CPI-0610, a Bromodomain and Extraterminal Domain Protein (BET) Inhibitor, As Monotherapy in Advanced Myelofibrosis Patients Refractory/Intolerant to JAK Inhibitor: Update from Phase 2 MANIFEST Study

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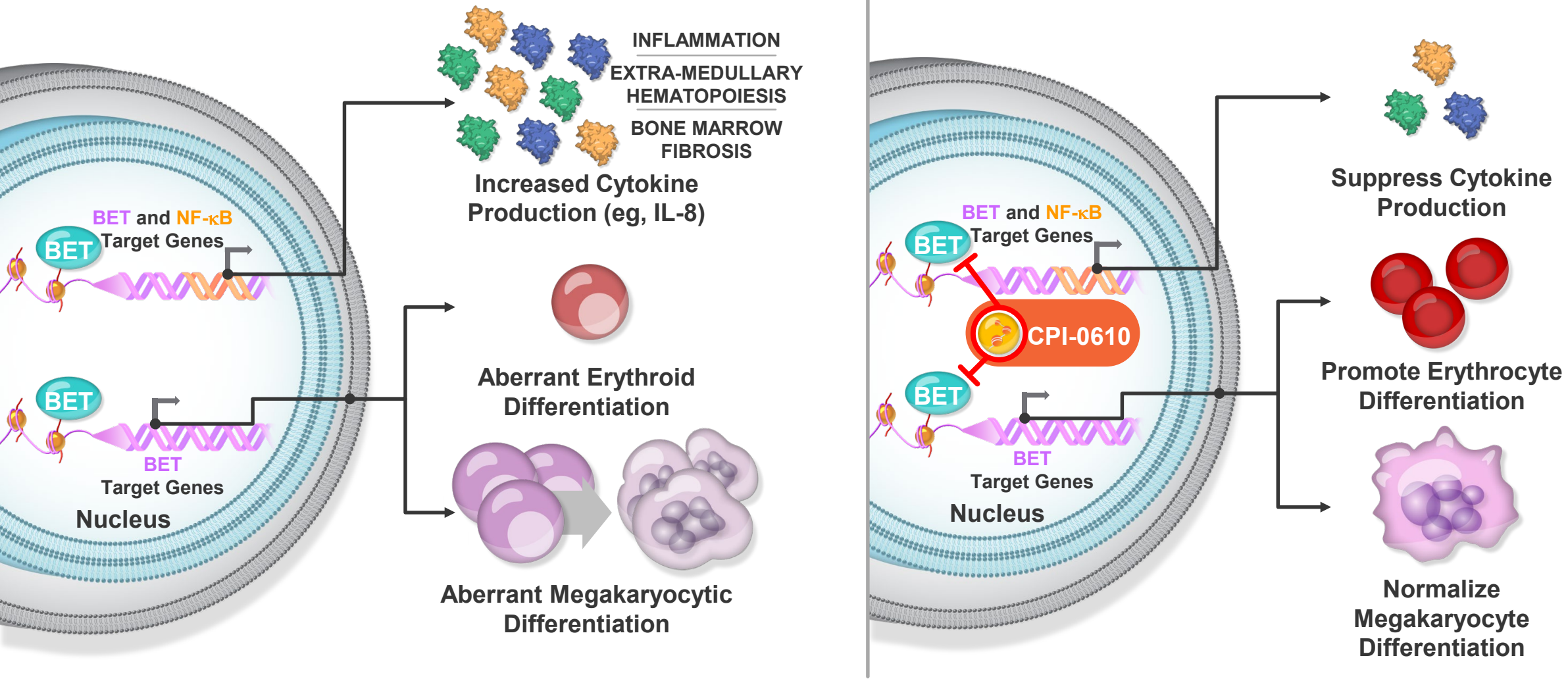
BET Inhibitor CPI-0610 in Myelofibrosis



