Pelabresib (CPI-0610) Monotherapy in Patients With 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 Oh,[9] Jeanne Palmer,[10] Raajit K Rampal,[11] Lino Teichmann,[12] Qing Li,[13] Jean-Pierre Eliane,[13] Tzuu-Wang Chang,[13] Sandra Klein,[13] Gozde Colak,[13] Claire Harrison[14], *on behalf of the MANIFEST study investigators*

[1]Università degli Studi di Milano; Fondazione I.R.C.C.S. Ca' Granda Ospedale Maggiore Policlinico, Milano, 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.

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Disclosures

- Consulting or Advisory role
  - AbbVie; AMOMED Pharm GmBH; Celgene/Bristol-Myers Squibb; Karyopharm Therapeutics; Novartis; Roche; Sandoz; Sierra Oncology; Sumitomo Dainippon Pharma Oncology
- Speakers' Bureau
  - AbbVie; AOP Orphan Pharmaceuticals; Celgene/Bristol-Myers Squibb; Novartis

BET inhibition in essential thrombocythemia

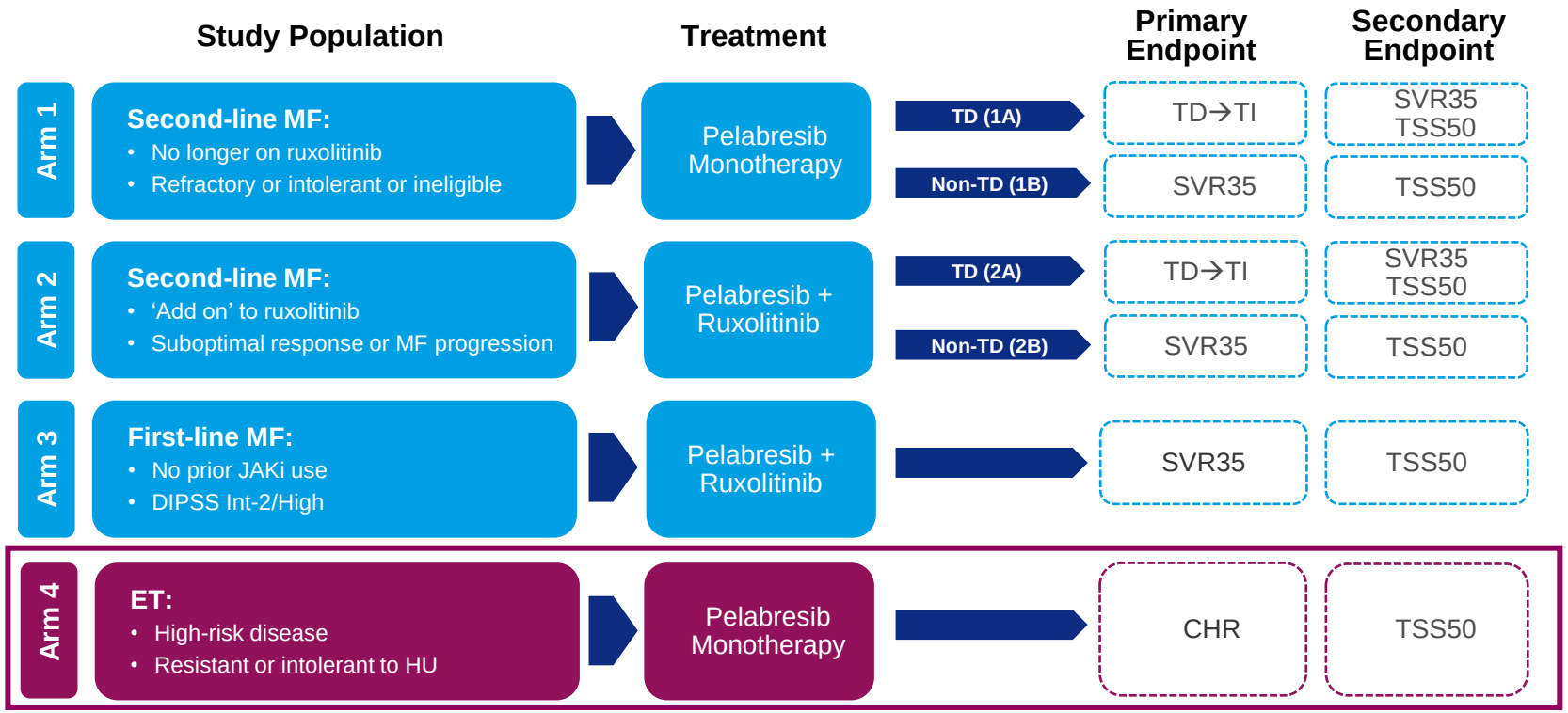
- Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized by progressive thrombocytosis, thrombohemorrhagic events and systemic symptoms[1]
- An unmet medical need persists due to the resistance or intolerance to first-line cytoreductive treatments, such as hydroxyurea and interferon 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 by[4,5]:
  - increasing BET protein recruitment to hyperacetylated chromatin*[6]
  - modulating NF-κB target gene expression, which 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 these genes[5,7]
- Pelabresib, an oral, small-molecule, investigational BET inhibitor, has the potential to modify the pathogenic pathways that contribute to the progression of MPNs[8]

