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 prolonged suppression of BET proteins.

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

**Results**

- **Patient Characteristics**
  - Bone Marrow Assessment Cohorts 1-5
  - No Dose Limiting Toxicities (DLTs) through 140 mg QD
  - The most frequent reported treatment emergent adverse events (TEAEs) regardless of causality included: fatigue (n=10), international normalized ratio increased (n=5), proteinuria (n=5), and dyspnea (n=5). Most were grades 1-2.

**Bone Marrow Assessment Cohorts 1-5**

- **Conclusions**
  - PLX2853 was generally well tolerated and demonstrated encouraging evidence of clinical activity.

**Study PLX124-02 Trial Design and Methodology**

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

**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 (RPD).

**Secondary Objectives:**
- To evaluate the preliminary efficacy of PLX2853 as measured by:
  - Overall complete remission (CR) rate, based on the following definitions:
    - AML: Complete Remission (CR) or CR with incomplete hematologic recovery (CRi)
    - MDS: CR or PR
  - 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
  - Duration of response (DOR);
  - Event-free survival (EFS);
  - Progression-free survival (PFS);
  - Overall survival (OS).

**Explorative Objectives:**
- 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 RPD of PLX2853.

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