MANIFEST Arm 1: CPI-0610 monotherapy in patients resistant/refractory, intolerant to ruxolitinib or ineligible for JAKi

Study Population

- No longer on ruxolitinib
- Refractory/ intolerant to ruxolitinib or ineligible for JAKi
- DIPSS Int-2 or higher[1]
- Platelet count ≥ 75 x 10^9/L
- TD cohort: ≥2 units of RBC transfusions/mo for 12 wks
- Non-TD cohort must have baseline spleen size of >450 cm^3

Arm/Cohort

Transfusion Dependent (TD) (Cohort 1A)

Non-transfusion Dependent (Non-TD) (Cohort 1B)

	TD Cohort (1A)	Non-TD Cohort (1B)
Primary Endpoint		
	Conversion from Transfusion Dependent (TD) to Transfusion Independent (TI), defined as absence of RBC transfusions over any consecutive 12-wk period	SVR35: Spleen volume response defined as ≥35% reduction from baseline (MRI or CT) after 24-wk
Key Secondary Endpoints		
	SVR35 TSS50: Total symptom score response defined as ≥50% total symptom score reduction from baseline after 24-wk	TSS50

Study is active and enrollment ongoing. ClinicalTrials.gov Identifier: NCT02158858
DIPSS: Dynamic International Prognostic Scoring System
[1]Patients with DIPSS Int-1 were allowed to enroll prior to the protocol amendment
Data presented per the data cut off 29 Sep 2020

Patient disposition

	TD	Non-TD	Overall
Enrolled (n)	19	27	46
Ongoing [n (%)]	9 (47)	14 (52)	23 (50)
Discontinued [n (%)]	10 (53)	13 (48)	23 (50)
Reason for treatment discontinuation [n (%)]			
Progressive disease	5 (26)	2 (7)	7 (15)
AE or lab abnormality	1 (5)	1 (4)	2 (4)
Withdrew consent	2 (11)	2 (7)	4 (9)
PI decision	1 (5)	6 (22)	7 (15)
Alternate therapy	1 (5)	1 (4)	2 (4)
Eligible for stem cell transplant	0 (0)	1 (4)	1 (2)
Treatment duration as of 29 Sep 2020 (wk)			
Median (min, max)	32 (5, 78)	51 (2, 147)	49 (2, 147)

Baseline demographics and disease characteristics

		TD	Non-TD	Overall
		N=19	N=27	N=46
Age (years)	Mean (SD)	71 (8)	68 (9)	70 (9)
Gender	Male, n (%)	12 (63)	14 (52)	26 (57)
DIPSS	Int-1, n (%)	1 (5)	7 (26)	8 (17)
	Int-2, n (%)	13 (68)	13 (48)	26 (57)
	High, n (%)	5 (26)	7 (26)	12 (26)
MF subtype	Primary MF, n (%)	11 (58)	19 (70)	30 (65)
	Post PV MF, n (%)	4 (21)	4 (15)	8 (17)
	Post ET MF, n (%)	3 (16)	2 (7)	5 (11)
	Missing, n (%)	1 (5)	2 (7)	3 (7)
Prior JAKi therapy[1]	≥6 months, n (%)	6 (32)	21 (78)	27 (59)
	<6 months, n (%)	7 (37)	3 (11)	10 (22)
	Ruxolitinib naïve, n (%)	4 (21)	3 (11)	7 (15)
	Missing[2], n (%)	2 (11)	0 (0)	2 (4)
Prior lines of therapy	Median (Min-Max)	2 (1-6)	2 (1-5)	2 (1-6)
Mutations	≥3 mutations[3], n (%)	11 (58)	12 (44)	23 (50)
	HMR[4], n (%)	11 (58)	14 (52)	25 (54)
	ASXL1, n (%)	8 (42)	13 (48)	21 (46)
	JAK2 V617F, n (%)	13 (68)	17 (63)	30 (65)
Hemoglobin (g/dL)	Median (Min-Max)	8.5 (6.1, 10.3)	9.5 (7.6, 15.3)	8.9 (6.1, 15.3)
	<10 g/dL, n (%)	18 (95)	17 (63)	35 (76)
Platelet ($x10^9$/L)	Median (Min-Max)	175 (88, 1262)	186 (68, 895)	181 (68, 1262)
Spleen volume (cc)	Median (Min-Max)	1389 (281, 8352)	2267 (635, 9155)	2046 (281, 9155)
TSS	Median (Min-Max)	16 (1, 56)	26 (8, 50)	21 (1, 56)