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

BET, bromodomain and extraterminal; MPN, myeloproliferative neoplasm; NF-κB, nuclear factor kappa B; PV, polycythemia vera.

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.

MANIFEST: Ongoing, global, open-label Phase 2 study investigating pelabresib in myelofibrosis and essential thrombocythemia



NCT02158858

CHR, complete hematologic response; HU, hydroxyurea; SVR35, ≥35% reduction in spleen volume at Week 24; TD, transfusion dependent; TI, transfusion independent; TSS50, ≥50% reduction in total symptom score from baseline.

1. ClinicalTrials.gov. NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed May 30, 2023; 2. Constellation. Data on file (CPI-0610).

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

Study Population

- High-risk ET
- Refractory or intolerant to hydroxyurea*[3]
- ≥ two symptoms of average score ≥3 or TSS ≥15 per MPN-SAF in the prior 7 days
- Platelets >600 × 10^9/L

Pelabresib monotherapy 225 mg PO QD in 21-day cycles (14 days on, 7 days off) N=21

Endpoints

Primary Endpoint

Complete hematologic response at anytime (confirmed)
Normalization of platelet count (≤400 × 10^9/L) and WBC (≤10 × 10^9/L), confirmed 3 weeks later and a normal spleen size

Secondary Endpoints

Partial hematologic response at anytime (confirmed)
Platelets 400–600 × 10^9/L and WBC within the normal range (≤10 × 10^9/L), confirmed 3 weeks later

Symptom improvement
The proportion of patients with a ≥50% reduction from baseline in the MPN-SAF total score

Exploratory Endpoints

Translational assessment of *IL-8* expression change, cytokines and mutation status

*Refractory or intolerant criteria, as per Barosi, et al. 2007.
TSS, total symptom score; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form.
1. ClinicalTrials.gov. NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed May 30, 2023; 2. Constellation. Data on file (CPI-0610); 3. Barosi G, et al. *Leukemia* 2007;21:277–280.

MANIFEST Arm 4: 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 (%)	12 (60)
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 (× 10^9/L)	Median (min–max)	7.9 (4–12.3)
Spleen volume (cc)	Median (min–max)	402 (124–907)
Spleen not palpable (n)	n (%)	18 (90)†
TSS (MPN-SAF)	Median (min–max)	32.7 (6.9–123)
Prior HU duration‡	Median (min–max)	103 mo (0.7–245)
≥2 prior line of therapies	n (%)	12 (60)
Prior thrombosis	n (%)	3 (15)
***JAK2, CALR, ASXL1, MPL* mutations**	n (%)	9 (45), 8 (40), 3 (15), 1 (5)
MF-HMR	n (%)	4 (20)

*Patient met eligibility criteria at screening. Hydroxyurea and anagrelide were allowed until 24 hrs prior to C1D1. †Two patients were missing palpation assessment. ‡One patient missing start date of prior hydroxyurea.
MF-HMR: *ASXL1, EZH2, IDH1/2, SRSF2, U2AF1*.
HU, hydroxyurea; MF-HMR, myelofibrosis high-molecular risk; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, total symptom score.

