Abstract Submission

16. Myeloproliferative neoplasms - Clinical

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CPI-0610, A BROMODOMAIN AND EXTRATERMINAL DOMAIN PROTEIN (BET) INHIBITOR, AS MONOTHERAPY IN ADVANCED MYELOFIBROSIS PATIENTS REFRACTORY/INTOLERANT TO JAK INHIBITOR: UPDATE FROM PHASE 2 MANIFEST STUDY

Moshe Talpaz[*1], Raajit Rampal[2], Srdan Verstovsek[3], Claire Harrison[4], Mark Drummond[5], Jean-Jacques Kiladjian[6], Alessandro Vannucchi[7], Marina Kremyanskaya[8], Gary Schiller[9], Andrea Patriarca[10], Gwendolyn Van Gorkom[11], Prithviraj Bose[3], Ronald Hoffman[8], Sujan Kabir[12], Jennifer Mertz[12], Gozde Colak[12], James Shao[12], Suresh Bobba[12], Patrick Trojer[12], Adrian Senderowicz[12], John Mascarenhas[8]

[1]University of Michigan, Rogel Cancer Center, Ann Arbor, [2]Memorial Sloan-Kettering Cancer Center, New York, [3] Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, United States, [4]Guy's and St. Thomas' Hospital, London, [5]Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom, [6]Hôpital Saint-Louis, Université de Paris, Paris, France, [7]Azienda Ospedaliero Universitaria Careggi, Firenze, Italy, [8]Division of Hematology/Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, [9]David Geffen School of Medicine at UCLA, Los Angeles, United States, [10]Azienda Ospedaliero Universitaria Maggiore della Carità di Novara SCDU Ematologia, Novara, Italy, [11]Universiteit Maastricht Academisch Ziekenhuis Maastricht, Maastricht, Netherlands, [12]Constellation Pharmaceuticals, Boston, United States

Background: CPI-0610 is an oral, selective small molecule inhibitor of BET (BETi) proteins, transcriptional regulators of oncogenic pathways and important drivers of inflammation in myelofibrosis (MF). Many MF patients (pts) have suboptimal responses or are resistant to the JAK inhibitor (JAKi) ruxolitinib (rux) or develop anemia and transfusion-dependence (TD), which may lead to discontinuation. Here we present an update from Arm 1 of MANIFEST, a global, open label Phase 2 study investigating CPI-0610 monotherapy in advanced MF pts refractory/intolerant to JAKi. 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 monotherapy in MF pts refractory/intolerant to rux.

Methods: Eligibility: MF pts treated with, but intolerant/resistant/refractory/lost response to or ineligible for JAKi, 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]; 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 bone marrow (BM) morphology/fibrosis. Pts with assessment at or post wk 24 and those discontinued after wk 12 are included in the analysis of the corresponding endpoint.

Results: As of 9 Jan 2020, 27 pts were treated in non-TD cohort (median duration: 21 wks, range: 2-109.1 wks). At wk 24, 20% (2/10) pts achieved SVR35 (median change: -26.8%, range: -51.9, 4.7), 36.4% (4/11) pts achieved TSS50 (median change: -38.7%, range: -90.1, 32.2) (Fig 1), and 81.8% (9/11) had improved PGIC status (6 much improved). Improvement in BM fibrosis ≥1 grade was reported in 30% pts (3/10) pts. Improvement in Hgb levels was observed over time in non-TD pts, with 59.1% (13/22) pts achieving ≥1.5 g/dL increase in Hgb levels without transfusion during the previous 12 wks. In TD cohort, 16 pts were treated (median duration: 14.8 wks, range: 7.1-64.6 wks). 6 pts were evaluable including 3 pts with ≥24 wks of treatment and 3 pts discontinued prior to wk 24. 33.3% (2/6) of TD pts converted to TI. At wk 24, median spleen volume change is -11% (range: -23.9%, 17.6%); 0/6 SVR35. One pt had 5.8% reduction in TSS at wk 24 (the other two pts missing baseline). 40% (2/5) pts had minimally improved status per PGIC at wk 24. Of the 4 pts with BM data available, no improvement in BM fibrosis grade observed. 43 pts were evaluable for safety. The most common hematological treatment emergent adverse events (TEAEs) of any grade were thrombocytopenia (25.6%, ≥Gr3: 14%) and anemia (9.3%, ≥Gr3: 7%). The most common non-hematological TEAEs

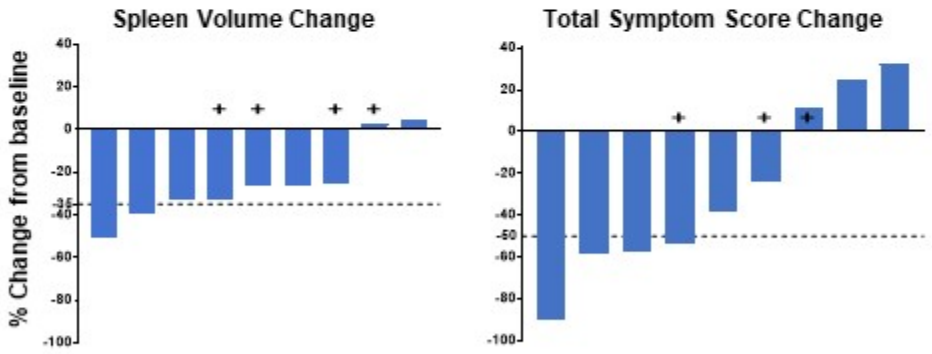
were diarrhea (30.2%, ≥Gr3: 4.7%), nausea (30.2%, no ≥Gr3), infections (27.9%, no ≥Gr3), dysgeusia and cough (20.9% each, no ≥Gr3). 2 pts discontinued treatment because of TEAEs (blood creatinine increase, fatigue and pleuritic pain). No Gr5 TEAEs.

Image/Pictures:

Table 1. Demographics and Baseline Characteristics

	TD (N=16)	Non-TD (N=27)
Age (years) [Median (Min-Max)]	68 (61-88)	69 (46-82)
Male/Female [n (%)]	11 (68.8)/5 (31.3)	14 (51.9)/13 (48.1)
Primary Myelofibrosis [n (%)]	10 (62.5)	19 (70.4)
Anemic (Hgb <10g/dL) [n (%)]	15 (93.8)	17 (63.0)
DIPSS ≥Int 2 [n (%)]	14 (87.5)	22 (81.5)
Platelet [Median (Min-Max)]	160 (88-686)	186 (68-895)
Spleen Volume (cc) [Median (Min-Max)]	1294 (281-8352)	2587.5 (136-7371)
Total Symptom Score [Median (Min-Max)]	18 (1-56)	25 (8-50)
HMR [n (%)]	9 (56.3)	14 (51.9)
JAK2 [n (%)]	11 (68.8)	17 (63.0)
Prior Rux ≥6 months [n (%)]	4 (25.0)	20 (74.1)

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



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)

Summary/Conclusion: The results indicate that CPI-0610 monotherapy is generally well-tolerated and provides clinical benefits in MF pts refractory/intolerant to rux. In non-TD cohort, SVR35 and symptomatic improvement were observed. Majority of non-TD pts demonstrated ≥1.5 g/dL increase in Hgb, a potential disease-modifying effect of CPI-0610. Based on the results, TD cohort is expanded to further investigate the effect of CPI-0610 monotherapy in this setting.

Keywords: Epigenetic, Myelofibrosis, Ruxolitinib