

# A PHASE 2 RANDOMIZED STUDY OF ORAL SELICICLIB IN PATIENTS WITH PREVIOUSLY TREATED NASOPHARYNGEAL CARCINOMA

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## ABSTRACT

**Background:** Seliciclib is a selective inhibitor of cyclin dependent kinases (CDKs) 2, 7 and 9. In a Phase 1 study of 2 weeks of oral administration, clinical antitumor activity was observed in patients with treatment-naive nasopharyngeal carcinoma (NPC) and biological effects consistent with CDK inhibition were detected in tumor biopsy samples. We are conducting a multicenter, randomized Phase 2 study to evaluate the safety and efficacy of prolonged administration of seliciclib in patients with previously treated NPC. The study has a lead-in stage where the safety and tolerability of 2 dosing schedules of seliciclib are to be confirmed in patients with advanced solid tumors (including NPC) before being used in the randomized stage of the study where only NPC patients are eligible to participate. The primary efficacy endpoint is 6-month progression free survival. Here we report interim findings from the lead-in stage.

**Methods:** Eligible patients must be ≥18 years with previously treated NPC or other incurable solid tumors; must have measurable disease according to RECIST, ECOG 0-1, and adequate bone marrow, hepatic and renal function. The planned sample size is 6 to 12 patients per dosing schedule. A dosing schedule is considered tolerable for proceeding to the randomized stage if <33% patients experienced dose-limiting toxicities (DLT) during the first treatment cycle.

**Results:** 23 patients (age 38 - 74) were enrolled and treated. DLTs were observed in 4: grade 3 increase in ALT or AST (n=3), treatment delay > 2 weeks for grade 1 creatinine (n=1). Common adverse events (all grades, regardless of causality) included fatigue, nausea/vomiting, constipation, cough, fever, hypokalemia, hyponatremia, and elevation in ALT/AST, most of which were mild to moderate in intensity. Eleven patients had prolonged stable disease (7 of which had NPC).

**Conclusions:** These interim data confirm that both dosing schedules are tolerable for proceeding to the randomized stage. Majority of stable disease occurred in NPC patients. Updated data will be presented at the meeting.

## SELICICLIB (R-roscovitine, CYC202)

Orally bioavailable  
Tri-substituted purine (enantiomer of roscovitine)  
Selective and potent inhibitor of CDK 2, ~7, ~9 via ATP binding sites  
Biological activities include anti-proliferation, apoptosis induction and transcription inhibition  
Active in xenograft experiments as a single agent and in combination with chemotherapy, and EGFR inhibitors  
In clinical trials as a single agent and in combination with other anti-cancer drugs, the toxicity profile is

- Similar among different dosing schedules
- Predominantly non-hematological
- Reversible and manageable

## STUDY DESIGN

Multi-center, randomized, Phase 2 study to evaluate the safety and efficacy of two dosing schedules of seliciclib in patients with previously treated NPC

- Part A (lead-in stage): to establish tolerability of two dosing schedules by enrolling 6 -12 solid tumor or NPC patients to each schedule sequentially:
  - 400 mg *b.i.d.* x 4 consecutive days every week
  - 800 mg *q.d.* x 4 consecutive days every week
- Part B (randomized stage): to establish the efficacy of two dosing schedules based on 6-month progression free survival (PFS)  
One treatment cycle is 3 weeks  
The first repeat tumor imaging study is conducted after 2 cycles of treatment and subsequently every 3 cycles

## STUDY RATIONALE

Cell cycle dysregulation has been found in most human cancers. In NPC, p16 and p27, the biological inhibitors of CDKs 2 and 4, are often underexpressed, usually through gene deletion or promoter methylation. Their absence will lead to uncontrolled cellular proliferation. In NPC, the loss of p16 and p27 has been reported to correlate with poor prognosis and loco-regional recurrence respectively. In a Phase 1 biomarker study of seliciclib, clinical antitumor activity was observed in patients with treatment-naive NPC and biological effects consistent with CDK inhibition were detected in NPC biopsy samples. The dosing schedule of 400 mg *b.i.d.* x 4 days/week is similar to the dosing schedule used in the Phase 1 biomarker study where clinical antitumor activity was observed. Rationale for evaluating the 800 mg *q.d.* schedule: may have a higher area under the curve (AUC) which may lead to greater efficacy and once daily dosing is more convenient for patients.