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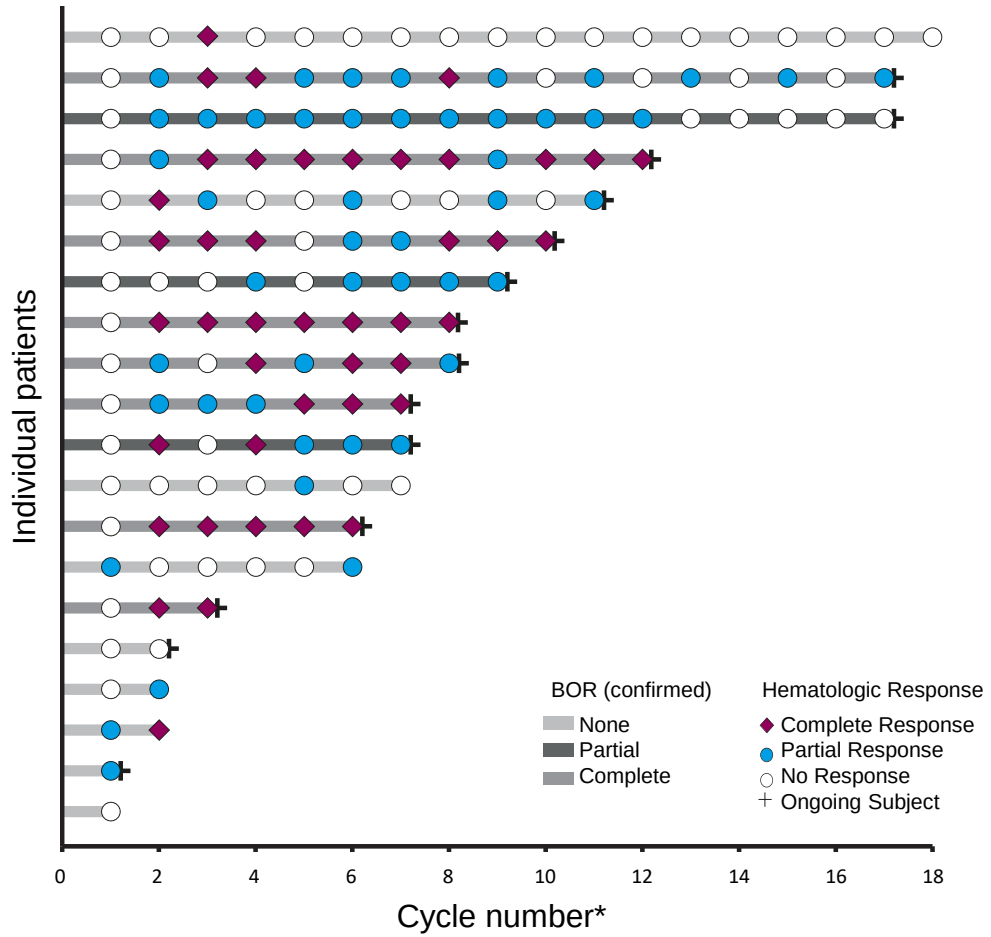
MANIFEST Arm 4: Hematologic responses

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%)

- At data cut off, 7/20 patients were treated for ≥6 months (8 cycles)
  - 14/20 patients continue to undergo treatment
    - Of these, 6 patients had CHR, 6 patients had PHR, and 2 patients without response by the end of this observation period

*Cycles of 14 days of daily dosing and 7-day break.
Confirmed, when conditions are met in two consecutive cycles; unconfirmed, when conditions are met in one cycle but not in the next one.
BOR, best overall response; CHR, complete hematologic response; PHR, partial hematologic response.

