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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

10^3/uL). 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

Authors: Marina Kremyanskaya MD, PhD[1], Ronald Hoffman MD[2], John Mascarenhas MD[3], Prithviraj Bose MD[4], Vikas Gupta MD[5], Gary J. Schiller MD[6], Elena Liew MD[7], Claudia Lebedinsky MD[8], Adrian Mario Senderowicz MD[8], Jennifer Mertz PhD[8], Patrick Trojer PhD[8], Srdan Verstovsek MD, PhD[4]

[1] Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, USA; [2] Tisch Cancer Institute, Department of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, USA; [3]Division of Hematology/Medical Oncology/Pathology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai; Myeloproliferative Neoplasm Research Consortium (MPN-RC), New York, USA; [4] Department of Leukemia, M.D. Anderson Cancer Center, Houston, TX, USA; [5] Princess Margaret Hospital, Toronto, Canada, [6] University of California, Los Angeles, USA; [7] University of Alberta Hospital, Alberta, Canada; [8] Constellation Pharmaceuticals, Cambridge, MA, USA