Pelabresib (CPI-0610) as Add-on to Ruxolitinib in Myelofibrosis: Durability of Response and Safety Beyond Week 24 in the Phase 2 MANIFEST Study

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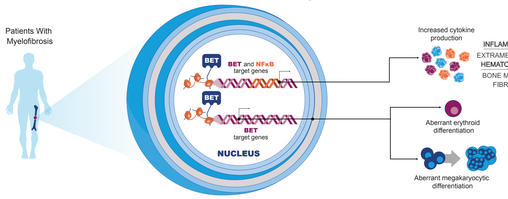
Introduction

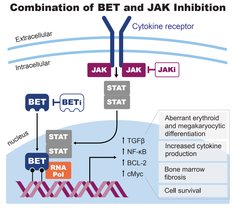
Simultaneous inhibition of BET and JAK in myelofibrosis

A potential therapeutic approach to address heterogenous disease pathology

Role of BET Proteins in Myelofibrosis



Combination of BET and JAK Inhibition



- JAK inhibition with ruxolitinib is the standard of care in patients with higher risk MF who are ineligible for HSCT, but unmet medical need persists due to limited efficacy with currently available JAKi monotherapy, high rates of discontinuation and toxicities[1]
- Preclinical data indicated synergistic effects of BET and JAK inhibition in MF[2]
- Pelabresib, a BET inhibitor, downregulates the expression of genes that contribute to the heterogenous pathology of MF[3–7]

Study Design

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

	Study Population	Treatment		Primary Endpoint	Key Secondary Endpoints
Arm 1	Second-line MF • No longer on ruxolitinib • Refractory or intolerant or ineligible	Pelabresib monotherapy	TD (1A)	TD→TI	SVR35 TSS50
			Non-TD (1B)	SVR35	TSS50
Arm 2	Second-line MF • Add on' to ruxolitinib • Suboptimal response or MF progression	Pelabresib + Ruxolitinib	TD (2A)	TD→TI	SVR35 TSS50
			Non-TD (2B)	SVR35	TSS50
Arm 3	First-line MF • No prior JAKi use • DIPSS Int-2/High	Pelabresib + Ruxolitinib		SVR35	TSS50
Arm 4	ET • High-risk disease • Resistant or intolerant to HU	Pelabresib monotherapy		CHR	TSS50

Data cutoff 29 July 2022.
Clinicaltrials.gov. NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed November 10, 2022.

Arm 2: Pelabresib as 'add-on' to ruxolitinib in patients with suboptimal response to ruxolitinib

Study Population

- Suboptimal response or MF progression
- ≥6 months of ruxolitinib and stable dose for a minimum of 8 weeks, have disease that is not being adequately controlled by ruxolitinib
- DIPSS Int-2 or higher*
- TD cohort must receive an average of ≥2 RBC transfusions per month during the 12 wks prior to enrollment
- Non-TD cohort must have baseline spleen size of >450 cm^3

Arm/Cohort

- Transfusion Dependent (TD) (Cohort 2A) N=58
- Nontransfusion Dependent (Non-TD) (Cohort 2B) N=29

Endpoints

TD cohort (2A)	
Primary Endpoint	Key Secondary
TD to TI	SVR35, TSS50

Non-TD cohort (2B)	
Primary Endpoint	Key Secondary
SVR35	TSS50

*Patients with DIPSS Int-1 were allowed to enroll prior to the protocol amendment.
Clinicaltrials.gov. NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed November 10, 2022.

ABBREVIATIONS: BET, bromodomain and extraterminal domain; CHR, complete hematologic response; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; HMR, high-molecular risk; HU, hydroxyurea; Int, intermediate; JAKi, Janus kinas inhibitor; *JAK2*, Janus kinase 2; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; NF-κB, nuclear factor kappa B; PV, polycythemia vera; RTI, respiratory tract infection; STAT, signal transducer and activator of transcription; SVR25, ≥25% reduction in spleen volume from baseline; SVR35, ≥35% reduction from baseline (MRI or CT) after 24 wks; TD, transfusion dependent; TEAE, treatment emergent adverse event; TGFβ, transforming growth factor β; TI, transfusion independent; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score at Week 24.