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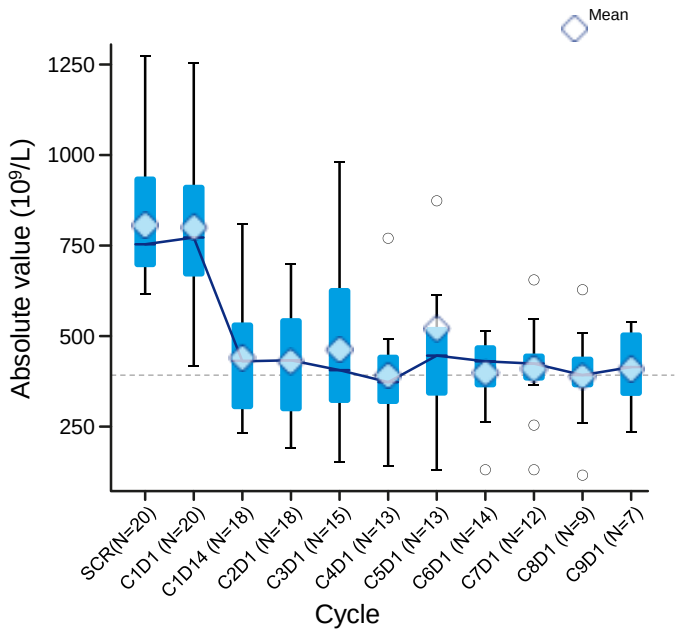
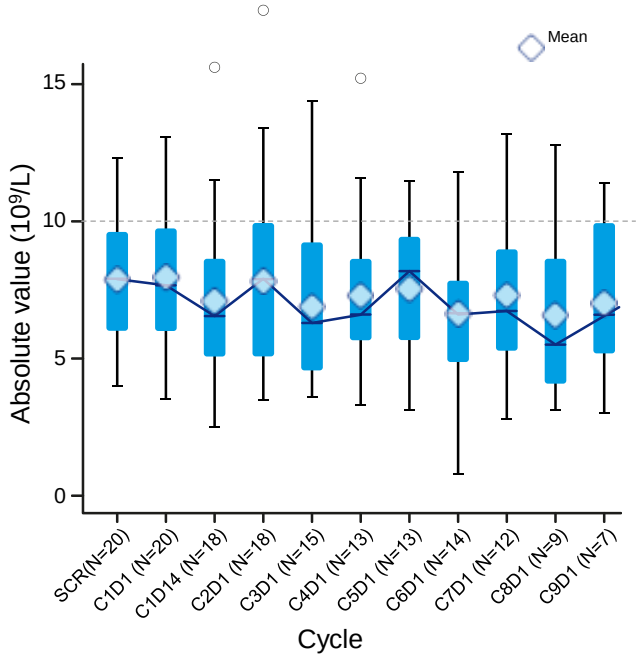
MANIFEST Arm 4: Platelet count, white blood cell count and hemoglobin

Platelets over time



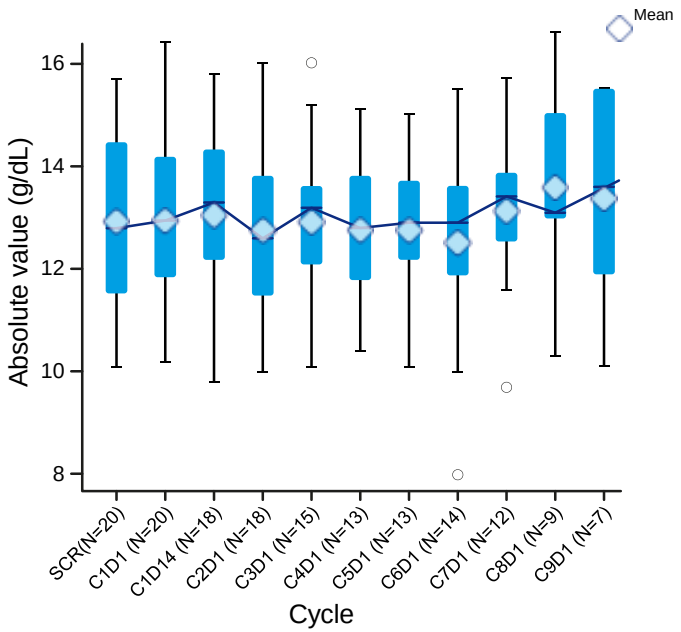
	Platelet count
≤400 × 10^9/L	60% (12/20)
Median at Wk 12	446 × 10^9/L
Median % change at Wk 12	–40%

WBC over time



	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 over time



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

CXDX, Cycle X Day X; SCR, screening.

