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S168 PELABRESIB (CPI-0610) MONOTHERAPY IN PATIENTS WITH HIGH-RISK ESSENTIAL THROMBOCYTHEMIA REFRACTORY OR INTOLERANT TO HYDROXYUREA: PRELIMINARY RESULTS FROM MANIFEST STUDY

Topic: MPN and MDS: Targeting red cells and platelets

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Background:

High-risk essential thrombocythemia (HR ET) is characterized by thrombocytosis, thrombohemorrhagic events and systemic symptoms. Patients (pts) can experience intolerance, inadequate response or loss of response to first-line cytoreductive therapies (hydroxyurea [HU] or interferon alfa-2a). Bromodomain and extraterminal (BET) domain protein inhibition is a novel therapeutic strategy that downregulates inflammatory cytokines and may inhibit differentiation and proliferation of abnormal megakaryocytes involved in ET pathogenesis. Results from the Phase 2 MANIFEST study (NCT02158858) suggested potentially encouraging clinical efficacy in pts with myelofibrosis treated with pelabresib (PELA), an oral, small-molecule, investigational BET inhibitor.

Aims:

To present preliminary results from Arm 4 of the MANIFEST study investigating PELA monotherapy in pts with HR ET refractory or intolerant to HU.

Methods:

Eligible pts had platelets >600 x 10^9/L and ≥2 symptoms (average score ≥3/total symptom score [TSS] ≥15 in Myeloproliferative Neoplasm Symptom Assessment Form [MPN-SAF]). Pts received oral PELA monotherapy 225 mg QD. The primary endpoint was complete hematologic response (CHR; normalization of platelet count (≤400 x 10^9/L), white blood cell (WBC) count (≤10 x 10^9/L) confirmed after one cycle [after 3 weeks]) and normal spleen size. Secondary endpoints included partial HR (PHR; platelets 400–600 x 10^9/L and WBC ≤10 x 10^9/L), symptom improvement (≥50% reduction in MPN-SAF TSS) and safety. Pharmacodynamic biomarker assessments included genotyping, circulating cytokines and gene expression changes during treatment via peripheral blood sampling and bone marrow biopsies.

Results:

As of July 2022, 20 pts with HR ET received PELA; 70% (14/20) of pts were ongoing treatment, and 35% (7/20) reached 24 wks. Median age was 64 yrs (42–83), median Hgb 13 (10–16) g/dL, median platelet count 772 (418–1255) x 10^9/L and median TSS 32.7 (6.9–123).

The majority of pts had a hematologic response (90% [18/20] unconfirmed CHR or PHR); confirmed CHR was observed in 40% (8/20) (Table 1). Median platelet and WBC count at Wk 12 was 446 x 10^9/L and 8.2 x 10^9/L, respectively. TSS reduction was reported in 86% (12/14 pts); median TSS reduction at Wk 12 was –31%. Hgb levels remained stable through Wk 24.

The most common nonhematologic AEs were nausea (60%; 10% Gr 3), diarrhea (35%; 5% Gr 3) and dysgeusia (35%; no Gr 3). Hemorrhagic or thromboembolic events were reported in 30% of pts (15% Gr 3). No events of thrombocytopenia and no Gr 4 events or higher were reported.

Baseline mutation data were available for 17 pts: *JAK2*V617F (8/17 pts; variant allele frequency [VAF] range 8–67%), *CALR* (8/17 pts; VAF range 14–27%) and *MPL* (1/17 pts; VAF 25%). Among the six patients with *JAK2* mutation, two patients with highest *JAK2* VAF showed a VAF decrease with PELA treatment (67% to 20% at end of treatment, and 52% to 40% at 24 wks). A cluster of seven cytokines (hepcidin, MMP-9, BDNF, TIMP-3, MMP-1, DKK-1 and RANTES) were downregulated post PELA at 2 wks (13/13 pts). A 65% ± SD 0.246 decrease in *IL8* gene expression was also observed 4 hrs after first PELA dose (n=18), 41% ± SD 0.778 at 2 wks (n=13), and 22% ± SD 0.982 at 6 wks (n=11).

Conclusion:

Preliminary results from Arm 4 of the MANIFEST study suggest potential clinical benefit with PELA monotherapy in pts with HR ET refractory or intolerant to HU as supported by hematologic responses and symptom improvement. Safety data suggest a tolerable and manageable safety profile. Mutation data and other pharmacodynamic analyses indicate potential biomarker changes after PELA monotherapy.

Best response (N=20)	**CHR, n (%) [Primary endpoint]**	
	Confirmed*	8 (40)
	Unconfirmed†	12 (60)
	- WBC count ≤10 x 10^9/L	19 (95)
	- Platelet count ≤400 x 10^9/L	12 (60)
	PHR, n (%)	
	Confirmed*	4 (20)
	Unconfirmed†	6 (30)
Symptom improvement (N=14)	TSS50	7 (50)
	Median TSS reduction, Wk 12, %	–31%

*Confirmed CHR/PHR: conditions met in two consecutive cycles

†Unconfirmed CHR/PHR: conditions met in one cycle but not the next

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