[1]All prior JAKi therapy include ruxolitinib

[2] Data entry pending

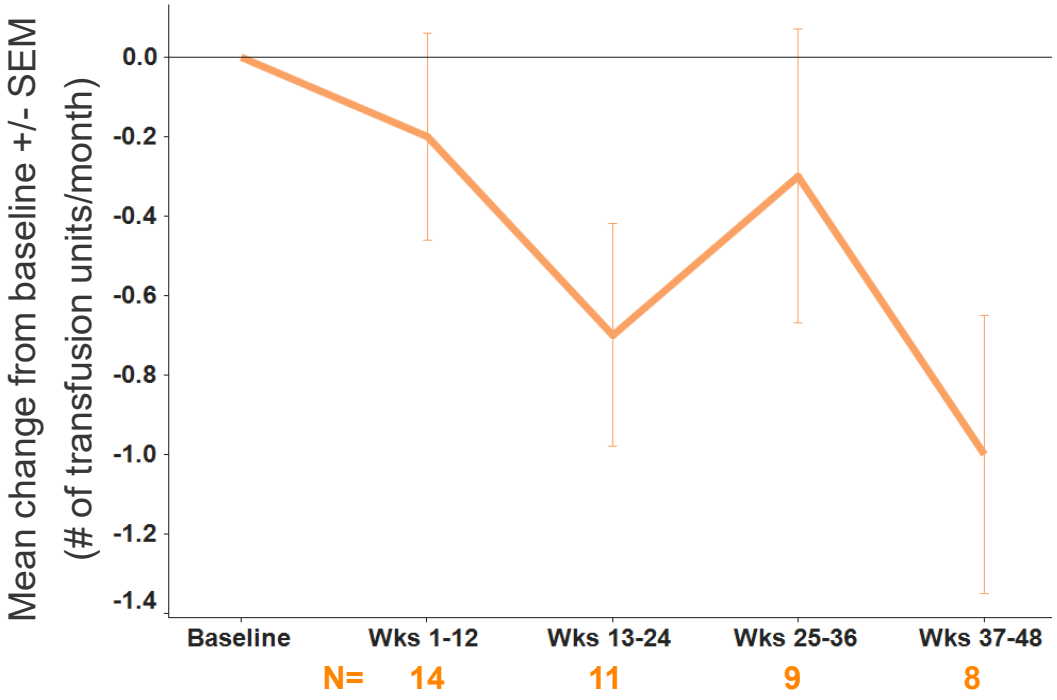
[3]Mutations: *ASXL1, CALR, CBL, CUX1, DNMT3A, EED, ETV6, EZH2, GATA2, GNAS, IDH1/2, JAK2, KRAS, MPL, NRAS, PHF6, PTPN11, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, ZRSR2*

[4]HMR: High molecular risk mutations; *ASXL1, EZH2, IDH1/2, SRSF2, U2AF1*

CPI-0610 monotherapy Transfusion Dependent (TD) cohort primary endpoint: 21% of patients converted to Transfusion Independence (TI)