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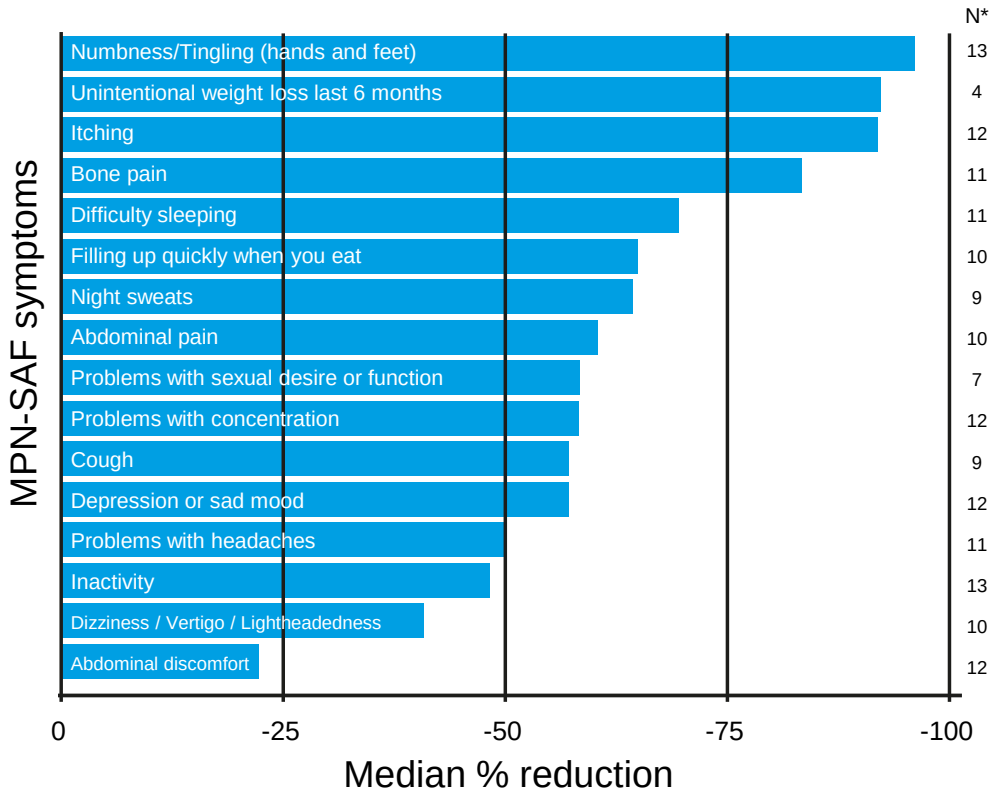
MANIFEST Arm 4: Total symptom score

Best percentage 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 nonmissing and nonzero baseline symptom score.

Fever not depicted in the figure due to zero baseline.
MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, total symptom score assessed based on MPN-SAF; TSS50, ≥50% reduction in total symptom score from baseline.

