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A Phase 2 Study of CPI-0610, a Bromodomain and Extraterminal Protein Inhibitor (BETi) alone or with Ruxolitinib (RUX), in Patients with Myelofibrosis (MF)

Background: BETi have been shown to regulate NF-κB, MYC, BCL2, and TGF-β signaling, important drivers of marrow fibrosis. Preclinical studies have suggested that combined BETi and JAK2 inhibition synergistically reduce MF-related splenomegaly, bone marrow fibrosis and the malignant allele burden (Kleppe, 2018). CPI-0610 is a selective and potent oral BETi, being evaluated in the first study of a BETi in MF

Methods: Phase 2 trial with 3 arms: CPI-0610 monotherapy (Arm 1) or RUX + CPI-0610 “add-on” (Arm 2) in pts who have progressed/ had an inadequate response to RUX, or CPI-0610 + RUX in JAK inhibitor-naïve pts with anemia (Arm 3). Arms 1 and 2 are stratified: transfusion dependence (TD) yes: A/no: B. The primary objectives are to evaluate the effect of CPI-0610 on transfusion dependence (TD, 1A and 2A) and spleen volume (1B, 2B and 3). A Simon two-stage design: if 2 responses are seen will advance to the 2nd stage

Results: 4 pts enrolled in Arm 1, 14 pts in Arm 2, no pts accrued to Arm 3 yet. Median age: 69 years (46–83), gender: 9 male pts; 11pts received ≥1 prior therapy besides RUX. JAK2/MPL/CALR mutations: 17/18 pts, ≥3 mutations: 10 pts, ASXL1 mutations: 11 (61%) pts. Hemoglobin <10 g/dL at baseline: 11 (61%) pts. 6 pts received ≥ 24 weeks of CPI-0610 treatment at this analysis. 2 TD pts in Arm 2 became transfusion independence, both remain on treatment free of transfusions. Hgb increase of ≥1.5 g/dL from baseline was observed with successive cycles of therapy in anemic pts: 2/2 pts in Arm 1(100%) and 3/9 pts in Arm 2, (33%). Spleen volume reduction, by MRI (6–44%) was observed in all 10 evaluable pts irrespective of their driver mutation. Symptom improvement and reductions of cytokine levels were observed. In Arm 1: 2/2 evaluable pts had marrow fibrosis improvement with Hgb increase; additionally, thrombocytosis resolved in 2/2 pts (baseline ≥791
10³/µL). Most common adverse events were mild diarrhea, nausea/vomiting; and reversible and non-cumulative thrombocytopenia

**Conclusions:** CPI–0610 is a well-tolerated, and an effective therapeutic agent for the treatment of MF. Collectively, these data indicate that CPI–0610 +/− RUX might have disease modifying effects. Updated data will be provided

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