P1005 A PHASE 1, OPEN-LABEL, DOSE-ESCALATION STUDY OF SELINEXOR PLUS RUXOLITINIB IN PATIENTS WITH TREATMENT-NAÏVE MYELOFIBROSIS

Topic: 16. Myeloproliferative neoplasms - Clinical

Haris Ali1, Ashwin Kishtagari2, Keri Maher3, Sanjay Mohan2, Amitabha Mazumder4, Kamal Chamoun5, Igor Karasik6, Eric Sbar5, Laura Dugom5, Sharon Tamir5, Xulong Wang5, Josef Prchal6, Srinivas Tantravahi6

1 City of Hope, Duarte, United States; 2 Vanderbilt Ingram Cancer Center, Nashville, United States; 3 VCU Massey Cancer Center, Richmond, United States; 4 The Oncology Institute of Hope & Innovation, St. Petersburg, United States; 5 Karyopharm Therapeutics, Newton, United States; 6 Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, United States

Background: Myelofibrosis (MF) is a myeloproliferative neoplasm commonly associated with gene mutations in JAK2, CALR, or MPL caused by the unregulated proliferation of clonal myeloid precursors in the bone marrow. The JAK 1/2 inhibitor, ruxolitinib (RUX), has shown reductions in spleen volume and improvement in MF-related symptoms when used in the frontline. Despite the significant improvements of RUX, most patients (pts) eventually progress and lose response to treatment over time. Therefore, novel combinations are critical to improve responses and delay progression. Selinexor (SEL) is an oral selective inhibitor of nuclear export (SINE) compound, specifically inhibiting exportin-1 (XPO1), that has been approved for use in multiple myeloma and diffuse large B-cell lymphoma. Preclinical studies of the combination SEL and RUX have demonstrated significant activity. In clinical studies of MF refractory to JAK inhibitors, SEL monotherapy has exhibited robust clinical activity with a tolerable safety profile (NCT03627403).

Aims: Here, we present the initial results of a phase 1 dose escalation study to determine the optimal dose and preliminary efficacy of once weekly (QW) SEL in combination with RUX in pts with treatment-naïve MF.

Methods: In the ongoing multicenter, open-label, Phase 1/2 study (NCT04562389) using a 3+3 design, two dose levels of SEL were evaluated, 40 mg and 60 mg QW plus RUX twice daily (BID) as per label in 28-day cycles. For nausea prophylaxis, all pts received a 5-HT3 antagonist. Primary study objectives include safety, maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), and preliminary efficacy. Secondary objectives include spleen volume, symptom and anemia response, and overall survival (OS).

Results: As of 24 Feb 2022, 10 pts have been dosed in 2 dose levels 40 mg (n=3), and 60 mg (n=7) SEL QW plus RUX. The starting dose of RUX was 20 mg in 8 pts, 15 mg in one patient and 10 mg in one patient. The median age was 64 (range 45-76) and 7 pts had primary MF and 3 had post-essential thrombocythemia (ET) MF. The Dynamic International Prognostic Scoring System (DIPSS) risk category was int-1 (n=4), int-2 (n=4) and high risk (n=2). There were no dose limiting toxicities reported for either SEL dose levels. Due to dizziness, one patient had a dose interruption and after 5 months of therapy discontinued treatment from new onset of atrial fibrillation and pulmonary hypertension (unrelated to SEL and RUX). Currently, all other pts remain on study. Hemoglobin levels were maintained without significant worsening in majority of patients. Low grade nausea (30%) was the most common treatment-emergent adverse event. All pts experienced an improvement in their white blood cell count. Of the 6 evaluable pts, 5 had a ≥35% spleen volume reduction at week 12.

Summary/Conclusion: In pts with treatment-naïve MF, QW SEL in combination with RUX is well tolerated with a manageable side effect profile. Based on current data there have been no observed dose limiting toxicities in cohort 1 of QW oral SEL 40 and 60 mg with RUX.