Results

Patient disposition, demographics and baseline characteristics

Patient Disposition

		TD	Non-TD	Overall
Patient status	Enrolled (n)	58	29	87
	Ongoing [n (%)]	12 (21)	2 (7)	14 (16)
	Discontinued [n (%)]	46 (80)	27 (93)	73 (84)
Primary reason for treatment discontinuation [n (%)]	Progressive disease*	11 (19)	8 (28)	19 (22)
	AE* or lab abnormality	8 (14)	4 (14)	12 (14)
	Withdrew consent	7 (12)	1 (3)	8 (9)
	PI decision	7 (12)	7 (24)	14 (16)
	Death	3 (5)	0	3 (3)
	Eligible for stem cell transplant	2 (3)	3 (10)	5 (6)
	Other	5 (9)	3 (10)	8 (9)
	Missing†	3 (5)	1 (3)	4 (5)

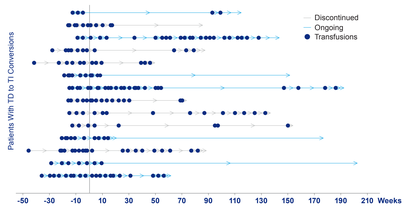
Patient Demographics and Baseline Characteristics

		TD n=58	Non-TD n=29	Overall N=87
Age (years)	Mean (SD)	70 (9)	63 (8)	68 (9)
Gender	Male, n (%)	40 (69)	16 (55)	56 (64)
DIPSS	Int-1, n (%)	0	7 (24)	7 (8)
	Int-2, n (%)	39 (67)	16 (55)	55 (63)
	High, n (%)	19 (33)	6 (21)	25 (29)
MF subtype	Primary MF, n (%)	41 (71)	16 (55)	57 (66)
	Post-ET MF, n (%)	5 (9)	7 (24)	12 (14)
	Post-PV MF, n (%)	10 (17)	6 (21)	16 (18)
	Missing†, n (%)	2 (3)	0	2 (2)
Hemoglobin (g/dL)	Median (Min, Max)	8 (6, 11)	10 (7, 13)	9 (6, 13)
	<10 g/dL, n (%)	55 (95)	14 (48)	69 (79)
Platelet (× 10^9/L)	Median (Min, Max)	144 (63, 1114)	224 (86, 673)	164 (63, 1114)
Spleen volume (cc)	Median (Min, Max)	1776 (121, 4763)	2383 (123, 6851)	1861 (121, 6851)
TSS	Median (Min, Max)	20 (1, 62)	15 (2, 61)	20 (1, 62)
Mutation	HMR‡, n (%)	33 (57)	20 (69)	53 (61)
	ASXL1, n (%)	28 (48)	17 (59)	45 (52)
	JAK2 V617F, n (%)	30 (52)	18 (62)	48 (55)
	CALR, n (%)	14 (24)	4 (14)	18 (21)
	MPL, n (%)	4 (7)	3 (10)	7 (8)
	Triple negative, n (%)	8 (14)	4 (14)	12 (14)

- Median treatment duration: 13 months (Min, Max: 0.23, 61)
- 87 patients were enrolled in Arm 2; 58 in the TD and 29 in the non-TD cohorts
- 63% and 29% of patients had disease that was DIPSS intermediate-2 or high, respectively
- Median duration of previous ruxolitinib treatment: 30 months (range: 4–101)

*Two patients discontinued due to PD, and two patients discontinued treatment due to AE; they were later reported to have Grade 5 TEAE (death); †Pending data entry; ‡HMR: High-molecular risk mutations: *ASXL1, EZH2, IDH1/2, SRSF2, U2AF1*.

Arm 2A: TD to TI conversion (primary endpoint)



Arm 2A : TD to TI conversion	
TD to TI conversion	36.8% (14/38)
Median TI duration	37 weeks (range 15–192)
Median time to TI conversion	66 weeks

- An increase in TD to TI conversion rate was observed with longer follow up

The TD to TI conversion (primary endpoint for TD cohort) is defined as the absence of red blood cell transfusions over any 12-week period. Patients evaluable if nonmissing baseline, ongoing and received 12 weeks of treatment or discontinued at any time point. TI duration: Longest duration between transfusions for TI pts; Time to TI conversion: Time to last transfusion prior to conversion for TI pts.

