Phase 1b Study of BET Inhibitor PLX2853 in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndrome (MDS)

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Background

PLX2853 is an orally bioavailable, 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 improve tolerability by allowing transient yet substantial target engagement followed by time for recovery after daily dosing. This clinical trial is registered at clinicaltrials.gov: **NCT#03787498.**

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: Complete Remission (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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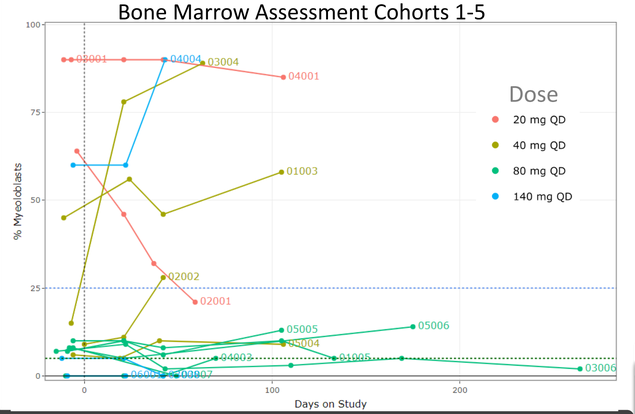
Results

Patient Characteristics

Cohort[a] (Dose)c	N	Age (Mean)	Age (Range)	Male (N)	Female (N)	AML n (%)	MDS n (%)
1 (20 mg QD)	3	62.7	47 - 77	2	1	3 (100%)	0 (0%)
2 (40 mg QD)	4	73	65 - 77	3	1	3 (75%)	1 (25%)
3 (80 mg QD)	3	58	51 - 63	2	1	1 (33%)	2 (67%)
4 (80 mg QD)	3	70.3	67 - 77	1	2	1 (33%)	2 (67%)
5 (140 mg QD)	3	62	53 - 76	1	2	1 (33%)	2 (67%)
Total	16	65.2	47 - 77	9	7	9 (56%)	7 (44%)

[a]Cohorts 1-3 utilized 5 mg strength tablets. Cohort 4-5 utilized 20 mg strength tablets

Bone Marrow Assessment Cohorts 1-5



PLX124-02 Treatment Emergent Adverse Events

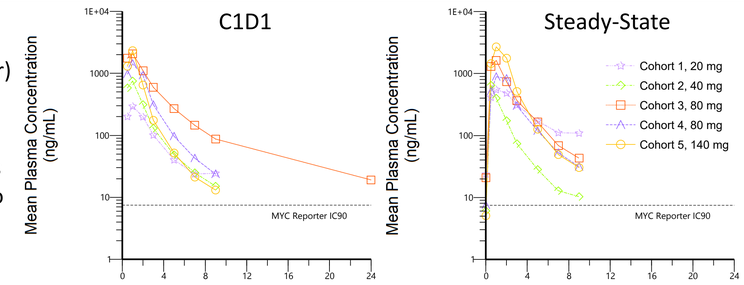
No Dose Limiting Toxicities (DLTs) through 140 mg QD

AE Preferred Term	≥Grade 3, n	All ,n (%)
Fatigue		10 (63%)
Decreased appetite	1	10 (63%)
Anemia	8	9 (56%)
Nausea	1	8 (50%)
Blood bilirubin increased	5	8 (50%)
White blood cell count decreased	5	7 (44%)
Constipation		6 (38%)
Hypokalemia		6 (38%)
Febrile neutropenia	5	5 (31%)
Diarrhea		5 (31%)
Vomiting		5 (31%)
Edema peripheral		5 (31%)
International normalized ratio increased		5 (31%)
Proteinuria		5 (31%)
Dyspnea	1	5 (31%)
Pyrexia		4 (25%)
Bacteremia		4 (25%)
Sepsis	4	4 (25%)
Hyperglycemia		4 (25%)
Hypoalbuminemia		4 (25%)
Hyponatremia		4 (25%)
Hypophosphatemia		4 (25%)
Dizziness		4 (25%)
Insomnia		4 (25%)
Platelet count decreased	4	4 (25%)

Most frequent AEs regardless of relationship reported per CTCAE v5.0 through 20OCT2020

