Abstract Submission

16. Myeloproliferative neoplasms - Clinical

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CPI-0610, BROMODOMAIN AND EXTRATERMINAL DOMAIN PROTEIN (BET) INHIBITOR, AS "ADD-ON" TO RUXOLITINIB (RUX), IN ADVANCED MYELOFIBROSIS PATIENTS WITH SUBOPTIMAL RESPONSE: UPDATE OF MANIFEST PHASE 2 STUDY

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Background: The majority of myelofibrosis pts show suboptimal responses to ruxolitinib (rux), with limited evidence of disease modification. In addition, ≥Gr3 anemia (45.2%) and thrombocytopenia (12.9%) are concerns with rux treatment. CPI-0610 is a selective small molecule inhibitor of BET (BETi) proteins, which may act synergistically in combination with rux in advanced MF. Here we present updated results from Arm 2 of Phase 2 MANIFEST study, investigating CPI-0610 as "add-on" to rux in advanced MF pts with suboptimal response to rux. Pts are stratified as transfusion dependent (TD, defined as ≥2U RBCs/month over 12 wks, IWG-MRT criteria], and non-transfusion dependent (non-TD).

Aims: To evaluate CPI-0610 "add-on" to rux in advanced MF pts with suboptimal response to rux.

Methods: Eligibility: MF pts treated with rux for ≥6 months on a stable dose for ≥8 wks, having a suboptimal or lost response to rux, DIPSS ≥Int-2, platelets ≥75 x 10^9/L, ≥2 symptoms measurable (score ≥ 1) per MFSAF v4.0, RBC TD (TD cohort) or spleen volume of ≥ 450 cc by CT/MRI (non-TD cohort). 1°endpoints-TD cohort: TD to TI (transfusion independence) [defined as no transfusion for 12 wks per IWG-MRT criteria]; non-TD cohort: SVR35 (≥35% spleen volume reduction) at wk 24. 2° endpoints: TSS50 (≥50% total symptom score reduction) per MFSAF v4.0 at wk 24, safety and PK. Exploratory: changes in proinflammatory plasma cytokine levels and BM morphology/fibrosis. Pts with an assessment at or post wk 24 and those who discontinued after wk 12 are included in the analysis of the corresponding endpoint.

Results: As of 9 Jan 2020, 36 pts have been treated in the TD cohort (median treatment duration: 21.5 wks, range: 1.1-128.6 wks). Baseline characteristic (Table 1) represent a poor prognosis TD population; 97.2% with DIPSS ≥Int-2. 36.8% (7/19) of TD pts converted to TI (median TI duration: 14.1 wks). At wk 24, 16.7% (3/18 evaluable) pts achieved SVR35 (median change: -19.4%, range: -53.6%, 47.9%), and 55.6% (10/18 evaluable) pts achieved TSS50 (median change: -58.8%, range: -100%, 24.4%) (Fig 1) and 70.6% (12/17 evaluable) pts had improvement per PGIC. Improvement in BM fibrosis by ≥1 Gr was reported in 64% (9/14) of evaluable TD pts. In non-TD cohort, 25 pts were treated (median treatment duration: 26.9 wks, range: 1.9-111.3 wks). Of the 14 evaluable pts at wk 24, none achieved SVR35 (median change: -10.9%, range: -26.5%, 16.3%); 30.8% (4/13) pts achieved TSS50 (median: -42.6%, range: -85%, 21.9%) and 57.1% (8/14) pts had improvement per PGIC. Improvement in BM fibrosis by ≥1 Gr was observed in 16.7% (2/12) pts. 2 non-TD pts discontinued study to undergo bone marrow transplantation after 37 and 5 cycles of treatment, respectively.

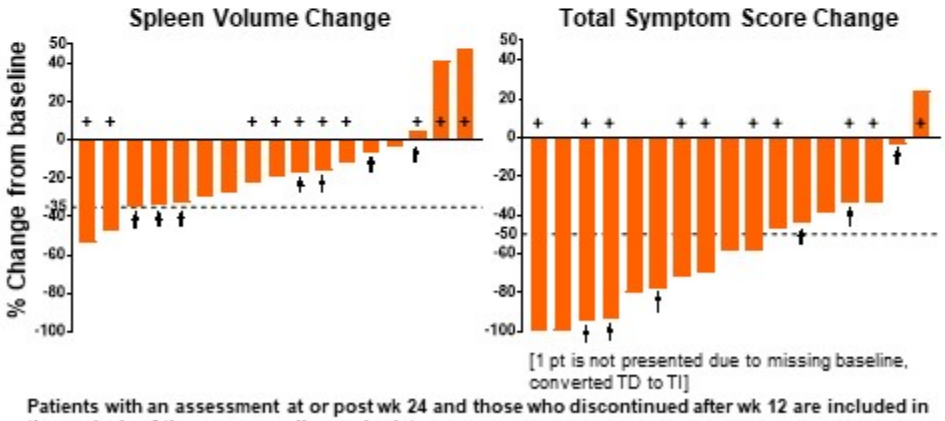
61 pts were safety evaluable. The most common hematological treatment-emergent adverse events (TEAEs) of any grade were thrombocytopenia (44.2%, ≥Gr3: 21.3%) and anemia (9.8%, ≥Gr3: 8.2%). The most common non-hematological TEAEs were infections (49.2%, ≥Gr3: 4.9%), diarrhea (45.9%, ≥Gr3: 4.9%), nausea (32.8%, ≥Gr3: 1.6%), abdominal pain (18%, ≥Gr3: 1.6%), vomiting (16.4%, ≥Gr3: 1.6%) and dysgeusia (16.4%, no ≥Gr3). 7 pts discontinued treatment due to AEs including 3 previously reported Gr5 AEs.

Image/Pictures:

Table 1. Demographics and Baseline Characteristics

	TD (N=36)	Non-TD (N=25)
Age (years) [Median (Min-Max)]	72 (41.0, 83.0)	65 (49.0, 75.0)
Male/Female [n (%)]	23 (63.9)/13 (36.1)	12 (48.0)/13 (52.0)
Primary Myelofibrosis [n (%)]	26 (72.2)	14 (56.0)
Anemic (Hgb <10g/dL) [n (%)]	36 (100.0)	10 (40.0)
DIPSS ≥Int 2 [n (%)]	35 (97.2)	19 (76)
Platelet [Median (Min-Max)]	152 (70.0, 631.0)	224 (86.0, 673.0)
Spleen Volume (cc) [Median (Min-Max)]	1844.5 (121.0, 5089.0)	2401.0 (123.0, 8489.0)
Total Symptom Score [Median (Min-Max)]	19 (1.0, 44.0)	21.5 (3.0, 61.0)
HMR [n (%)]	20 (55.6)	20 (80.0)
JAK2 [n (%)]	22 (61.1)	20 (80.0)
Prior Rux ≥6 months [n (%)]	32 (88.9)	22 (88.0)

Figure 1. Spleen Volume and TSS Percent Change from Baseline at wk 24 in TD Patients



[1 pt is not presented due to missing baseline, converted TD to TI]

Patients with an assessment at or post wk 24 and those who discontinued after wk 12 are included in the analysis of the corresponding endpoint.

✚ : HMR (High molecular risk) ↑ : TD to TI conversion

Summary/Conclusion: Early clinical data indicate that CPI-0610 as “add-on” to rux is generally well-tolerated. The combination therapy provided clinical benefits in TD pts by conversion to TI, in addition to SVR, symptomatic responses and BM fibrosis improvement, indicating potential MF disease modification by CPI-0610.

Keywords: Epigenetic, Myelofibrosis, Ruxolitinib