Phase 1b/2a Study of PLX2853, a Small Molecule BET Inhibitor, in Subjects with Advanced Solid Tumors and Lymphoma

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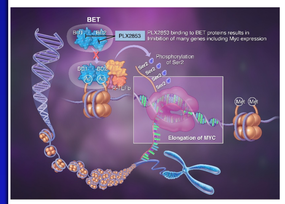
Background



The BET (bromodomain and extraterminal) family of human bromodomain (BRD) containing proteins consists of four members (BRD2, BRD3, BRD4 and BRDt). These epigenetic readers recognize acetylated histone lysine residues and modulate gene transcription by recruiting chromatin modifying enzymes and transcription factors to the promoters and enhancers of target genes. The most widely studied example is the oncogene MYC.

PLX2853 is a potent, orally active small molecule BET inhibitor with a unique pharmacokinetic (PK) profile. The short half-life allows time for recovery after each dose and is anticipated to yield less thrombocytopenia and improved tolerability. Despite transient target engagement, a prolonged pharmacodynamic (PD) response was observed for some target genes.

Trial Design and Methodology

Phase 1b/2a, open-label, multi-dose, dose escalation (NCT03297424)

Objectives:

- Primary: Establish PLX2853 single agent safety and PK
  - Establish single agent maximum tolerated dose/recommended phase 2 dose (MTD/RP2D)
- Secondary: Evaluate efficacy by Objective Response Rate by RECIST 1.1 including Duration of Response and Progression-Free Survival (PFS)
- Exploratory: Assess changes in gene expression and other biomarkers in peripheral blood & tumor tissue

Methodology:

- Standard 3 + 3 dose escalation in adults with solid tumor (including lymphoma) who have relapsed or refractory disease
- Dose limiting toxicity (DLT) Criteria:
  - General non-hematologic DLT: any grade ≥ 3 (adverse event (AE)/lab) toxicity despite adequate supportive care; exceptions made for clinically insignificant or non-clinically significant transient events
  - Heme DLT: grade ≥ 3 neutropenia, thrombocytopenia; grade 4 anemia
- PLX2853 was administered orally under fasted conditions with continuous dosing

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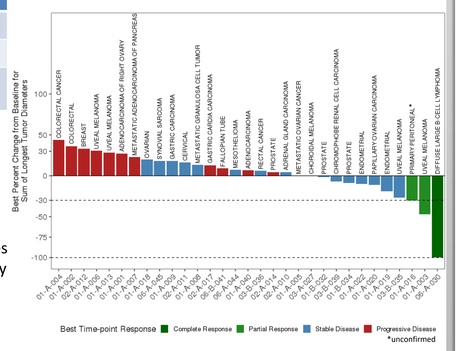
Results

Patient Characteristics and Clinical Responses

All Patients (N=46)	
Age, median [range]	65 [39,84]
Sex, male, n (%)	21 (45%)
Prior therapies, median [range]	5 [1,19]

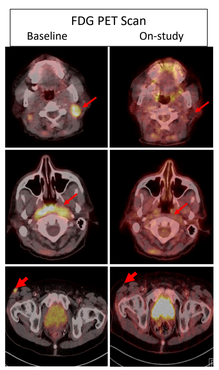
*Evaluable patients as of 26Apr2021

One patient with diffuse large B-cell lymphoma (DLBCL) had a complete metabolic response (ongoing 12+ months), 2 patients had partial responses (1 uveal melanoma, 1 primary peritoneal cancer), and 19 patients had stable disease. The median PFS was 84 days (range: 21 – 295 days).



DLBCL Subject Clinical Summary

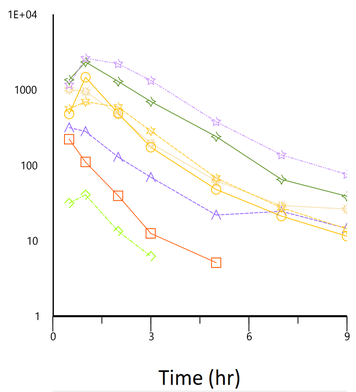
- 63 yo male with stage IVA relapsed DLBCL (non-germinal center) and BCL6 gene rearrangement status post R-CHOP; RICE followed by R-ESHAP; autologous SCT with relapse at day +100; nodal recurrence above and below the diaphragm and nasopharyngeal disease refractory to STRO-001
- Initiated PLX2853 treatment at 120 mg QD (subsequently dose reduced due to asymptomatic Grade 4 thrombocytopenia) and came off study on Cycle 3 Day 14
- Complete metabolic response on Cycle 2 Day 20 (ongoing 12+ months)