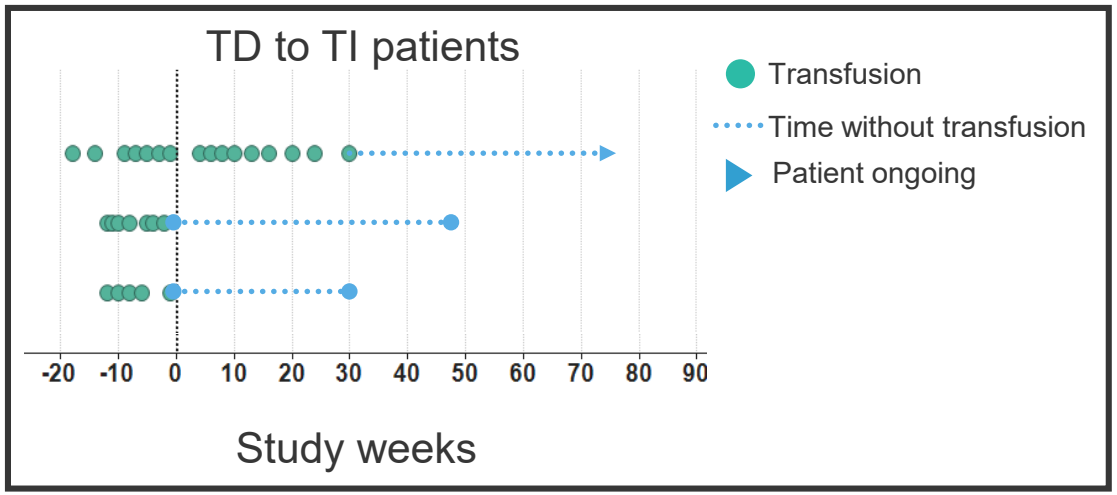
- 57% (8/14) of patients had ≥30% reduction in transfusion intensity

Change in Transfusion Intensity Over Time



TD Cohort Primary Endpoint	
TD to TI conversion	21% (3/14)
Median duration of TI*	32 wk (range 20, 38)