Pharmacokinetics

- Rapid absorption (T_{max} ~1 hr)
- Short terminal half-life ($T_{1/2}$ < 3 hr)
- No significant accumulation observed up to 140 mg
- Near dose-proportional increases in C_{max} and AUC values from 20 to 140 mg
- Plasma concentrations are above the IC_{90} for >9 hr at all doses



Dose (Cohort)	C1D1 T_{max} hr	C1D1 C_{max} ng/mL	C1D1 AUC_{0-12} hr*ng/mL	C1D1 AUC_{0-24} hr*ng/mL	C1D1 $T_{1/2}$ hr	C1D15 T_{max} hr	C1D15 C_{max} ng/mL	C1D15 C_{min} ng/mL	C1D15 AUC_{0-12} hr*ng/mL	C1D15 AUC_{0-24} hr*ng/mL	C1D15 $T_{1/2}$ hr	Accum Ratio
20 mg (Cohort 1) n=3	1 (1-2)	243 (94.6)	666 (86.6)	676 (87.8)	1.92 (22.8)	1 (1-2)	390 (189)	13.1 (121)	1340 (323)	1400 (345)	2.39 (46.1)	2.1
40 mg (Cohort 2) n=4	0.75 (0.5-1)	648 (105)	1080 (131)	1080 (132)	1.38 (63)	0.5 (0.5-1)	565 (91.3)	7.04 (14)	826 (73.2)	836 (73)	2.08 (20.4)	0.8
80 mg (Cohort 3) n=3	1 (0.5-1)	1530 (130)	2700 (251)	2740 (262)	2.07 (59.7)	1 (0.5-1)	1630 (59.7)	11.6 (58.3)	2680 (113)	2700 (114)	2.05 (13.5)	1.0
80 mg (Cohort 4) n=3	1 (1)	1330 (51.6)	2990 (45.5)	3020 (44.7)	1.95 (26.6)	1 (1-2)	1040 (32.4)	15 (176)	2420 (40.2)	2450 (39.8)	2.04 (51.3)	0.8
140 mg (Cohort 5) n=3	1 (0.5-1)	2110 (87.3)	3640 (75.5)	3700 (78.4)	1.05 (111)	1 (1)	2640 (26.8)	11.3 (86.1)	4970 (41.2)	4990 (41.3)	1.74 (7.55)	1.3

All values are geometric means (%CV), except T_{max} which is median (min-max)

Conclusions

- In an ongoing Phase 1b study, PLX2853 has been investigated in five dosing cohorts (20 – 140 mg QD) for 16 subjects with relapsed or refractory AML or high-risk MDS. As dose escalation continues, PK, PD, preliminary safety and efficacy data will be assessed further to determine the clinical significance of target engagement.
- The most frequent reported treatment emergent adverse events (TEAEs) regardless of causality included: fatigue (n=10), decreased appetite (n=10), anemia (n=9), nausea (n=8), blood bilirubin increased (n=8), white blood cell increased (n=7), constipation (n=6), hypokalemia (n=6), febrile neutropenia (n=5), diarrhea (n=5), vomiting (n=5), edema peripheral (n=5), international normalized ratio increased (n=5), proteinuria (n=5), and dyspnea (n=5). Most were grades 1-2.
- No DLTs have been observed through 140 mg QD.
- Following a 20, 40, 80, or 140 mg daily dose of PLX2853, the median T_{max} was 1 hour and the $T_{1/2}$ was < 3 hours.
- The following best overall responses have been observed: 1 subject with a confirmed marrow CR (MDS), 2 subjects with a PR (myeloid sarcoma and MDS), 9 subjects with stable disease, 1 subject with progressive disease, and 3 subjects not evaluable.
- PLX2853 was generally well tolerated and demonstrated encouraging evidence of clinical activity