Spleen volume response at Week 24 and best reduction at any timepoint

Spleen Volume Reduction at Week 24, by Local Review

- SVR35 was achieved in 17% of patients at Week 24

N=87	
SVR35 at Wk 24	All: 17% (15/86) TD: 16% (9/57) Non-TD: 21% (6/29)
SVR25 at Wk 24	26% (22/86)
Median % SVR	–17%

Best Reduction in Spleen Volume at Any Time, by Local Review

- SVR35 was achieved at any time in 31% of patients

N=87	
SVR35 at any time	31% (27/86)

*Patient converted from TD (transfusion dependent) to TI (transfusion independent) for ≥12 weeks.
Patients are evaluable for SVR35 at Week 24 if they have had Week 24 assessment by the data cutoff date or discontinued without Week 24 assessment at any time. One patient was nonevaluable for SVR35 due to missing baseline. The SVR35 response rate decreased from the previously reported rate at ASH 2021 due to change in the source data of one patient.

Spleen volume reduction over time

Spleen Volume Mean Percentage Change Over Time

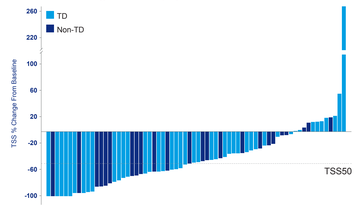
*Kaplan–Meier estimate of duration of splenic response.

N=87	
Median duration of splenic response*	11 months (min, max: 8.4, NA)
Median treatment duration of patients with splenic response at 24 weeks	21 months (min, max: 12, 35)

- Spleen volume reduction was maintained beyond Week 24

Change in total symptom score at Week 24

Change in Total Symptom Score at Week 24



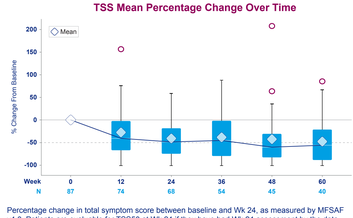
Percentage change in total symptom score between baseline and Wk 24, as measured by MFSAF v4.0. Patients are evaluable for TSS50 at Wk 24 if they have had Wk 24 assessment by the data cutoff date or discontinued without Wk 24 assessment at any time.

N=87	
TSS50 at Wk 24	All: 38% (32/85) TD: 37% (21/57) Non-TD: 39% (11/28)
Median TSS % change	–48%

- Symptom reduction was observed at Week 24

Change in total symptom score over time

TSS Mean Percentage Change Over Time



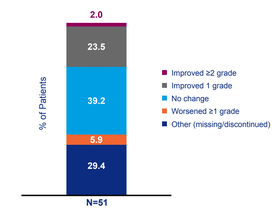
Percentage change in total symptom score between baseline and Wk 24, as measured by MFSAF v4.0. Patients are evaluable for TSS50 at Wk 24 if they have had Wk 24 assessment by the data cutoff date or discontinued without Wk 24 assessment at any time.

TSS50	
Week 24	38% (32/85)
Week 48	33% (28/85)
Week 60	26% (22/84)
At any time	55% (47/85)

- Patients had durable symptom responses over 60 weeks

Change in bone marrow fibrosis grade at Week 24

Change in Bone Marrow Fibrosis Grade at Week 24, by Central Pathology Review



- 26% (13/51) of patients showed ≥1 grade improvement at Week 24
  - This improvement was maintained in 54% of (7/13) patients at the next available assessment or longer
- 35% (18/51) of patients showed ≥1 grade improvement at any time

Patients evaluable if nonmissing baseline or discontinued without Week 24 bone marrow assessment; bone marrow fibrosis grade assessed by three independent and blinded pathologists per central pathology review, maturing data with central review ongoing.
65% (33/51) of patients had Grade 3 bone marrow fibrosis at baseline; 11% (2/18) of patients with Grade 1/2 bone marrow fibrosis at baseline had worsening.

Summary of adverse events

Treatment-Emergent Adverse Events of All Grades That Occurred in ≥20% of Patients		All Grade N=85* n (%)	Grade 3 N=85* n (%)	Grade 4 N=85* n (%)
Hematologic Events	Thrombocytopenia†	46 (54%)	22 (26%)	6 (7%)
	Anemia	26 (31%)	18 (21%)	2 (2%)
Nonhematologic Events	**Gastrointestinal Events**			
	Diarrhea	48 (57%)	3 (4%)	0
	Nausea	33 (39%)	2 (2%)	0
	Abdominal pain‡	20 (24%)	3 (4%)	0
	Other Nonhematologic Events			
	Asthenic conditions§	38 (45%)	5 (6%)	0
	Respiratory tract infection¶	33 (39%)	7 (8%)	0
	Cough	24 (28%)	0	0
	Dysgeusia	23 (27%)	0	0
	Appetite decrease	20 (24%)	2 (2%)	0
	Bruising**	18 (21%)	0	0
	Dizziness††	18 (21%)	0	0
	Musculoskeletal pain‡‡	17 (20%)	0	0
	Epistaxis	17 (20%)	2 (2%)	0

