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Updated Results From MANIFEST Arm 2: Efficacy and Safety of Pelabresib (CPI-0610) as Add-on to Ruxolitinib in Myelofibrosis

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OBJECTIVE

To present updated updated safety and efficacy results of the investigational drug pelabresib as 'add-on' to ongoing ruxolitinib in patients with suboptimal/lost response to ruxolitinib.

SUMMARY

In Arm 2 of the Phase 2 MANIFEST study, pelabresib as 'add-on' to ruxolitinib in patients with a suboptimal/lost response to ruxolitinib monotherapy resulted in durable and deepening splenic and symptom responses beyond Week 24.

A clinically meaningful anemia improvement and reduced transfusion burden was observed.

No new safety signals were observed with a longer follow-up of 11 additional months. The most common treatment-emergent adverse events were low grade.

References: 1. Mascarenhas J, et al. *Cancer* 2022;128:2717–2727; 2. Mascarenhas J, et al. *J Clin Oncol* 2023:JCO2201972; 3. Harrison CN, et al. *Future Oncol* 2022;18:27:2987–2997; 4. Kleppe M, et al. *Cancer Cell* 2018;33:29–43.e7; 5. Clinicaltrials.gov. NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed May 24, 2023; 6. Clinicaltrials.gov. NCT04603495. Available at: https://clinicaltrials.gov/ct2/show/NCT04603495. Accessed May 24, 2023.

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Abbreviations: *AKI, acute kidney injury;* AML, acute myelogenous leukemia; BET, bromodomain and extraterminal domain; BMF, bone marrow fibrosis; CHR, complete hematologic response; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Hgb, hemoglobin; HU, hydroxyurea; HMR, high-molecular risk; Int, intermediate; JAK, Janus kinase; JAKi, JAK inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; RBC, red blood cell; RTI, respiratory tract infection; SVR, spleen volume reduction; SVR25, ≥25% reduction in spleen volume from baseline; SVR35, ≥35% reduction in spleen volume from baseline; TEAE, treatment-emergent adverse event; TD, transfusion dependent; TI, transfusion independent; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

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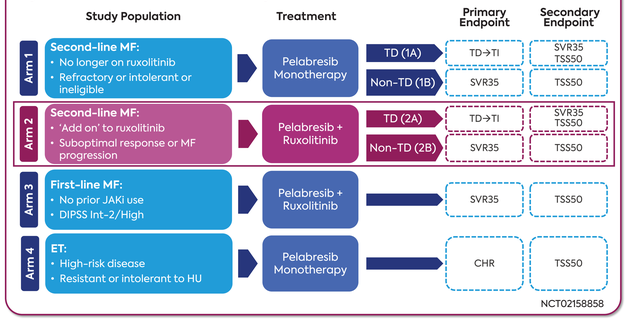
Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

INTRODUCTION

- An unmet need persists with JAKi monotherapy because a substantial proportion of patients discontinue treatment due to progressive disease and treatment-emergent adverse events, such as anemia and thrombocytopenia, and have a poor prognosis[1–3]
- Preclinical data indicated overlapping effects of BET and JAK inhibition in MF[4]
- Pelabresib, a BET inhibitor, downregulates the expression of genes that contribute to the heterogeneous pathology of MF[2]
- The combination of BET and JAK inhibition in patients with MF may represent a potential therapeutic approach to address disease pathology which requires further investigation[2–4]

STUDY DESIGN

Figure 1. MANIFEST: Ongoing, global, open-label Phase 2 study investigating pelabresib in myelofibrosis and essential thrombocythemia



RESULTS

Table 1. 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)

- Median treatment duration: 13 months (Min, Max: 0.23, 61)

*Two patients discontinued due to progressive disease, and two patients discontinued treatment due to an AE; they were later reported to have Grade 5 TEAE (death); †Pending data entry.

Table 2. Patient demographics and baseline characteristics

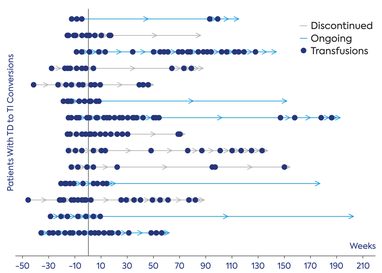
		TD n=58	Non-TD n=29	Overall N=87
Age (years)	Mean (SD)	70 (9)	63 (8)	68 (9)
Gender	Male, n (%)	40 (69)	16 (55)	56 (64)
DIPSS	Int-1, n (%)	0	7 (24)	7 (8)
	Int-2, n (%)	39 (67)	16 (55)	55 (63)
	High, n (%)	19 (33)	6 (21)	25 (29)
MF subtype	Primary MF, n (%)	41 (71)	16 (55)	57 (66)
	Post-PV MF, n (%)	5 (9)	7 (24)	12 (14)
	Post-ET 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)	2393 (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 duration of previous ruxolitinib treatment: 30 months (range 4–101)

*Pending data entry; †HMR mutations: *ASXL1, EZH2, IDH1/2, SRSF2, U2AF1.*

Data cutoff 29 July 2022

Figure 1. TD to TI conversion

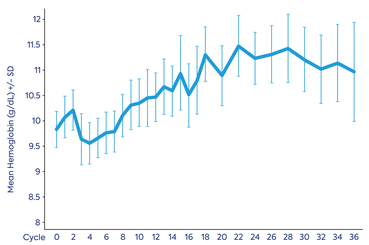


TD to TI conversion	
TD to TI conversion	36.8% (14/38)
Median TI duration	37 weeks (range 15–192)
Median time to TI conversion	66 weeks

Conversion from TD to TI was reported in 36.8% of patients

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 were 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 patients; time to TI conversion: time to last transfusion prior to conversion for TI patients.