Disclosures: **Mims:** Jazz Pharmaceuticals: Data Safety Monitoring Board; Syndax Pharmaceuticals: Membership on an entity's Board of Directors or advisory committees, Abbvie: Membership on an entity's Board of Directors or advisory committees, Kura Oncology: Membership on an entity's Board of Directors or advisory committees, Leukemia and Lymphoma Society: Senior Medical Director for Beat AML Study; Agios: Consultancy; Novartis: Speakers Bureau. **Solh:** None. **Borate:** Genentech: Membership on an entity's Board of Directors or advisory committees, Daiichi Sankyo: Membership on an entity's Board of Directors or advisory committees, Takeda: Membership on an entity's Board of Directors or advisory committees, Research Funding; Novartis: Membership on an entity's Board of Directors or advisory committees, Research Funding; Jazz Pharmaceuticals: Research Funding; Abbvie: Investigator in AbbVie-funded clinical trials, Pfizer: Membership on an entity's Board of Directors or advisory committees, Research Funding. **Pemmaraju:** Pacylex Pharmaceuticals: Consultancy; Affymetrix: Grant Support, Research Funding; SagerStrong Foundation: Grant Support; Incyte: Honoraria; Novartis: Honoraria, Research Funding; LFB Biotechnologies: Honoraria; Stemline Therapeutics: Honoraria, Research Funding; Celgene: Honoraria; AbbVie: Honoraria, Research Funding; MustangBio: Honoraria; Celgene: Honoraria; Roche Diagnostics: Honoraria; Blueprint Medicines: Honoraria; DAVA Oncology: Honoraria; Samus Therapeutics: Research Funding; Cellectis: Research Funding; Daiichi Sankyo: Research Funding; Plexxikon: Research Funding; ASH Communications Committee: Other; ASCO Leukemia Advisory Panel: Other; Dana's House of Hope: Other; HemOnc Times/Oncology Times: Other. **Borthakur:** Treadwell Therapeutics: Consultancy; Nkarta Therapeutics: Consultancy; BioTherix: Consultancy; BioLine Rx: Consultancy; PTC Therapeutics: Consultancy; Argenx: Consultancy; FTC Therapeutics: Consultancy; Curio Science LLC: Consultancy; Oncoceutics: Research Funding; Xbiotech USA: Research Funding; Polaris: Research Funding; AstraZeneca: Research Funding; BMS: Research Funding; BioLine Rx: Research Funding; Cyclacel: Research Funding; GSK: Research Funding; Jannsen: Research Funding; Abbvie: Research Funding; Novartis: Research Funding; Incyte Research Funding; PTC Therapeutics: Research Funding. **Roboz:** Agios: Consultancy; Amphivena: Consultancy; Astex: Consultancy; Celgene: Consultancy; Janssen: Consultancy; Novartis: Consultancy; Pfizer: Consultancy; Abbvie: Consultancy; Array BioPharma: Consultancy; Bayer: Consultancy; Celltrion: Consultancy; Eisai: Consultancy; Jazz: Consultancy; Roche/Genentech: Consultancy; Sandoz: Consultancy; Actinium: Consultancy; Argenx: Consultancy; Astellas: Consultancy; Daiichi Sankyo: Consultancy; AstraZeneca: Consultancy; Orsenix: Consultancy; Otsuka: Consultancy; Takeda: Consultancy; Trovagene: Consultancy; Cellectis: Research Funding; Jasper Therapeutics: Consultancy; Epizyme: Consultancy; Helsinn: Consultancy; MEI Pharma: Consultancy. **Powell:** Plexxikon Inc.: Employment; **Severson:** Plexxikon Inc.: Employment; **Matusow:** Plexxikon Inc.: Employment; **Halladay:** Plexxikon Inc.: Employment; **Hsu:** Daiichi Sankyo Inc.: Employment; **Watkins:** Plexxikon Inc.: Employment; **Zhang:** Plexxikon Inc.: Employment; **Walling:** Plexxikon Inc.: Consultancy; Aduro Biotech: Consultancy; Arch Oncology: Consultancy; CytomX Therapeutics: Consultancy; Harpoon Therapeutics: Consultancy; ImmuNext: Consultancy; Myovant Sciences: Consultancy; Nurix Therapeutics: Consultancy; Que Oncology: Consultancy; Sesen Bio: Consultancy; Amgen: Consultancy; Aminex: Consultancy; Crown Bio: Consultancy; Leap Therapeutics: Consultancy; Prothena Corporation: Consultancy; Puma Biotechnology: Consultancy; Rhizen Pharmaceuticals: Consultancy; Shanghai Pharmaceuticals: Consultancy; Stealth Biotherapeutics: Consultancy; Sunesis Pharmaceuticals: Consultancy; Upsher-Smith Laboratories: Consultancy; Flag Therapeutics: Consultancy; January Therapeutics: Consultancy. **Tsiatis:** Plexxikon Inc.: Employment; **Dezern:** Celgene: Consultancy, Honoraria; Astex: Research Funding; Abbvie: Consultancy; MEI: Consultancy