## PATIENT POPULATION (Lead-in stage)

- Age ≥18 years old with advanced solid tumors including NPC for whom there is no curative or effective therapy
- ECOG performance status 0-1 with a life expectancy ≥ 3 months
- Measurable disease according to RECIST
- Adequate bone marrow, liver and renal function
- ≥ 3 weeks from prior systemic treatments, and/or ≥ 7 days from prior radiation therapy with resolution of poor toxicities to ≤ grade 1 or baseline except for alopecia
- ≥ 3 weeks from major surgery
- Able to swallow capsules
- No previously untreated or progressive CNS metastasis
- No prior treatment with a CDK inhibitor
- No other cancers have been treated with chemotherapy or biological therapy in past 5 years with exception of adequately treated in situ cervical cancer or basal cell skin cancer
- No uncontrolled illnesses
- No history of active hepatitis B and/or hepatitis C infection
- Not known to be HIV-positive
- Signed informed consent form

## DEFINITION OF DLT AND RD

- Dose Limiting Toxicity (DLT) is defined as the occurrence of any of the following events when judged to be clinically significant and definitely, probably and possibly related to the study drug during the first treatment cycle
  - Grade 3/4 nausea, vomiting or diarrhea despite maximum supportive care
  - Other grade 3/4 non-hematological toxicity with the exception of alopecia
  - Neutropenic fever or grade 4 neutropenia lasting >5 days
  - Grade 3 thrombocytopenia associated with bleeding or grade 4 thrombocytopenia
- Treatment delay >2 weeks due to adverse events definitely, probably and possibly related to seliciclib
- Recommended Phase 2 dose (RD) for Part B
- RD is dose at which <33% patients experienced a DLT

## TABLE A: DEMOGRAPHICS

Both schedules 4 days every week	400 mg <i>b.i.d.</i> (n=11)	800 mg <i>q.d.</i> (n=12)
Age in years, median (range)	56 (42 - 69)	55 (38 - 74)
Gender		
Male	5	6
Female	6	6
Race		
Caucasian	1	-
Asian	10	11
Hispanic	-	1

## TABLE B: DISEASE CHARACTERISTICS

Both schedules 4 days every week	400 mg <i>b.i.d.</i> (n=11)	800 mg <i>q.d.</i> (n=12)
Tumor type		
NPC	3	7
Breast	2	-
Non-small cell lung	2	1
Rectal	1	-
Hepatocellular	1	-
Bladder	-	1
Renal cell	-	1
Uterine sarcoma	1	-
Ovarian leiomyosarcoma	-	1
Retroperitoneal sarcoma	-	1
Malignant histiocytoma	1	-
Prior systemic therapies		
0	1	1
1-3	5	9
4 or more	5	2

## TABLE C: SAFETY

Both schedules 4 days every wk	400 mg <i>b.i.d.</i> (n=11)	800 mg <i>q.d.</i> (n=12)
Median number of cycles: Received cycles	1	2
1 - 2	7	6
3 - 4	1	1
5 - 6	2	2
7 or more	1	3
Number of patients with DLTs	1 (Gr 3 ↑ALT (n=1))	3 (Gr 1 ↑ creatinine >2 wks (n=1) Gr 3 ↑ ALT (n=1) Gr 3 ↑ ALT/AST (n=1))
Patients required dose reduction	-	2
Patients discontinued from study for unacceptable toxicities	1 (Gr 3 ↑ ALT)	1 (Gr 1 ↑ creatinine >2 wks)

## TABLE D: COMMON ADVERSE EVENTS (maximum grade, all cycles, regardless of causality)

Both schedules 4 days every week	400 mg <i>b.i.d.</i> (n=11)		800 mg <i>q.d.</i> (n=12)	
	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4
Anemia	1	-	1	2
Constipation	2	-	2	-
Cough	4	-	1	-
Dizziness	2	1	1	-
Fatigue	6	-	7	-
Fever	3	-	3	-
Hypokalemia	2	2	2	-
Hyponatremia	2	1	1	-
ALT increased	1	1	1	2
AST increased	1	-	2	1
Creatinine increased	2	-	2	-
Insomnia	2	-	2	-
Loss of appetite	2	-	2	-
Nausea	3	-	5	-
Seeing bright lights/light sensitivity	1	-	5	-
Vomiting	2	-	2	-

## TABLE F: STABLE DISEASE IN NPC

Dosing schedule	Histology	Prior treatment for recurrence/metastasis	Stable disease (months)	Total cycles
400 mg <i>b.i.d.</i>	Undifferentiated	Gemcitabine/ carboplatin, erlotinib	3.6	5
	Undifferentiated	Gemcitabine/ cisplatin	10.3	15
	Poorly differentiated	Gemcitabine / cisplatin/ adriamycin, gemcitabine/ carboplatin	3.1	5
800 mg <i>q.d.</i>	Undifferentiated	Cisplatin/ radiation	1.9	3
	Undifferentiated	Gemcitabine/ carboplatin, erlotinib	3.6	5
	Squamous cell	Gemcitabine/ carboplatin, erlotinib	> 10.2	> 19
	Poorly differentiated	Gemcitabine	8.4	14

## SUMMARY

Seliciclib could be safely administered on a schedule of 4 days per week  
Both 400 mg *b.i.d.* and 800 mg *q.d.* schedules are well tolerated and meet the criteria for proceeding to the randomized stage  
Prolonged stable disease observed in previously-treated NPC patients suggesting seliciclib inhibits tumor growth in NPC  
Further clinical development in NPC as a single agent or in combination with other anti-cancer agents should be considered

Abstract #6026, ASCO Annual Meeting, May 29 – June 2, 2009 in Orlando, Florida. Supported by Cyclacel Ltd, Dundee, UK. Poster contains interim study data (unaudited) of the lead-in stage of an ongoing study as of May 2009.