MANIFEST, a Phase 2 Study of CPI-0610, a Bromodomain and Extraterminal Domain Inhibitor (BETi), as Monotherapy or "Add-On" to Ruxolitinib, in Patients with Refractory or Intolerant Advanced Myelofibrosis

John Mascarenhas, MD[1], Marina Kremyanskaya, MD, PhD[1], Ronald Hoffman, MD[1], Prithviraj Bose, MD[2], Moshe Talpaz, MD[3], Claire Harrison, MD, FRCP, FRCPath[4], Vikas Gupta, MD, FRCP, FRCPath[5], Brian Leber, MD[6], Shireen Sirhan, MD[7], Sujan Kabir, MD[8], Adrian Senderowicz, MD[8], James Shao, MS[8], Jennifer Mertz, PhD[8], Patrick Trojer, PhD[8], Srdan Verstovsek, MD, PhD[2]

[1]Division of Hematology/Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States, [2]Department of Leukemia, MD Anderson Cancer Center, Houston, United States, [3]Rogel Cancer Center, University of Michigan, Ann Arbor, United States, [4]Guy's and St. Thomas' Hospital, London, United Kingdom, [5]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada, [6]Division of Hematology and Thromboembolism, Department of Medicine, McMaster University, Hamilton, Canada, [7]Division of Hematology, Jewish General Hospital, Montreal, Canada, [8]Constellation Pharmaceuticals, Cambridge, United States

Background: CPI-0610, a selective and potent small molecule BETi, has shown clinical activity and a wide therapeutic window in a Phase 1 lymphoma study (Blum KA, 2018). BET proteins regulate key oncogenic pathways, including NFκB and TGFβ signaling which are important drivers of pro-inflammatory cytokine (Ck) expression and bone marrow fibrosis, respectively, and are implicated in myelofibrosis (MF) pathogenesis. Ruxolitinib (rux), a Janus kinase 1/2 inhibitor (JAKi), is the only approved therapy for MF, and primarily reduces spleen volume and provides symptomatic relief. Patients (pts) receiving rux may achieve suboptimal responses or can develop treatment-emergent anemia and worsening transfusion dependence. There is no approved treatment for pts who are refractory/intolerant to rux. Preclinical studies suggest that a combination of BETi and JAKi can result in synergistic reduction of splenomegaly, bone marrow (BM) fibrosis and mutant cell burden (Kleppe, 2018). Our objective is to evaluate CPI-0610 alone or "add-on" to rux (CPI-0610 + rux) in MF pts who are refractory/intolerant or have inadequate response to rux.

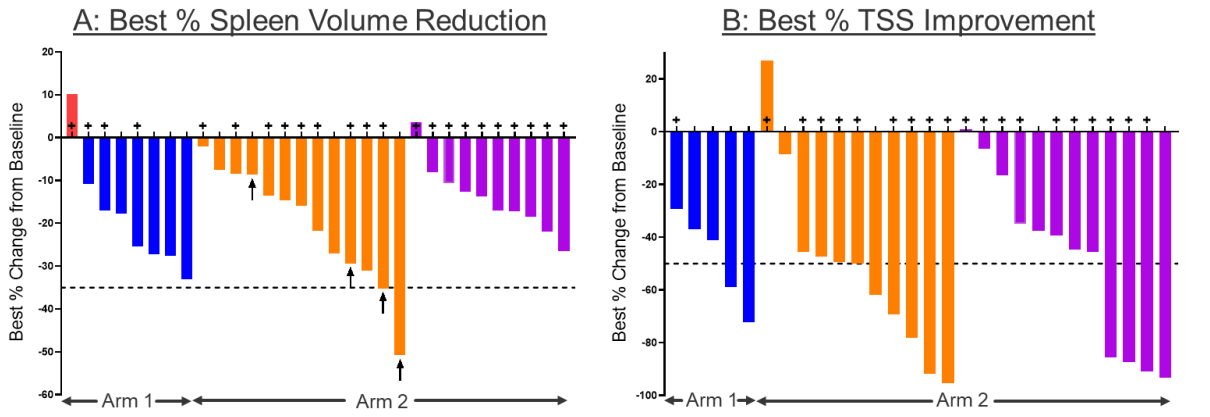
Method: This is a global, multicenter, open label Phase 2 study (MANIFEST) of CPI-0610 monotherapy in MF pts who are refractory/intolerant to rux (Arm 1) or CPI-0610 + rux in MF pts who have suboptimal response to rux (Arm 2). Pts are further stratified based on transfusion dependence status [transfusion dependent (TD), defined as an average of ≥2 units per month over 12 wks, or non-TD cohorts]. The starting dose of CPI-0610 is 125 mg daily on days 1-14 of a 21-day cycle in both arms. Primary endpoint: spleen volume response (SVR) for non-TD cohorts or TD to transfusion independence (TI, no transfusion for consecutive 12 wks) conversion for TD cohorts; secondary endpoints: change in total symptom score (TSS) per MFSAF v4.0, patient global impression of change (PGIC), safety and PK; additional endpoints: changes in proinflammatory Ck levels, BM morphology and mutant allele burden.