*Transfusion-free duration after 12 weeks conversion time

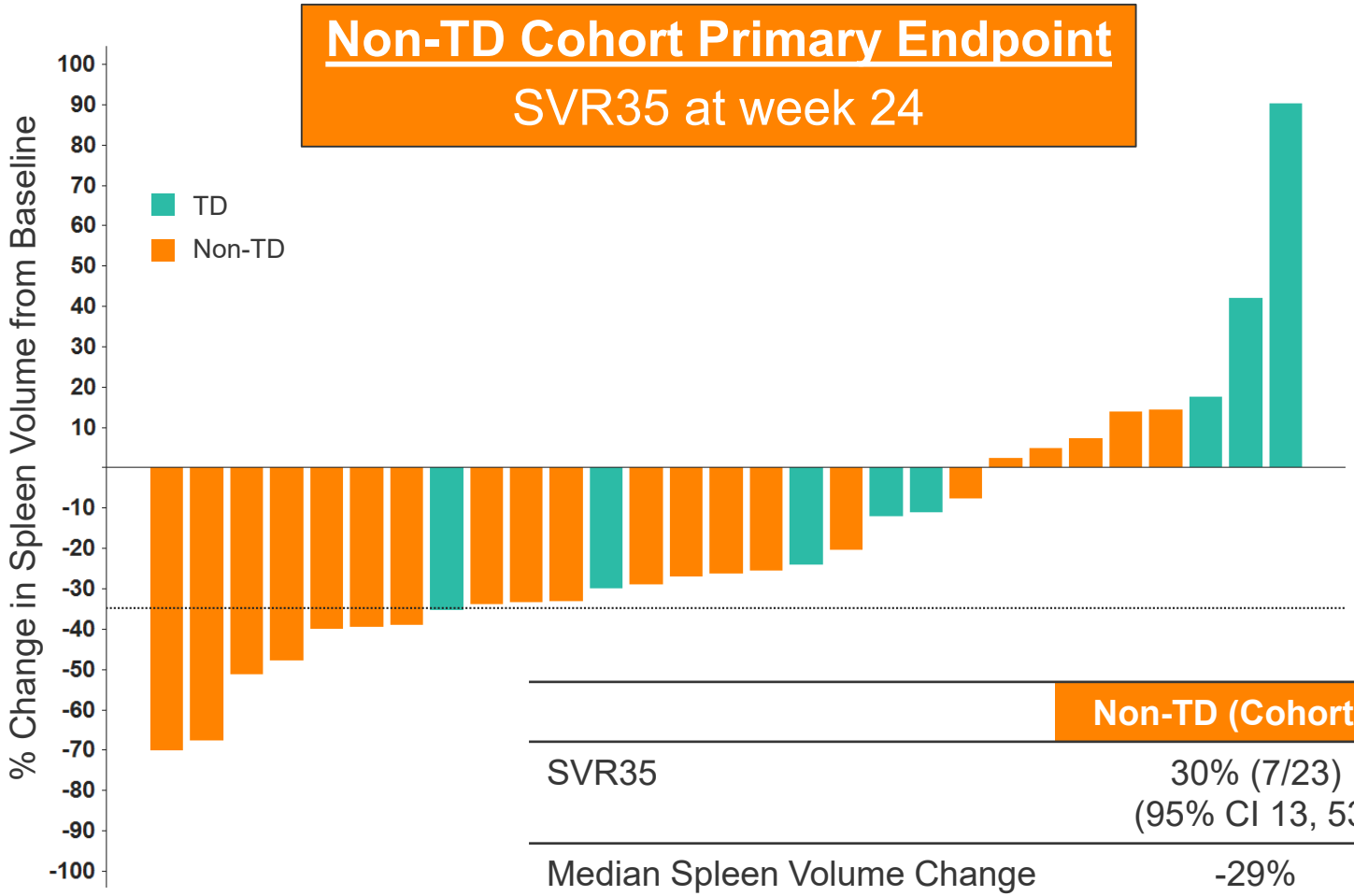


Baseline transfusion intensity= Average # of transfusion units per month (4 weeks) during 16 weeks prior to study entry

Post-baseline transfusion intensity= Average # of transfusion units per month (4 weeks) during 12 weeks period