*Safety-evaluable population: received at least one dose of the study drug as of the data cut; †Includes TEAE platelet count decrease; ‡Includes TEAE abdominal pain lower and abdominal pain upper; §Include TEAEs of asthenia, fatigue, lethargy and malaise; ¶Includes TEAEs of RTI, lower RTI, bronchitis, tracheitis, sinusitis, rhinitis, nasopharyngitis, pneumonia and COVID-19; **Includes TEAEs of contusion, ecchymosis and increased tendency to bruise; ††Includes TEAEs of balance disorder and vertigo; ‡‡Includes TEAEs of arthralgia and myalgia.

- Serious adverse events reported in ≥2 pts were anemia (7 pts), pneumonia (6 pts) and abdominal pain, noncardiac chest pain, pyelonephritis, urinary tract infection, platelet count decreased, acute kidney injury, respiratory failure and peripheral ischemia (2 pts each)
- Twenty-six pts (30%) reported TEAEs that led to pelabresib discontinuation
- Seven Grade 5 TEAEs were reported:
  - –Acute kidney injury (AKI), intracranial hemorrhage, brain stem hemorrhage (no concurrent thrombocytopenia), disease progression, transformation to AML, congestive heart failure and heart attack
  - –All were assessed by the PI as not related to pelabresib, except AKI

Conclusions

- **In Arm 2 of the MANIFEST study, pelabresib as 'add-on' to ruxolitinib in patients with a suboptimal/lost response to ruxolitinib monotherapy resulted in durable splenic and symptom responses**
- **Clinical efficacy was observed beyond Week 24**
  - **–In Cohort 2A, 36.8% of patients converted from TD to TI**
  - **–SVR35 was achieved by 17% at Week 24, 19% at Week 60 and 31% at any time**
  - **–TSS50 was achieved by 38% at Week 24, 26% at Week 60 and 54% at any time**
- **At Week 24, ≥1 grade improvement in bone marrow fibrosis was reported in 26% of patients; 35% of patients showed ≥1 grade improvement at any time**
- **Safety data were consistent with previous results; no new safety signals were observed with longer follow-up of 11 additional months**
  - **–The most common treatment-emergent adverse events were low grade**
- **MANIFEST-2, a Phase 3 randomized double-blind trial of pelabresib + ruxolitinib vs placebo + ruxolitinib in JAKi treatment-naïve patients with myelofibrosis, has been initiated and is open for enrollment (NCT04603495)[8]**

Additional ASH 2022 MANIFEST abstracts

Pelabresib (CPI-0610) Combined With *Ruxolitinib for JAK Inhibitor Treatment-Naïve Patients With Myelofibrosis: Durability of Response and Safety Beyond Week 24*
— Mascarenhas J, et al. Oral presentation 238, Dec 10, 2:45 pm EST

Clinical Benefit Associated With Biomarker Changes Indicative of Disease Modification in Patients With Myelofibrosis Treated With the BET Inhibitor Pelabresib as Monotherapy or in Combination With Ruxolitinib
— Scandura J, et al. Oral presentation 630, Dec 11, 5:45 pm EST

References

1. Verstovsek S, et al. *Haematologica* 2015;100:479–488; 2. Kleppe M, et al. *Cancer Cell* 2018;33:29–43.e7; 3. Stratton MS, et al. *F1000Res* 2017;6:F1000 Faculty Rev–1015; 4. Ding N, et al. *PNAS* 2015;112:15713–15718; 5. Ceribelli M, et al. *PNAS* 2014; 111:11365–11370; 6. Tefferi A, et al. *J Clin Oncol* 2011;29:573–582; 7. Keller P, et al. *Hemasphere* 2021;5(Suppl 2):515; 8. Clinicaltrials.gov. NCT04603495. Available at: https://clinicaltrials.gov/ct2/show/NCT04603495. Accessed November 10, 2022.

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