POSTER No. 7019

Pelabresib (CPI-0610) Monotherapy in High-Risk Essential Thrombocythemia Refractory or Intolerant to Hydroxyurea: **Preliminary Results From the MANIFEST Study**

Francesco Passamonti,[1*] Andrea Patriarca,[2] Steven Knapper,[3] Candido Rivera,[4] Joseph M Scandura,[5] Timothy Devos,[6] Nikki Granacher,[7] Adam Mead,[8] Stephen T Oh,[9] Jeanne Palmer,[10] **Raajit K Rampal**,[11] Lino Teichmann,[12] Jie Cui,[13] Sandra Klein,[13] Gozde Colak,[13] Claire Harrison[14], on behalf of the MANIFEST study investigators.

[1]University of Insubria, Varese, Italy; [2]Hematology Unit, Department of Translational Medicine, University of Eastern Piedmont and AOU Maggiore della Carità, Novara, Italy; [3]Department of Haematology, Division of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, Wales, UK; [4]Mayo Clinic Florida , Jacksonville, FL, USA; [5]The Richard T. Silver, M.D. Myeloproliferative Neoplasms Center, Division of Hematology and Oncology, Cornell Medicine, New York, NY, USA; [6]Department of Hematology, University Hospitals Leuven and Laboratory of Molecular Immunology (Rega Institute), KU Leuven, Leuven, Belgium; [7]Ziekenhuis Netwerk Antwerpen, Antwerp, Belgium; [8]MRC Molecular Haematology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK; [9]Washington University School of Medicine in St. Louis, St. Louis, MO, USA; [10]Mayo Clinic Arizona, Phoenix, AZ, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Universitätsklinikum Bonn, Bonn, Germany;, [13]Constellation Pharmaceuticals, Inc., a MorphoSys Company, Boston, MA, USA; [14]Guy's and St Thomas' NHS Foundation Trust, London, UK.

*Current affiliation: University of Milan, Milan, Italy.

Contact: francesco.passamonti@unimi.it

OBJECTIVES

To investigate the efficacy and safety of the investigational drug pelabresib monotherapy in patients with high-risk essential thrombocythemia refractory or intolerant to hydroxyurea

SUMMARY

In Arm 4 of the Phase 2 MANIFEST study, pelabresib monotherapy resulted in hematologic response and symptom improvement in patients with high-risk ET and resistance/intolerance to hydroxyurea

Safety results are as expected in the underlying population and consistent with the known safety profile of pelabresib

These preliminary safety and efficacy results in patients with high-risk ET continue to provide evidence for the potential clinical benefit of pelabresib in myeloid diseases

References: 1. Accurso V, et al. *Clin Med Insights: Blood Dis* 2020;13:1–8; 2. Barosi G, et al. *Leukemia* 2007;21:277–280; 3. Tefferi MD and Pardanani A. *N Engl J Med* 2019;381:2135–2144; 4. Wang N, et al. *Signal Transduct Target Ther* 2021;6:23; 5. Kleppe M, et al. *Cancer Cell* 2018;33:29–43; 6. Shorstova T, et al. *Br J Cancer* 2021;124:1478–1490; 7. Albrecht BK, et al. *J Med Chem* 2016;59:1330–1339; 8. Blum KA, et al. *Canc Res Comms* 2022;2:795–805; 9. ClinicalTrials.gov. NCT02158858. Available at:https:/ /clinicaltrials.gov/ct2/show/NCT02158858. Accessed April 19, 2023; 10. Constellation. Data on file (CPI-0610); 11. Mascarenhas J, et al. *J Clin Oncol* 2023:JCO2201972.

Acknowledgements: Thank you to the patients, caregivers and study investigators. This study was supported by Constellation Pharmaceuticals, Inc., a MorphoSys Company. Editorial and writing support was provided by Laura Travers, PhD, of LiNK Health, funded by MorphoSys AG.

Abbreviations: AE, adverse event; BET, bromodomain and extraterminal; BOR, best overall response; CHR, complete hematologic response; ET, essential thrombocythemia; Gr, grade; Hgb, hemoglobin; HU, hydroxyurea; MPN, myeloproliferative neoplasm; NF-κB, nuclear factor kappa B; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; PHR, partial hematologic response; PI, principal investigator; PO, per oral; PV, polycythemia vera; QD, once per day; SD, standard deviation; SVR35, ≥35% reduction in spleen volume at Week 24; TD, transfusion dependent; TEAE, treatment-emergent adverse event; TI, transfusion independent; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline; WBC, white blood cell.

Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

INTRODUCTION

- ET is a myeloproliferative neoplasm characterized by thrombocytosis, thrombohemorrhagic events and systemic symptoms[1]
- An unmet medical need persists due to resistance or intolerance to first-line cytoreductive treatments, such as hydroxyurea and interferon alfa-2a. Resistant/intolerant patients have limited options and adverse outcomes[2,3]
- BET proteins are epigenetic modulators of gene expression and transcription factors that play a role in the development of MPNs, such as ET, PV and MF[4,5] by:
  - increasing BET protein recruitment to hyper-acetylated chromatin[6*]
  - modulating NF-κB target gene expression and may result in increased levels of proinflammatory cytokines and aberrant megakaryocyte differentiation[5]
- BET protein inhibition is a novel therapeutic strategy that downregulates the expression of genes that contribute to the pathology of ET, PV and MF[5,7]
- Pelabresib, an oral, small-molecule, investigational BET inhibitor, has the potential to modify the pathogenic pathways that contribute to the pathogenesis of MPNs[8]

*Based on BET activity in neoplasms, not specifically in MPNs.[5]

STUDY DESIGN[9,10]

Figure 1. MANIFEST: Ongoing, global, open-label Phase 2 study

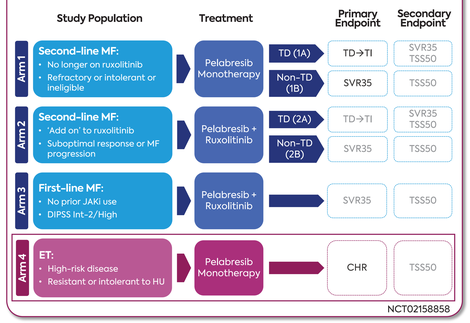
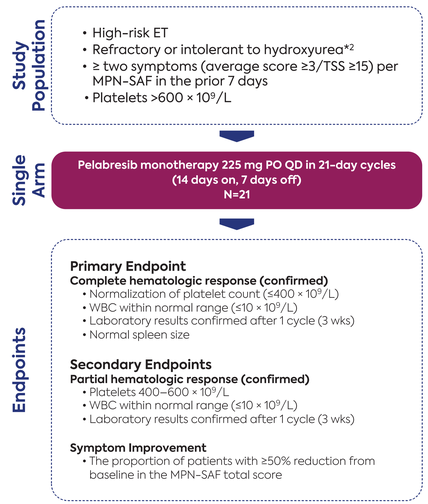


Figure 2. MANIFEST Arm 4: Pelabresib monotherapy in patients with high-risk ET refractory or intolerant to hydroxyurea



*Refractory or intolerant criteria, as per Barosi, et al. 2007.

RESULTS

Table 1. Patient Disposition

		n (%)
Patient status	Enrolled	20 (100)
	Ongoing	14 (70)
	Discontinued	6 (30)
Primary reason for treatment discontinuation	Withdrew consent	3 (15)
	AE or lab abnormality	2 (10)
	PI decision	1 (5)
Treatment duration	≥12 weeks	14 (70)
	≥24 weeks	7 (35)

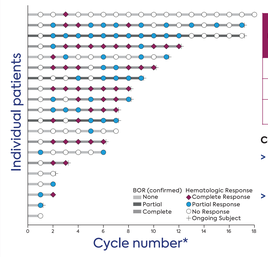
- 25% (5/20) of patients had thrombosis or hypertension prior to enrollment
- 45% (9/20) of patients had ≥1 grade bone marrow fibrosis at baseline
- 60% (12/20) of patients had ≥2 prior line of therapies (range: 1–4)

Table 2. Patient Demographics and Baseline Characteristics

		N=20
Age (years)	Mean (SD) Median (range)	62.4 (12.95) 64 (42–83)
Patients <60 yrs old	n (%)	8 (40)
Gender	Male, n (%)	8 (40)
Hemoglobin (g/dL)	Median (min–max)	13 (10–16)
Platelet (× 10^9/L)	Median (min–max)	722 (418–1255)
WBC (x10^9/L)	Median (min–max)	7.9 (4–12.3)
Spleen volume (cc)	Median (min–max)	402 (124–907)
Spleen by palpitation (n)	Not palpable	18*
TSS (MPN-SAF)	Median (min–max)	32.7 (6.9–123)
HU treatment duration	Median (min–max)	103 mo (0.7–245)
Time from diagnosis (mo)	Median (min–max)	11.4 (1.9–35.3)

*Two patients missing palpation assessment.

Figure 3. Hematologic responses



Best response N=20	Confirmed n (%)	Unconfirmed n (%)
CHR	8 (40%)	12 (60%)
PHR	4 (20%)	6 (30%)
CHR or PHR	12 (60%)	18 (90%)

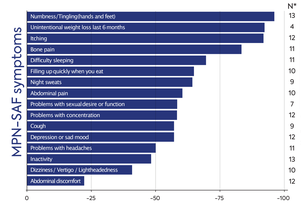
Confirmed vs Unconfirmed Response

- Confirmed CHR/PHR: When CHR/PHR conditions are met in two consecutive cycles*
- Unconfirmed CHR/PHR: When CHR/PHR conditions are met in one cycle but not in the next one

