

# Abstract Submission

## 16. Myeloproliferative neoplasms - Clinical

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### CPI-0610, A BROMODOMAIN AND EXTRATERMINAL DOMAIN (BET) INHIBITOR, REDUCES PRO-INFLAMMATORY CYTOKINES, BONE MARROW FIBROSIS AND THE NUMBER OF TRANSFUSIONS IN MYELOFIBROSIS PATIENTS

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**Does the study abide by applicable national and international regulations and guidelines, including but not limited to ethical committees, data protection and privacy regulations, informed consent and off-label use of drugs?:** Yes

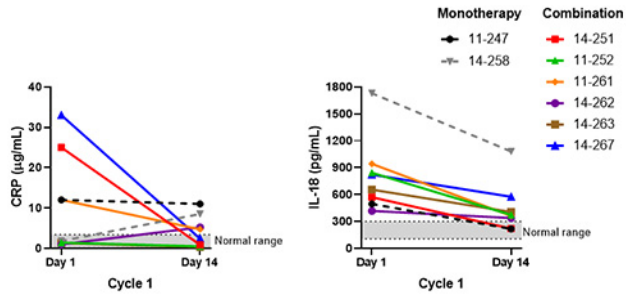
**Background:** Myelofibrosis (MF) is a myeloproliferative neoplasm associated with a cytokine (CK) milieu that leads to bone marrow (BM) fibrosis. Ruxolitinib (RUX) is the only approved therapy for MF, but patients (pts) can eventually relapse/have inadequate response. RUX can also worsen anemia and pts may require transfusions. BET proteins are transcriptional regulators that control key oncogenic pathways, including NF- $\kappa$ B, MYC, and BCL2 and TGF $\beta$  signaling, an important driver of fibrosis. Preclinical studies suggest that a combination of a BET inhibitor (BETi) and RUX results in a synergistic reduction of the hallmarks of MF: splenomegaly, BM fibrosis and the mutant (MUT) allele burden (Kleppe 2018). CPI-0610 is a selective and potent BETi that impacts megakaryocyte differentiation (unpublished data), cells responsible for pro-inflammatory CK production and is currently being evaluated in MF, alone or in combination with RUX in a clinical trial with 3 arms: CPI-0610 alone (Arm 1), CPI-0610+RUX in pts exposed to RUX/with an inadequate response to RUX (Arm 2), or CPI-0610+RUX in JAKi naïve pts with anemia (Arm 3). Arm 1 and 2 are stratified between transfusion dependence (TD) and splenomegaly at baseline.

**Aims:** Phase 2 study to assess CPI-0610 alone or “add-on” to RUX in MF pts. Primary endpoints: conversion of TD to transfusion independence (TI), spleen volume response, patient reported outcomes, safety and PK. Additional endpoints include: changes in pro-inflammatory CK levels, BM fibrosis and MUT profiling.

**Methods:** Pt samples were used to analyze CK levels, MUT profiles and BM fibrosis. CK analyses utilized Myriad-RBM InflammationMAP and CustomMAP and MUT analysis utilized the Rapid Heme Panel (Kluk, 2016).

**Results:** 23 pts were accrued to this multi-center study, with 18 pts analyzed: MUT profiles which revealed the following MUT: 11 *ASXL1*(61%), 10 *JAK2*(56%), 6 *CALR*(33%) and 2 *MPL*(11%). 10 pts (56%) had at least 3 MUTs and 17 pts (94%) had at least one driver MUT (*JAK2*, *CALR* or *MPL*). 1 pt (6%) was triple negative and 12 pts (67%) had a high MUT profile (HMR). Baseline CK levels were elevated, in pts who failed/inadequate response to RUX. CPI-0610 at a starting dose of 125 mg QD (days 1-14 of 21-day cycle) reduced CK levels in both monotherapy and combination arms. Suppression of IL-18 was observed in all pts analyzed (n=8) with >50% decrease in 4/8 pts. Trends were also observed for a number of other CK, including IL-8 and CRP. CK inhibition was sustained over multiple cycles of CPI-0610 (combination/monotherapy). Best spleen volume reduction ranged from 6-44% in 10 pts. Out of the 4 pts with BM assessments (pre and at least 1 post), 2 were TD at baseline. Three pts had one grade improvement in BM fibrosis (1 at 6 mth, 2 at 1 yr) and had Hgb increases of  $\geq 1.5$  g/dL for  $\geq 12$  weeks without transfusions. The other pt had a 1 grade improvement in the BM reticulin score (at 6 mth). Moreover, both of the TD pts became TI. Hepcidin levels and PK will be presented. The most common adverse events were Grade 1/2 diarrhea, nausea/vomiting and reversible and non-cumulative thrombocytopenia.

**Image/Pictures:**



**Summary/Conclusion:** CPI-0610 alone or in combination with Rux demonstrates encouraging clinical activity (spleen responses, conversion to TI and improvement in BM fibrosis) with good tolerability. Assessment of CK levels suggest that CPI-0610 therapy durably reduces pro-inflammatory CK. Notably, levels of individual CK were reduced to levels observed in normal healthy donors and were maintained during treatment. Genomic profiling data shows that majority of pts had HMR MUT at baseline. Updated data will be presented.

**Keywords:** Bone Marrow Fibrosis, Cytokine, Epigenetic, Myelofibrosis