Timepoints where N>4

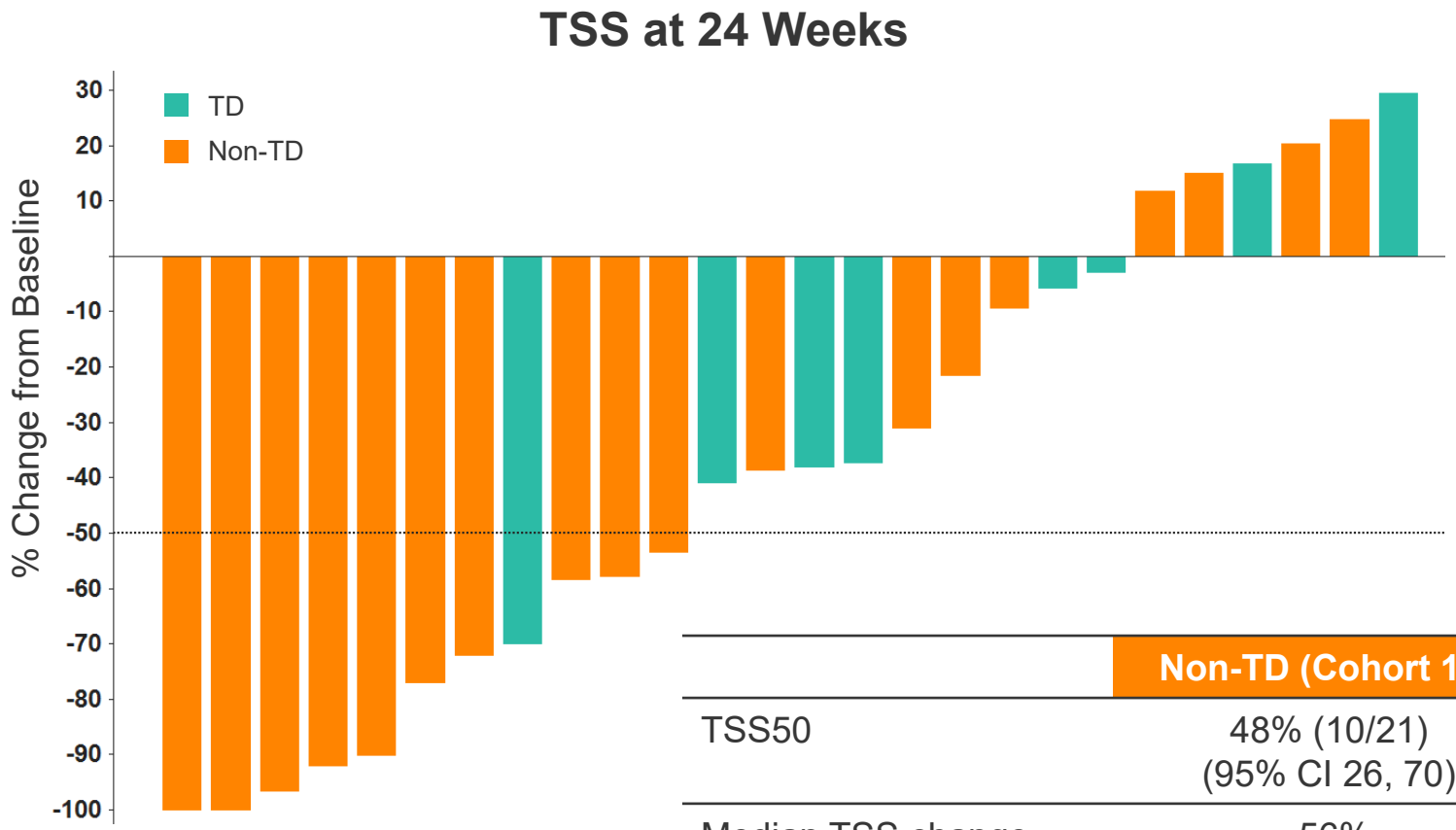
CPI-0610 monotherapy
Non-transfusion dependent cohort primary endpoint: 30% of patients had SVR35 response at week 24



	Non-TD (Cohort 1B)	TD (Cohort 1A)
SVR35	30% (7/23) (95% CI 13, 53)	8% (1/13) (95% CI 0, 36)
Median Spleen Volume Change	-29%	-11%

SVR: Spleen Volume reduction SVR35: ≥35% reduction in spleen volume from baseline
Patients are evaluable for SVR35 at wk 24 if they have had wk 24 assessment by the data cutoff date or discontinued after having had a wk 12 assessment.

CPI-0610 monotherapy
Key secondary endpoint: majority of patients had a reduction of TSS