*Representative images

Pharmacokinetics

- Rapid absorption (T_{max} 0.5-1.5 hr)
- Short $T_{1/2}$ (< 2.5 hr)
- No significant accumulation observed up to 120 mg after repeat dosing
- Dose-dependent increases in C_{max} and AUC values from 5 mg to 120 mg



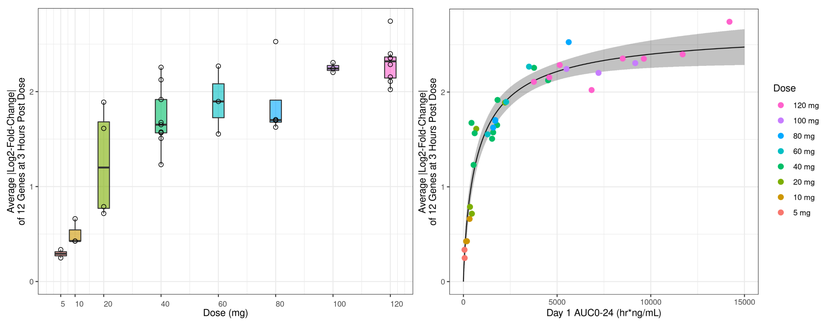
Treatment-Emergent Adverse Events
N = 46. Dose Levels: 5 mg to 20mg Total Daily Dose

AE Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All n (%)
Nausea	12	8	1		21 (45%)
Decreased appetite	8	8	1		17 (36%)
Fatigue	2	10	3		15 (32%)
Anaemia		3	9	1	13 (28%)
Vomiting	8	4	1		13 (28%)
Diarrhoea	10	2			12 (26%)
Dehydration	2	8	1		11 (23%)
Dysgeusia	9	2			11 (23%)
Dry mouth	7	1			8 (17%)
Thrombocytopenia	1		3	3	7 (15%)
Weight decreased	3	1	3		7 (15%)
Abdominal pain	2	3	2		7 (15%)
Headache	1	6			7 (15%)
Dizziness	4	3			7 (15%)
Pyrexia	7				7 (15%)

*Most frequent AEs (regardless of causality) reported per CTCAE v5.0 through 26Apr2021
*No Grade 5 toxicities reported
*No related thrombocytopenia at or below the RP2D

DLTs:
120 mg QD: (2) Grade 4 thrombocytopenia
40 mg BID: (1) Dose reduction in C1 for ≥ Grade 2 AE (Grade 3 fatigue)
60 mg BID: (1) Dose reduction in C1 for ≥ Grade 2 AE (Grade 3 thrombocytopenia)

Pharmacodynamics



PLX2853 modulates the expression of BET target genes. RNA-sequencing was performed on peripheral blood cells from 36 subjects to evaluate the response to a single dose of PLX2853. A 12-gene signature was generated comprising 6 up-regulated (HEXIM1, WDR47, GLS, G3BP1, CALM1, CIRBP) and 6 down-regulated (CCR1, CCR2, TNFRSF8, SCIMP, BTN3A2, KMO) target genes. The Y-axis shows the average of the absolute value of the Log2 fold change at 3 hours relative to baseline for the 12 genes. These analyses demonstrated a dose- and exposure-dependent pharmacodynamic response.

Conclusions

- **PLX2853 is an orally bioavailable, non-benzodiazepine, structurally distinct BET inhibitor**
- **Dose-dependent increases in exposures from 5 to 120 mg**
- **Based on safety, PK, and animal model data, the RP2D is 80 mg once daily (QD)**
- **PLX2853 is rapidly absorbed, has a short $T_{1/2}$ and high C_{max}**
- **RNA profiling provided evidence of a marked, dose-dependent, pharmacodynamic response indicative of BET inhibition**
- **PLX2853 was generally well tolerated with no related thrombocytopenia at dose levels at or below the RP2D and demonstrated encouraging evidence of clinical activity including a durable complete response in the only patient with DLBCL**
- **Further development of PLX2853 as single agent and in combination with other agents in solid tumors, AML/MDS and other hematological malignancies is ongoing (NCT03787498, NCT04493619, NCT04556617)**