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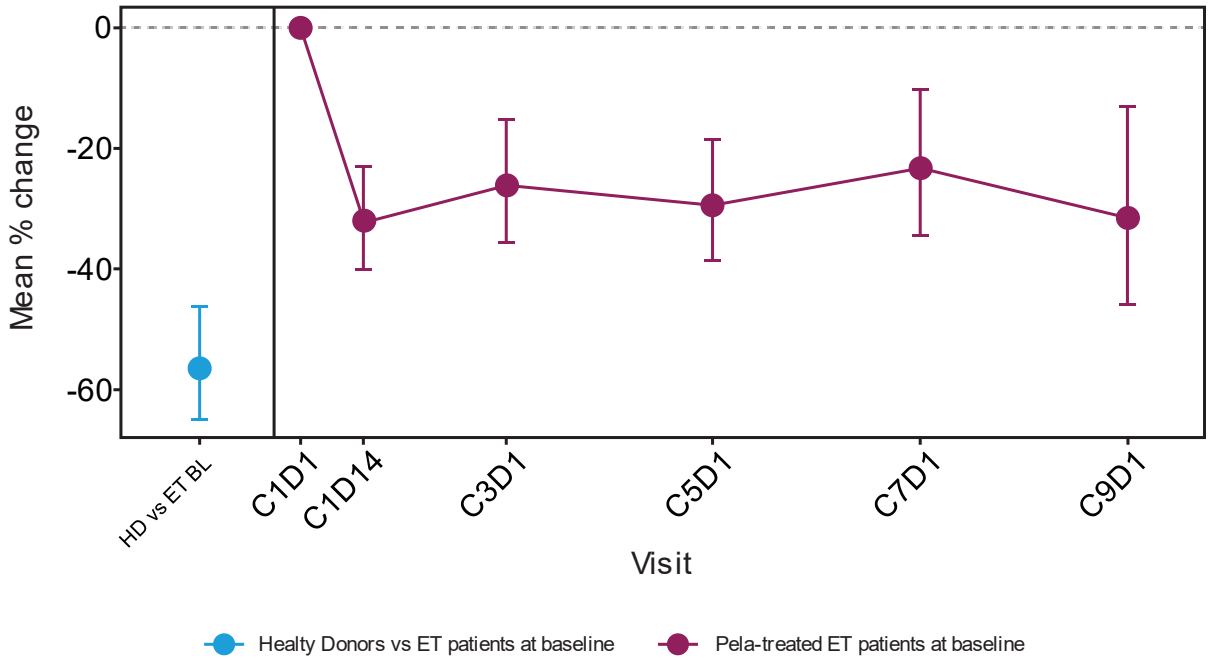
MANIFEST Arm 4: NF-κB target cytokine reduction

Mean % change of NF-κB target cytokines (95% CI)*



- A NF-κB target cytokine panel associated with bone marrow pathogenesis and inflammation was assayed
  - The cytokine panel included CD40, CD40-L, CRP, IL-6, IL-8, IL-18, IP-10, MMP-2, TNFα, thrombospondin-1, RANTES, VCAM-1, VEGF
- Pelabresib monotherapy demonstrated a durable reduction of NF-κB-driven cytokines associated with bone marrow abnormalities and inflammation

*Quantifying plasma cytokines and soluble factors level by multiplex bead-based analysis at baseline compared with healthy donors (N=10), and pelabresib-treated patients (N=13) were compared with the baseline. Means (95% CI) for the stated cytokine panel are provided.
BL, baseline; CXDX, Cycle X Day X; HD, healthy donor; NF-κB, nuclear factor kappa B.

