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


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PLX2853 is a potent, orally active small molecule BET inhibitor with a unique pharmacokinetic (PK) profile. The short half-life allows for 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.

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

**Objectives:**
- Primary: Establish PLX2853 single agent safety and PK
- Secondary: Establish maximum tolerated dose (MTD)/recommended phase 2 dose (MTD/RPD)
- Tolerability: 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 lymphomas) who have relapsed or refractory disease

**Pharmacodynamics**
- PLX2853 is rapidly absorbed, has a short T1/2 and high Cmax
- PLX2853 is generally well tolerated with no related thrombocytopenia at or below the RP2D
- No Grade 5 toxicities reported
- Most frequent AEs (regardless of causality) reported per CTCAE v5.0 through 26Apr2021

**Pharmacokinetics**
- Rapid absorption (Tmax 0-1.5h)
- Short T1/2 (< 2.5h)
- No significant accumulation observed up to 120 mg after repeat dosing
- Dose-dependent increases in Cmax and AUC values from 5 mg to 120 mg

### Patient Characteristics and Clinical Responses

**All Patients (N=46)**

| Grade 1 | Grade 2 | Grade 3 | Grade 4 | All (%)
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<td>8</td>
<td>4</td>
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<td>9</td>
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<td>10</td>
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<td>12 (26%)</td>
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**PLX2853 dosulates 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 (HER1M1, WDR47, GLS, G3BP1, CALM1, CIRBP) and 6 down-regulated (CCR1, CCR2, TNFRSF8, SCIMP, BTN3A2, KMO) target genes. The heatmap 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.

### Treatment-Emergent Adverse Events

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<th>N = 46. Dose Levels: 5 mg to 20mg Total Daily Dose</th>
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| **Preferred Term** | Grade 1 | Grade 2 | Grade 3 | Grade 4 | All (%)
| Nausea | 12 | 8 | 3 | 1 | 21 (45%)
| Decreased appetite | 8 | 8 | 1 | 17 (36%)
| Fatigue | 2 | 10 | 3 | 15 (32%)
| Anemia | 3 | 1 | 13 | 13 (28%)
| Vomiting | 8 | 4 | 1 | 13 (28%)
| Diarrhea | 10 | 2 | 1 | 12 (26%)
| Neutropenia | 2 | 2 | 1 | 11 (23%)
| Dysthesia | 9 | 2 | 11 (23%)
| Dry mouth | 7 | 1 | 8 (17%)
| Thrombocytopenia | 1 | 3 | 3 | 7 (15%)
| Weight decreased | 3 | 3 | 3 | 7 (15%)
| Abdominal pain | 2 | 3 | 3 | 2 (4%)
| Headache | 1 | 1 | 1 | 1 (2%)
| Dizziness | 4 | 3 | 3 | 7 (15%)
| *Most frequent AEs (regardless of causality) reported per CTCAE v5.0 through 26Apr2021*

**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 T1/2 and high Cmax
- 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 further hematologic malignancies is ongoing (NCT03787498, NCT04493619, NCT04556617)

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