Dose Escalation Study of BET Inhibitor PLX2853 in Patients with Relapsed or Refractory Acute Myeloid Leukemia or High Risk Myelodysplastic Syndrome

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Background

PLX2853 is an orally available, non-benzodiazepine bromodomain and extraterminal domain (BET) inhibitor that exhibits low nanomolar potency and a modest preference for binding to the second bromodomain (BD2) of the BET proteins. By regulating genes (e.g., *MYC* and *BCL2*) critical to leukemic cell growth and survival, PLX2853 demonstrated broad anti-leukemic activity both as a single agent and in combination with other therapeutic agents in preclinical models. The pharmacokinetic (PK) profiles in solid tumor subjects had high peak plasma concentrations and short terminal half-life values (< 3 hours) allowing for nearly complete elimination from the plasma by 9 hours post dose. Since strong and prolonged suppression of BET proteins likely have untoward effects in normal tissues, the PLX2853 PK profile is hypothesized to improved tolerability by allowing transient yet substantial target engagement followed by time for recovery after daily dosing.

Study PLX124-02 Trial Design and Methodology

Phase 1b open-label, dose-escalation of oral PLX2853 as a single agent:

Primary Objectives:

- To evaluate the safety and PK of orally administered PLX2853 as a single agent in subjects with relapsed or refractory AML or high-risk MDS.
- To establish the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D).

Secondary Objectives:

- To evaluate the preliminary efficacy of PLX2853 as measured by:
  - i) Overall complete remission (OCR) rate, based on the following definitions:
    AML: CR + CR with incomplete hematologic recovery (CRi)
    MDS: CR
  - ii) Overall response rate (ORR), based on standard response criteria for the relevant malignancy and the following definitions of overall response:
    AML: CR + CRi + partial remission (PR)
    MDS: CR + PR
  - iii) Duration of response (DOR);
  - iv) Event-free survival (EFS);
  - v) Progression-free survival (PFS);
  - vi) Overall survival (OS).

Exploratory Objective:

- To assess biomarkers in peripheral blood cells, tumor cells, and biopsy specimens.

Methodology: Dose escalation is guided by a modified continuous reassessment method (mCRM) using a Bayesian logistic regression model that follows the escalation with overdose control principle to determine the MTD and RP2D of PLX2853. Cycle 1 (21 days) is the DLT observation period.

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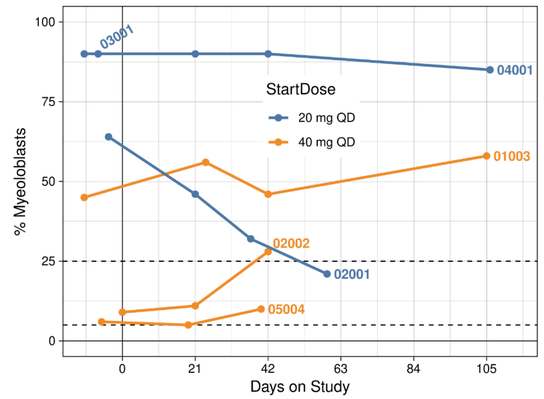
Results

Patient Characteristics

Cohort	Assigned Dose	Subjects Enrolled
1	20 mg QD	3
2	40 mg QD	4

	All (n=7)	Cohort 1 (n=3)	Cohort 2 (n=4)
Age, Median, [range]	73 [47-77]	64 [47-77]	75 [65-77]
Sex, Male, n (%)	5 (71%)	2 (67%)	3 (75%)
Malignancy, AML, n (%)	6 (86%)	3 (100%)	3 (75%)
Malignancy, MDS, n (%)	1 (14%)	0 (0%)	1 (25%)

Bone Marrow Assessment Cohorts 1 & 2



PLX124-02 Treatment Emergent Adverse Events

No Dose Limiting Toxicities (DLTs) to date or > Grade 3 AEs to date

AE Preferred Term	Grade 1 All	Grade 1 Related	Grade 2 All	Grade 2 Related	Grade 3 All	Grade 3 Related	Total n (%)
Decreased appetite	2				1	1	3 (43%)
Febrile neutropenia					3		3 (43%)
Hyperglycemia	1				2		3 (43%)
Dyspnea			2		1		3 (43%)
Nausea	3	2					3 (43%)
Hypertension					2	1	2 (29%)
Anemia					2		2 (29%)
Blood bilirubin increased			1	1	1		2 (29%)
Pulmonary edema			1		1		2 (29%)
Fatigue			2				2 (29%)
Headache			2				2 (29%)
Cough	1	1	1				2 (29%)
Peripheral edema	1		1				2 (29%)
Insomnia	1		1				2 (29%)
Diarrhea	2	2					2 (29%)
Oropharyngeal pain	2	1					2 (29%)
Localized edema	2						2 (29%)
Blood LDH increased	2						2 (29%)
Abdominal pain	1	1	1				2 (29%)
Bacteremia			2				2 (29%)

