A Phase I and Pharmacokinetic (PK) Study of Continuous Daily Administration of P1446A-05, a Potent and Specific Oral Cdk4 Inhibitor.

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ABSTRACT #3013

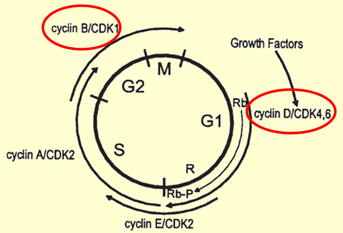
Background: P1446A-05 is a novel oral inhibitor of Cdk4-D1, Cdk1-B, and Cdk9-T, and has been shown to inhibit tumor growth both *in vitro* and *in vivo*. Pharmacodynamic studies demonstrate that activation of Cdk1 reappears within 48 hours after P1446A-05 is withdrawn, suggesting the need for prolonged administration hence, we sought to evaluate the feasibility, safety and tolerability of a continuous daily schedule of P1446A-05 in patients (pts) with advanced malignancies.

Methods: P1446A-05 was given at escalating doses of 75, 150, 250, 350 and 500mg. Samples were collected for PK at multiple time points over 24 hours on cycle 1 day 1 and 15, as well as at single time points on cycle 1 day 8, 22 and cycle 2 day 1.

Results: Thirty-nine pts (median age=63 years, 51% male, 51% ECOG PS=1) collectively received more than 100 cycles of P1446A-05. The majority of drug-related toxicities were ≤Grade 2, the most common of which were diarrhea (n=31), nausea/vomiting (n=21/12), fatigue (n=18) and anorexia (n=13). Two pts developed study-drug related diarrhea with hypokalemia/elevated creatinine and died during cycle 1. Dose-limiting toxicities (DLT) at 500mg [Table 2] led to subsequent de-escalation and expansion of the 350mg cohort. A total of 24 pts were treated at 350mg; only one patient experienced dose-limiting diarrhea. PK data are summarized in Table 3. Accumulation ratios across dose levels suggest moderate accumulation with continuous dosing. Nine pts achieved stable disease (SD) for at least 2 cycles. One pt with alveolar soft tissue sarcoma, whose disease was progressing at enrollment, remains on treatment with SD after 11 cycles. **Conclusions:** The recommend phase II dose of P1446A-05 is 350mg. The occurrence of diarrhea early in therapy should be closely monitored both clinically and with serum chemistries. Further Phase II studies at this dose will be conducted with potential enrichment strategies.

STUDY RATIONALE

- The cyclin-cyclin dependent kinase (Cdk) complexes, Cdk inhibitors and the retinoblastoma protein (pRb) play an important role in cell cycle progression.



- In human cancers, overexpression of cyclins or absent/diminished levels of Cdk inhibitors result in selective growth advantage for tumour cells.
- Inhibiting cyclins/Cdks therefore represents a potential therapeutic target.
- P1446A-05 is a novel oral Cdk inhibitor.
- In pre-clinical studies, P1446A-05 exhibits greater activity towards Cdk4-D1, Cdk1-B, and Cdk9-T as compared to other Cdks tested.
- P1446A-05 exhibited significant tumor reduction in xenograft tumor models of human colon cancer and non small cell lung cancer in SCID mice.
- It also demonstrated good oral bioavailability in preclinical studies.

OBJECTIVES

Primary Objective:

- To determine the maximum tolerated dose and dose limiting toxicity of P1446A-05 in patients with advanced refractory malignancies.

Secondary Objective:

- To determine the safety, tolerability, pharmacokinetics and clinical response of this regimen.
- To perform exploratory analysis of biomarkers

STUDY DESIGN

Standard eligibility criteria for phase I study was used, including:

- ECOG PS ≤ 2 (amended to ECOG PS ≤ 1 after July, 2010)
- Hematopoietic function:
  - a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
  - b. Platelets ≥ 100 x 10^9/L
  - c. Hemoglobin ≥ 90 g/L
- Hepatic Function:
  - i. bilirubin ≤ 1.5 institutional upper limit of normal (ULN)
  - ii. AST/ALT ≤ 2.5 institutional ULN
- Renal Function: creatinine ≤ 1.5 institutional ULN

Exclusion Criteria

- No active brain metastases
- No history of clinically significant cardiac conditions†
- Patients on warfarin (coumadin)‡

† Exclusion added after SAE at 500 mg dose level in patient with history of atrial fibrillation

‡ Exclusion added after 3 patients on coumadin while on study experienced an elevated INR suggesting a possible drug-drug interaction