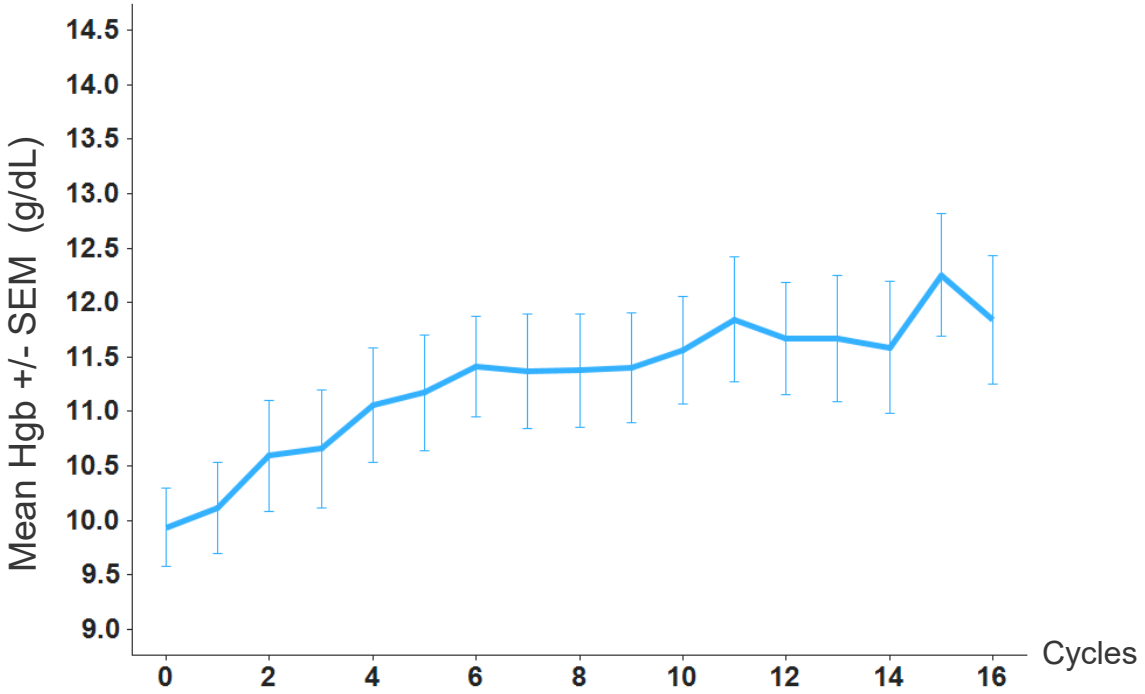
	Non-TD (Cohort 1B)	TD (Cohort 1A)
TSS50	48% (10/21) (95% CI 26, 70)	8% (1/13) (95% CI 0, 36)
Median TSS change	-56%	-22%

TSS: Total symptom score; TSS50: ≥50% reduction in total symptom score from baseline
Patients are evaluable for TSS50 at wk 24 if they have had wk 24 assessment by the data cutoff date or discontinued after having had a wk 12 assessment.

CPI-0610 monotherapy
Majority of patients in the non-TD cohort experienced meaningful improvement in their hemoglobin values

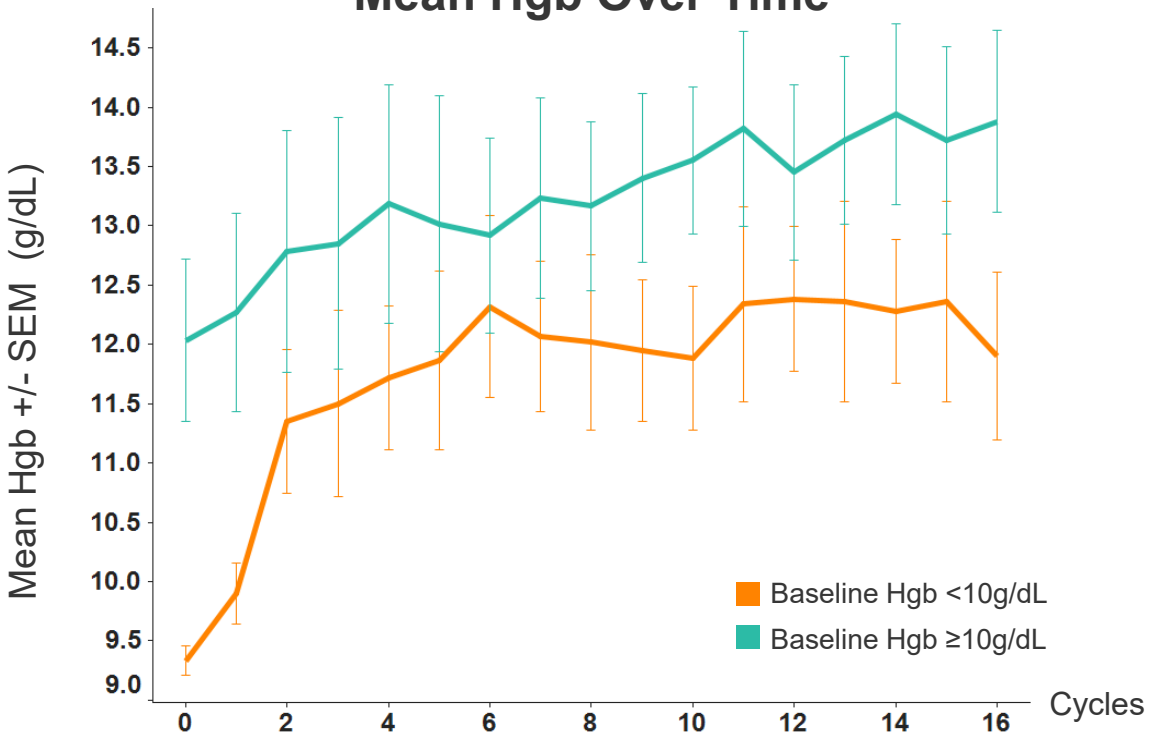
10/20 (50%) evaluable patients[1,2] had 1.5 g/dL Hgb increase without transfusions