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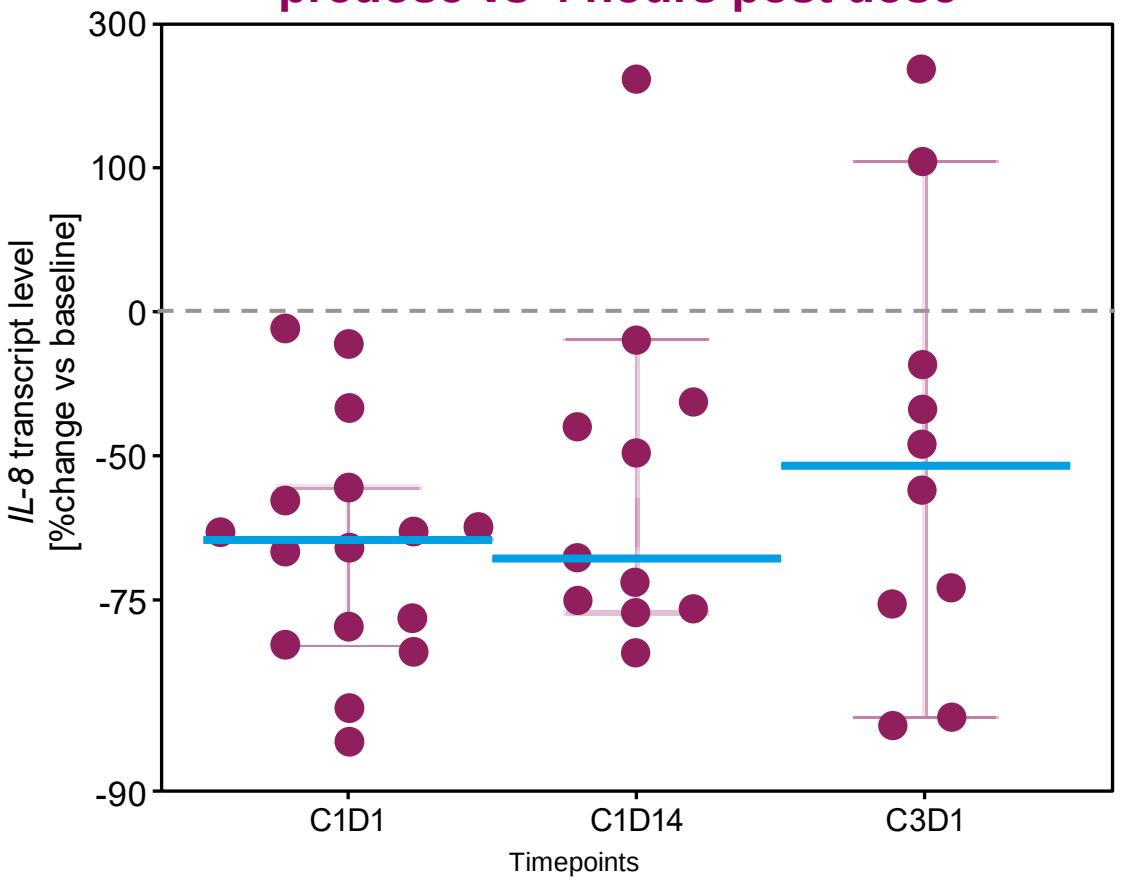
MANIFEST Arm 4: *IL-8* gene expression reduction

IL-8 gene expression in whole blood predose vs 4 hours post dose



	C1D1 N=16	C1D14 N=11	C3D1 N=10
Median *IL-8* expression change % (±95% CI)	–67% (–79%, –56.9)	–69% (–76.5, –12.2)	–52% (–85, 106.6)

> A rapid reduction in *IL-8* gene expression was observed

Quantification of *IL-8* messengers by qRT-PCR on predose and 4 hours postdose peripheral blood samples on C1D1, C1D14 and C3D1. 16 paired patients' samples were analyzed.
CXDX, Cycle X Day X.

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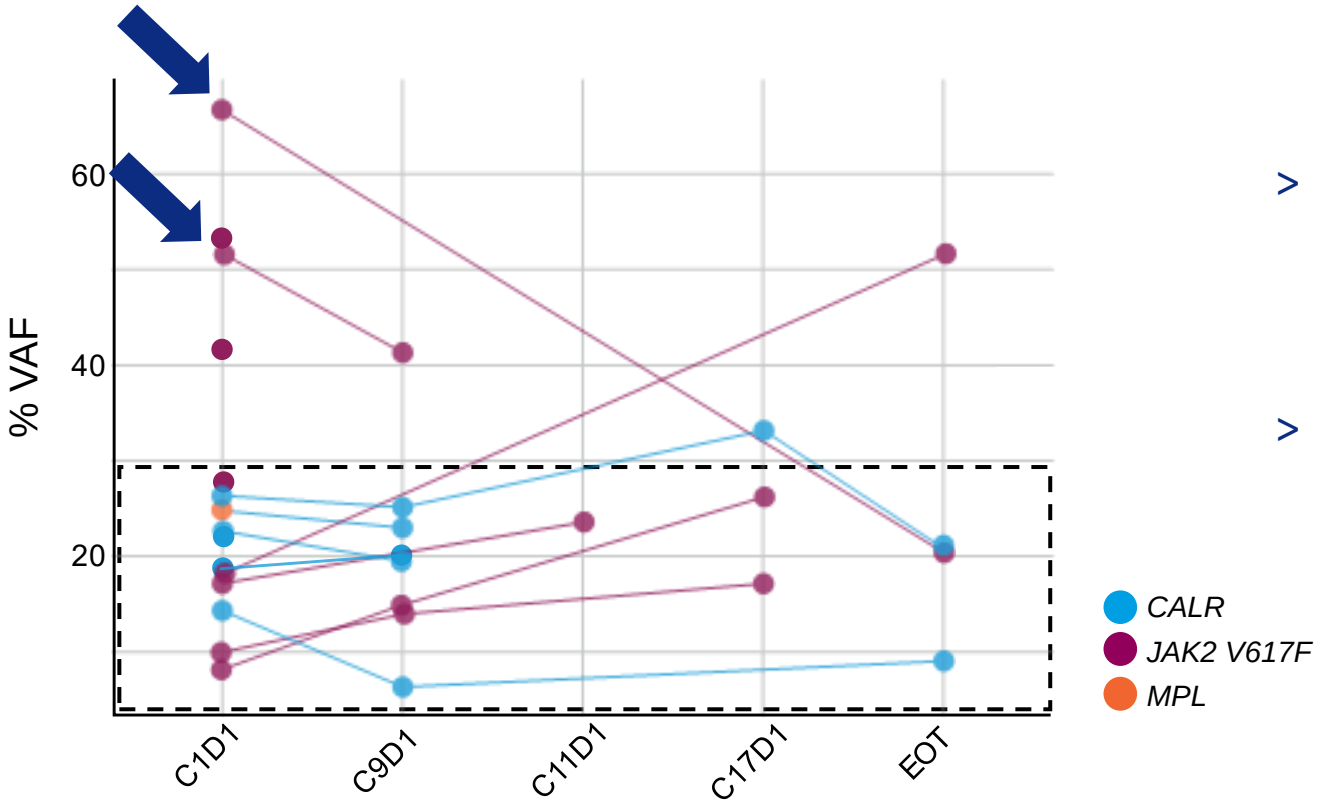
MANIFEST Arm 4: VAF reduction in driver mutations