Results: As of 27 June 2019, 48 pts enrolled- 12 treated with CPI-0610 monotherapy (Arm 1) and 36 with CPI-0610 + rux (Arm 2). At baseline, median age: 69 years (41-88), gender: 28 (58%) male, ECOG ≤1: 45 (94%) pts, primary MF: 33 (69%) pts, DIPSS score high: 10 (21%) pts, median platelet: 199 x 10^9/L (77-895), 34 (71%) pts with Hgb <10 g/dL, median spleen volume: 2183 cc (123-3909), median TSS: 17.6 (1.4-56), 46 (96%) pts had ≥1 *JAK2*/*MPL*/*CALR* mutations, and 34 (71%) pts had HMR (high molecular risk) mutations. 33 (69%) pts on treatment for ≥ 12 wks, 4 on treatment for > 18 months. Spleen volume

reduction observed in 29 of 31 (94%) pts (median best change: -17% [range: -50.7, 10.2]) (Fig. 1A). TSS improvement reported in 26 of 28 (93%) pts (median best change: -46.4% [range: -95.3%, 27%]), 11 (39%) pts with ≥50% TSS improvement (Fig. 1B). PGIC improvement score in 28 of 33 (85%) pts; 21 (64%) reported much or very much improved scores. Increase in hemoglobin by 1.5 mg/dL post-baseline observed with both CPI-0610 monotherapy (4 of 8, 50%) and CPI-0610 + rux (4 of 25, 16%)). Improvement in BM fibrosis and/or reticulin by ≥1 Gr reported in 7 of 12 (58%) evaluable pts with baseline and 1 post-baseline biopsy and as early as 6-months of CPI-0610 treatment. 4 TD pts in Arm 2 treated with CPI-0610 + rux converted to TI- 2 of whom are TI for >36 wks, no longer anemic, and showed spleen volume reduction, improvement in symptom and BM fibrosis; 12 additional pts are being monitored for potential TI conversion. 41 pts remain active on treatment and 7 pts discontinued, including 1 pt, initially transplant ineligible, underwent stem cell transplantation after 6 cycles of CPI-0610 + rux treatment. Most common (≥20%) treatment-emergent adverse events (TEAE) of any Gr include diarrhea, nausea, cough and upper respiratory tract infection. Most common (≥5%) ≥3 Gr TEAE include anemia (8.3%) and thrombocytopenia (8.3%, asymptomatic, non-cumulative and generally reversible).

Conclusions: Preliminary data indicate that CPI-0610 alone or "add-on" to rux is generally well-tolerated and provides clinical benefits in MF pts with inadequate responses or who are refractory to rux. Improvement in BM fibrosis and anemia responses indicate the potential for meaningful disease modification. Based on the available data, Arm 2 TD cohort has achieved proof-of-concept for TI. Further expansion of the MANIFEST study is ongoing. Updated data will be presented.

Figure 1: Spleen Volume Reduction and TSS Improvement with CPI-0610 Monotherapy [TD ( ), non-TD ( )] or CPI-0610 "Add-on" to Ruxolitinib [TD ( ), non-TD ( )]



↑ Patients converted from transfusion dependent (TD) → transfusion independent (TI)
+ Patients with HMR mutation at baseline (High Molecular Risk, ≥1 of these mutations: *ASXL1, EZH2, IDH1/2, SRSF2* and *U2AF1*)
Spleen volume evaluable population: Baseline and one post-baseline data available – n=31 @ ≥ 12 weeks
TSS evaluable population: Baseline and one post-baseline data available – n=28 @ ≥ 12 weeks