*Cycles of 14 days of daily dosing and 7-day break

Figure 4. Total symptom score improvement

Best percent reduction in MPN-SAF symptoms



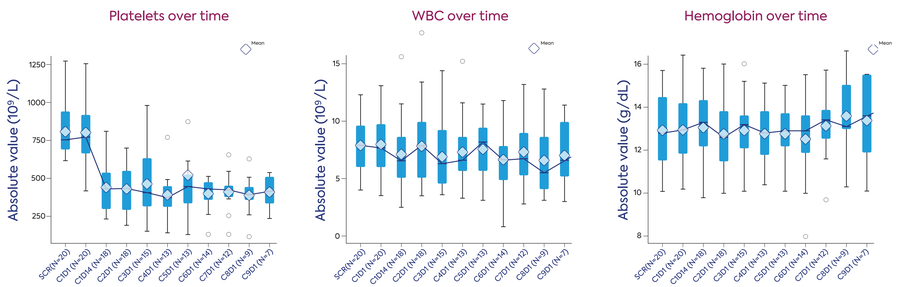
N=14*	MPN-SAF symptoms
TSS50 at anytime	50% (7/14)
Median % TSS reduction at Week 12	−31%

*Patients with non-missing and non-zero baseline symptom score

Majority of patients (90%) with high-risk ET had complete or partial hematologic responses

Symptom reduction was observed across all domains of MPN-SAF

Figure 5. Platelet count, white blood cell count and hemoglobin



Platelet count	
≤400 × 10^9/L	60% (12/20)
Median at Wk 12	446 × 10^9/L
Median % change at Wk 12	-40%

WBC count	
≤10 × 10^9/L	95% (19/20)
Median at baseline	7.9 × 10^9/L
Median at Wk 12	8.2 × 10^9/L

Hemoglobin	Baseline	Week 12 (N=13)	Week 24 (N=7)
Mean (g/dL)	13.0	13.0	13.6
Median (g/dL)	13.0	13.0	13.4

- Hgb levels remained stable through Wk 24

Data cutoff 29 July 2022

Table 3. Treatment-Emergent Adverse Events

All Grades That Occurred in ≥10% of Patients		All Grade N=20 n (%)	Grade 3 N=20 n (%)	Grade 4 N=20 n (%)
Hematologic Events	Leukopenia*	2 (10)	1 (5)	0
Nonhematologic Events	**Gastrointestinal Events**			
	Nausea	12 (60)	2(10)	0
	Diarrhea†	7 (35)	1 (5)	0
	Constipation	6 (30)	0	0
	Vomiting	5 (25)	0	0
	Dyspepsia	2 (10)	0	0
	Other Nonhematologic Events			
	Dysgeusia	7 (35)	0	0
	Ageusia	6 (30)	0	0
	Abdominal pain†	5 (25)	0	0
	Rash§	4 (20)	0	0
	Respiratory tract infection¶	3 (15)	0	0
	Weight decreased	3 (15)	0	0
	Muscle spasms	3 (15)	0	0
	Myalgia	2 (10)	0	0
	Headache	2 (10)	0	0
	Insomnia	2 (10)	0	0
	Pruritus	2 (10)	0	0
	Hypertension	2 (10)	1 (5)	0
	Fatigue	2 (10)	0	0
	Arthralgia	2 (10)	0	0

*Leukopenia includes neutropenia and decreased neutrophil count; †Diarrhea includes hemorrhagic diarrhea; ‡Abdominal pain includes upper abdominal pain; §Rash includes macular rash; ¶Respiratory tract infection includes nasopharyngitis, pharyngitis, rhinitis and upper respiratory tract infection.

- Serious adverse events reported in three patients: leukocytosis, thrombocytosis and eyelid bleeding in one patient; infection in one patient; dyspnea and pulmonary embolism in one patient
- 3/20 (15%) reported TEAEs that led to pelabresib discontinuation
- No Grade 5 TEAEs reported

Table 4. Hemorrhagic and thromboembolic events

	All Grade N=20 n (%)	Grade 3 N=20 n (%)
Pulmonary embolism*	1 (5)	1 (5)
Deep vein thrombosis*	1 (5)	0
Acute myocardial infarction*	1 (5)	0
Diarrhea hemorrhagic	1 (5)	1 (5)
Eyelid bleeding	1 (5)	1 (5)
Hematoma	1 (5)	0
Hematuria	1 (5)	0
Petechia	1 (5)	0

*AEs reported by the same patient.

- 6 (30%) patients reported hemorrhagic and thromboembolic events
  - These patients received ≥ 2 lines of prior therapies (max: 4)
  - 2 patients had previous history of thrombosis or hypertension
  - 3 patients achieved confirmed CHR and 3 patients achieved unconfirmed PHR
  - Pulmonary embolism (Gr3), deep vein thrombosis (Gr2) and acute myocardial infarction (Gr2) were reported in a 65 yo patient with a history of portal vein thrombosis and hypertension. All events were unrelated to pelabresib and resolved. The patient restarted and continued pelabresib treatment for 6 cycles
  - Eyelid bleeding (Gr3) occurred shortly after a chalazion removal and was unrelated to pelabresib

Presented at ASCO 2023, June 5, 2023