Administration: Oral once daily x 28 days

- Re-treatment criteria:
  - a. ANC ≥ 1.5 x 10^9/L
  - b. Platelets ≥ 100 x 10^9/L
- Dose Escalation Strategy: Modified Fibonacci dose escalation schema
- Dose limiting toxicities (DLTs) were defined as:
  - Any ≥ grade 3 non-hematologic toxicity
  - Any ≥ grade 4 hematologic toxicity lasting > 5 days or febrile neutropenia
  - Any study drug related toxicity necessitating treatment suspension for ≥ 5 days during cycle#1
  - Delay of > 7 days in initiating cycle#2 due to drug-related toxicity
  - Discontinuation of a subject due to study drug-related toxicity before completing cycle#1
- Maximum tolerated dose (MTD)
  - The next lower dose level below the one in which > 1/3 or ≥ 2/6 subjects experience DLT.

RESULTS

Table 1: Patient Characteristics

Characteristic	# Patients (n)
Total number of patients dosed	39
Male: Female	20:19
Median Age (range)	63 (29 - 77)
ECOG Performance Status 0 / 1 / 2	20 / 16 / 3
Median number of cycles (range)	2 (1-12)
Best Response (n=29 evaluable)	
PR / SD / PD	0 / 12 / 17
Median duration of SD (range)	16 weeks (8-48)
Tumour Type	
Colorectal	9
Non-small cell lung	7
Ovarian/Primary Peritoneal	5
Gastroesophageal	3
Small cell lung cancer	3
Renal Cell carcinoma	3
Other	9

Table 2: Dose Levels & Duration

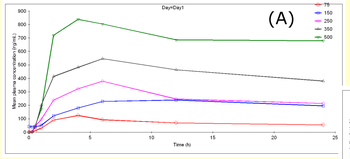
Dose Level (mg/day)	# Patients Dosed†	# Cycles Received	DLT Event Description
75	3	6	N/A
150	3	8	N/A
250	3	6	N/A
350	3+9+12	68	Diarrhea (1 pt)
500	6	12	Elevated INR (1 pt) Diarrhea (1 pt) Sudden Death (1 pt)

† 5 of the 39 patients did not complete cycle#1 (one was ineligible) therefore were not evaluable for DLT and were replaced. All patients were evaluable for toxicity.

Table 3: Pharmacokinetic Results

Dose (mg/day)	C_{max} (ng/mL)		T_{max} (h)		AUC_{0-t} (ng.h/mL)		Accumulation Ratio
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	
75	125.1	331.2	4	2	1726.8	5567.1	2.6
150	257.9	754.9	6	6	4852.9	16642.7	3.6
250	471.9	1047.8	4	4	6114.7	18537.1	3.0
350	623.5	1493.9	6	4	10395.5	26733.2	2.7
500	1135.9	2254.7	6	2	16370.5	40465.3	2.6

Figure 1: Plasma Concentration Over Time



LEGEND: Solid lines represent standard deviation.

Figure 1: Mean plasma concentration of P1446A-05 versus time curves after administration of P1446A-05 on (A) day 1 and (B) day 15.

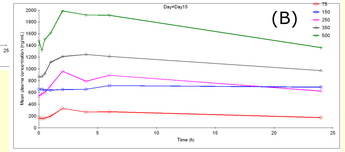


Table 4: Principle Toxicities†

	Grade					
Toxicity	1	2	3	4	5	Total‡
Diarrhea	23	6	1	0	1	31
Nausea	18	3	0	0	0	21
Fatigue	8	7	3	0	0	18
Anorexia	9	2	2	0	0	13
Vomiting	10	1	1	0	0	12
↓ magnesium	4	2	0	0	0	6
↓ potassium	3	0	2	0	0	5
Dysgeusia	4	1	0	0	0	5
Abdominal pain	3	1	0	0	0	4

† All toxicities occurring in ≥ 10% of patients.
‡ Number of subjects experiencing toxicity.

DISCUSSION & CONCLUSIONS

- Continuous daily administration of P1446A-05 has generally been well tolerated.
- Preliminary pharmacokinetics show a linear increase in exposure with increasing dose and moderate accumulation with daily dosing.
- The dose limiting toxicities at 500 mg were diarrhea, increased INR and sudden death.
- The recommend phase II dose of P1446A-05 is 350mg. The occurrence of diarrhea early in therapy should be closely monitored both clinically and with serum chemistries.
- One patient with small cell lung cancer remained on treatment with stable disease (SD) for 6 cycles, while another alveolar soft tissue sarcoma patient, whose disease was progressing at the time of enrollment, achieved SD as a best response and remained on treatment for 12 cycles.
- Further Phase II studies at this dose will be conducted with potential enrichment strategies.