Driver mutation levels



- 2/6 patients with post-baseline *JAK2* V617F mutation assessment showed a meaningful VAF reduction (67%→20% and 52%→40%)
- VAF levels were maintained in most patients with ≤30% driver mutations

Peripheral blood next-generation sequencing panel to quantify the frequency of allele mutations at baseline and on treatment.
One patient with the *MPL* mutation at baseline did not have a post-baseline assessment; therefore, post-baseline is not presented.
Mutation profile change analyzed in 18 patients. During pelabresib treatment, 11 patients were analyzed over 4 timepoints.
CXDX, Cycle X Day X; VAF, variant allele fraction.

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MANIFEST Arm 4: Summary of adverse events

Treatment-Emergent Adverse Events of 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

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

*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.

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MANIFEST Arm 4: Hemorrhagic and thromboembolic events

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.

- 1 (5%) patient had 3 thromboembolic events, ie, pulmonary embolism (Gr3), deep vein thrombosis (Gr2) and acute myocardial infarction (Gr2)
  - A 65-year-old male had a history of portal vein thrombosis and hypertension. All events were unrelated to pelabresib and resolved
  - The patient restarted and continued pelabresib treatment for six cycles and achieved unconfirmed PHR
- 5 (25%) patients reported hemorrhagic events
  - These patients received 2–4 lines of prior therapies
  - 1 patient had a previous history of hypertension
  - Eyelid bleeding (Gr3) occurred shortly after a chalazion removal and was unrelated to pelabresib
  - 3 patients achieved confirmed CHR, and 2 patients achieved unconfirmed PHR
- There were no Grade 4 or 5 hemorrhagic or thromboembolic events

CHR, complete hematologic response; PHR, partial hematologic response.

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MANIFEST Arm 4: Conclusions

- Pelabresib monotherapy resulted in hematologic response and symptom improvement in patients with high-risk essential thrombocythemia and who are resistant/intolerant to hydroxyurea
  - Majority of patients (90%) had complete or partial hematologic responses
  - 50% of patients had a TSS50 response; symptom reduction was observed across all domains of MPN-SAF
- Rapid and durable changes in clinical biomarkers were associated with pelabresib monotherapy
- 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 essential thrombocythemia continue to provide evidence for the potential clinical benefit of pelabresib in myeloid diseases

MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, total symptom score assessed based on MPN-SAF; TSS50, ≥50% reduction in total symptom score from baseline.

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