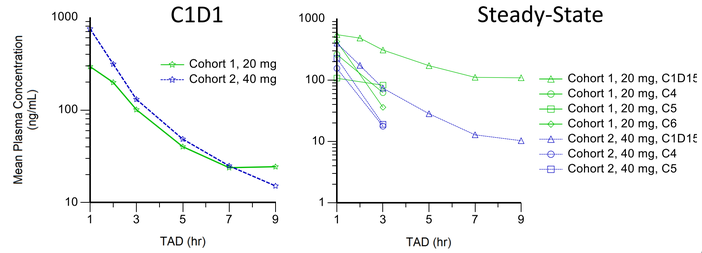
AEs reported per CTCAE v5.0 through 17OCT2019 with at least 2 occurrences

Pharmacokinetics

- Rapid absorption (T_{max} ~1 hr)
- Short terminal half-life ($T_{1/2}$ < 3 hr); no accumulation expected
- Near dose-proportional increases in C_{max} and AUC values from 20 to 40 mg
- Two of 3 subjects in Cohort 1 had higher exposures on C1D15 compared to C1D1
  - Elevated C1D15 exposures of PLX2853 were correlated with the specific conditions of the patients unrelated to PLX2853
  - PLX2853 concentrations decreased to expected steady-state levels by Cycle 4 as the conditions improved

Dose	C1D1 Tmax (hr)	C1D1 Cmax (ng/mL)	C1D1 AUC_{0-9} (hr*ng/mL)	C1D1 AUC_{0-24} (hr*ng/mL)	C1D1 $T_{1/2}$ (hr)	C1D15 Tmax (hr)	C1D15 Cmax (ng/mL)	C1D15 AUC_{0-9} (hr*ng/mL)	C1D15 AUC_{0-24} (hr*ng/mL)	C1D15 $T_{1/2}$ (hr)	Accum. Ratio
20 mg (Cohort 1) N=3	1 [a]	243	650	676	1.92	1 [a]	390	1280	1400	2.39	2.1
	1-2 [b]	94.6	85.5	87.8	22.8	1-2 [b]	189	304	345	46.1	-
40 mg (Cohort 2) N=4	0.75 [a]	648	1070	1080	1.38	0.5 [a]	565	810	836	2.08	0.8
	0.5-1 [b]	105	130	132	63	0.5-2 [b]	91.3	73.8	73	20.4	-

All values are geometric Means, except [a] Median; [b] Min-Max



Conclusions

- In an ongoing Phase 1b study, PLX2853 has now completed two dosing cohorts (20 mg and 40 mg QD) for seven subjects with relapsed or refractory AML or high risk MDS, and no DLT has been observed yet. As dose escalation continues, PK, PD, preliminary safety and efficacy data will be assessed further to determine the clinical significance of target engagement.
- Recurrent treatment emergent adverse events (TEAEs) regardless of causality included: decreased appetite (n=3), febrile neutropenia (n=3), hyperglycemia (n=3), dyspnea (n=3), nausea (n=3), hypertension (n=2), anemia (n=2), blood bilirubin increased (n=2), pulmonary edema (n=2), fatigue (n=2), headache (n=2), cough (n=2), peripheral edema (n=2), insomnia (n=2), diarrhea (n=2), oropharyngeal pain (n=2), localized edema (n=2), blood LDH increased (n=2), abdominal pain (n=2), and bacteremia (n=2). Most were grade 1-2.
- Higher grade recurrent TEAEs included: febrile neutropenia (n=3), hyperglycemia (n=2), hypertension (n=2), and anemia (n=2). No treatment-related serious AEs or DLTs have been observed.
- Following a 20 or 40 mg daily dose of PLX2853, the median T_{max} was 1 hour and the $T_{1/2}$ was < 3 hours.
- This clinical trial is registered at clinicaltrials.gov: **NCT#03787498.**

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