Figure 2: Hemoglobin improvement over time



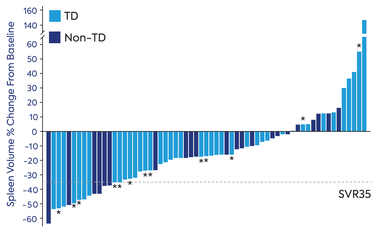
Non-TD	Hemoglobin Response*
Response Rate	24% (7/29)
Time to Response	55 wks (range 4–149)
Duration of Response	24 wks (range 12–108)

- 50% (31/62) of patients had at least 50% reduction in transfusion burden†

Hemoglobin response was observed in 24% (7/29) of non-TD patients

*Hemoglobin response is defined as the proportion of patients who enrolled as non-TD and achieved ≥1.5 g/dL Hgb increase from baseline over any consecutive 12-week period in the absence of RBC transfusions. †Defined as a reduction of ≥50% from baseline in the number of units of RBC transfusion during any 12-wk period post baseline. Patients are evaluable if receiving ≥4 RBC transfusion units at baseline.

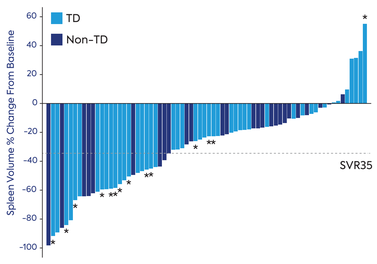
Figure 3. Spleen volume reduction at Week 24, by local review



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 at Wk 24	–17%

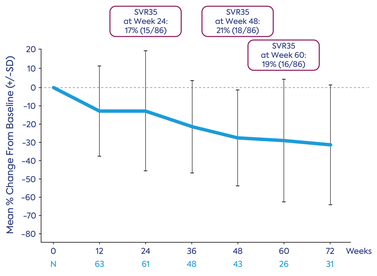
*Patient converted from TD to TI for ≥12 weeks. Patients are evaluable for SVR35 at Wk 24 if they have had a Wk 24 assessment by the data cutoff date or discontinued without a Wk 24 assessment at any time. One patient was nonevaluable for SVR35 due to missing baseline. The SVR35 response rate decreased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

Figure 4. Best reduction in spleen volume at any time, by local review



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

Figure 5. Spleen volume mean percentage change over time

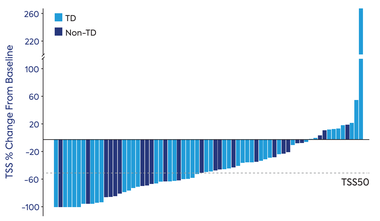


N=87	
Median duration of splenic response*	11 months (min, max: 8.4, NA)
Median treatment duration of patients with splenic response at 24 weeks	21 months (min, max: 12, 35)

*Kaplan–Meier estimate of duration of splenic response.

SVR35 response was observed in 17% (15/86) of patients at Week 24, 21% (18/86) at Week 48 and 19% (16/86) at Week 60

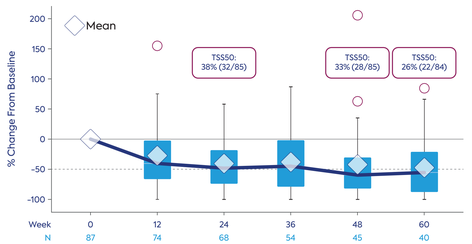
Figure 6. Total symptom score at Week 24



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

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 a Wk 24 assessment by the data cutoff date or discontinued without a Wk 24 assessment at any time.

Figure 7. TSS mean percentage change over time

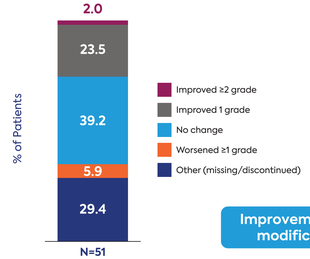


TSS50	
At any time	55% (47/85)

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 a Wk 24 assessment by the data cutoff date or discontinued without a Wk 24 assessment at any time.

TSS50 occurred in 38% (32/85) of patients at Week 24, 33% (28/85) at Week 48 and 26% (22/84) at Week 60

Figure 8. Change in bone marrow fibrosis grade at Week 24, by central pathology review



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

Improvement in BM fibrosis, as a marker of disease modification, was observed in 35% of patients

Patients were evaluable if nonmissing baseline or discontinued without a Week 24 bone marrow assessment; bone marrow fibrosis grade was 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.

Table 3. Treatment-emergent adverse events

TEAEs of all grades that occurred in ≥20% of patients		All Grade N=87* n (%)	Grade 3 N=87* n (%)	Grade 4 N=87* n (%)
Hematologic Events	Thrombocytopenia†	46 (54%)	22 (26%)	6 (7%)
	Anemia	26 (30%)	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 ≥3 pts were anemia (7 pts), pneumonia (6 pts) and abdominal pain, noncardiac chest pain, pyelonephritis, urinary tract infection, platelet count decreased, AKI, 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:

- 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