if there were at least 3 concentration values available at any time point.

Arithmetic mean serum concentration-time profiles of LY3022856 on semi-logarithmic scale, following administration of 5 mg/kg to 30 mg/kg LY3022856 every week (first infusion-left panel and fourth infusion-right panel) as IV infusion over approximately 1.5 hours, in cancer patients.

Figure 4. Serum Trough Concentrations (Part B, 30 mg/kg)

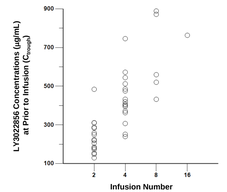
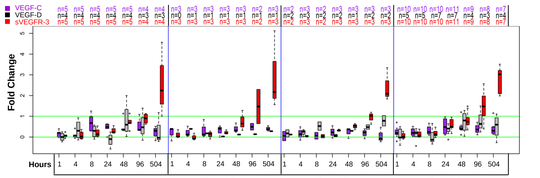


Figure 5. Measuring VEGF-C, VEGF-D and sVEGFR-3 in Plasma

sVEGFR3 increase during treatment was time-dependent, not dose-dependent.



Boxplot of fold changes grouped by hours after treatment and arms in cycle 1 week 1 to cycle 1 week 4
n: number of patients for each measurement at each time point

Table 3.Treatment-emergent Adverse Events

	PART A								PART B		TOTAL	
	Cohort 1 5 mg/kg (N = 6)		Cohort 2 10 mg/kg (N = 3)		Cohort 3 20 mg/kg (N = 3)		Cohort 4 30 mg/kg (N = 11)		30 mg/kg (N = 21)		(N = 44)	
TEAE*	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)
Nausea	1 (17)	0	0	0	2 (67)	0	6 (55)	1 (9)	9 (43)	1 (5)	18 (41)	2 (5)
Fatigue	0	0	1 (33)	0	0	0	4 (36)	0	9 (43)	1 (5)	14 (32)	1 (2)
Vomiting	1 (17)	0	1 (33)	0	2 (67)	0	5 (46)	1 (9)	4 (19)	0	13 (30)	1 (2)
Anorexia	2 (33)	0	0	0	0	0	3 (27)	0	7 (33)	0	12 (27)	0
Pyrexia	0	0	0	0	1 (33)	0	5 (46)	0	5 (24)	0	11 (25)	0
Edema	1 (17)	0	1 (33)	0	1 (33)	0	3 (27)	0	4 (19)	1 (5)	10 (23)	1 (2)
Urinary Tract Infection	0	0	1 (33)	0	1 (33)	0	2 (18)	1 (9)	5 (24)	2 (10)	9 (21)	3 (7)
Constipation	1 (17)	0	1 (33)	0	0	0	4 (36)	0	2 (10)	0	8 (18)	0
Cough	1 (17)	0	1 (33)	0	0	0	1 (9)	0	5 (24)	0	8 (18)	0
Hypoalbuminemia	1 (17)	0	0	0	0	0	1 (9)	1 (9)	5 (24)	0	7 (16)	1 (2)
Diarrhea	1 (17)	0	1 (33)	0	1 (33)	0	1 (9)	0	3 (14)	0	7 (16)	0

*TEAE that occurred in at least 15% of the total number of patients are shown. Grades are according to Common Terminology Criteria for Adverse Events version 3.0. Abbreviations: Gr = grade.

Table 4. Adverse Events of Special Interest

	PART A								PART B		TOTAL	
	Cohort 1 5 mg/kg (N = 6)		Cohort 2 10 mg/kg (N = 3)		Cohort 3 20 mg/kg (N = 3)		Cohort 4 30 mg/kg (N = 11)		30 mg/kg (N = 21)		(N = 44)	
AE	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)	All Grades n (%)	Gr ≥3 n (%)
Hepatobiliary disorders	0	0	0	0	0	0	1 (9)	1 (9)	2 (10)	1 (5)	3 (7)	2 (5)
Infusion-related reaction	1 (17)	1 (17)	0	0	0	0	1 (9)	0	1 (5)	0	3 (7)	1 (2)
Hypertension	0	0	0	0	0	0	0	0	3 (14)	1 (5)	3 (7)	1 (2)
Rectal hemorrhage	0	0	0	0	0	0	0	0	3 (14)	1 (5)	3 (7)	1 (2)
Deep vein thrombosis	0	0	0	0	0	0	0	0	2 (10)	0	2 (5)	0
Pulmonary embolism	1 (17)	1 (17)	0	0	0	0	0	0	0	0	1 (2)	1 (2)
Small intestinal hemorrhage	0	0	0	0	0	0	1(9)	0	0	0	1 (2)	0
Hematochezia	0	0	0	0	0	0	1(9)	0	0	0	1(2)	0
Renal hemorrhage	0	0	0	0	0	0	0	0	1 (5)	0	1 (2)	0
Epistaxis	0	0	0	0	0	0	0	0	1 (5)	0	1 (2)	0
Renal failure	0	0	0	0	0	0	1 (9)	1 (9)	0	0	1 (2)	1 (2)
Proteinuria	1 (17)	0	0	0	0	0	0	0	0	0	1(2)	0

Grades are according to Common Terminology Criteria for Adverse Events version 3.0. Abbreviations: Gr = grade.

Figure 6. Duration of Treatment – Part A

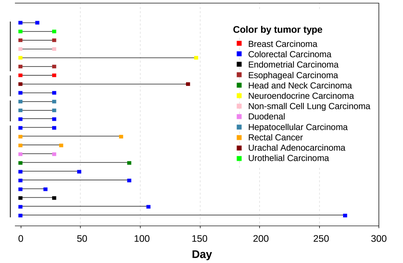
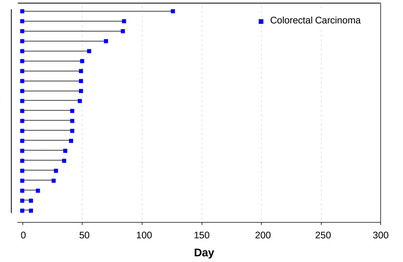


Figure 7. Duration of Treatment – Part B



CONCLUSIONS

- Dose escalation reached highest planned dose of 30mg/kg q1wk, with no clinical maximum tolerated dose (MTD) achieved. LY3022856 was well tolerated up to a dose of 30 mg/kg.
- Dose-related increases in exposure were observed following weekly infusions with approximately 2-fold accumulation. The clearance at steady state appeared similar across the doses tested, potentially indicating the saturation of target-mediated drug disposition.
- LY3022856 does not appear to have significant anti-tumor activity as monotherapy in mCRC refractory to standard therapy. There were 8 patients with best overall response of stable disease and no PR or CR.
- No significant changes in plasma VEGF-C/D levels were detected from patient samples after LY3022856 administration.
- LY3022856 appears to have target engagement as evidenced by an increase in soluble VEGFR-3 in plasma.
- Future development will be considered in indications in which lymphangiogenesis plays a prominent role.

References

1. Tammela T, et al. Nature 2008;454:656-660.
2. Smith NR, et al. Clin Cancer Res 2010;16:3548-3561.
3. Persaud K, et al. J Cell Sci. 2004;117:2745-2756.

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