All patients[1]
Mean Hgb Over Time



N	22	22	22	22	21	21	21	20	20	20	19	18	19	18	17	16	15

Patients Without Transfusions[1,3]
Mean Hgb Over Time



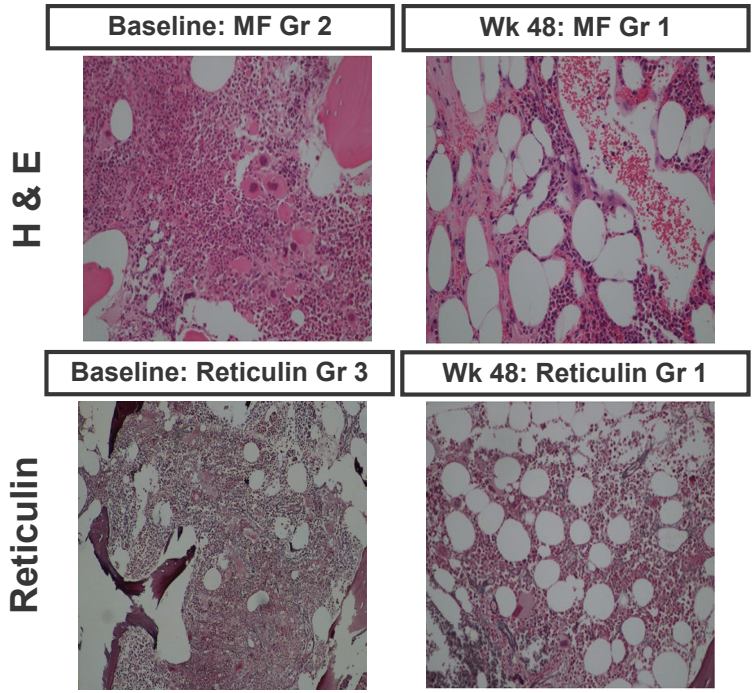
N	6	6	6	6	6	6	6	6	6	6	6	5	6	5	5	5	5
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5	6	5

[1] Patients on treatment ≥ 12 wks
[2] Received no transfusions 12 wks prior to C1D1
[3] Received no transfusions 12 wks prior to C1D1 and during treatment
Hgb: Hemoglobin

CPI-0610 monotherapy
Bone marrow fibrosis grade improvement

- 21% (6/29) of patients had at least one grade improvement in bone marrow fibrosis
- 2 patients had worsening in bone marrow fibrosis

Representative Example of Bone Marrow Biopsy



Assessments of bone marrow grade or reticulin grade per local pathology read.
Gr, grade; H&E, hematoxylin and eosin.

Summary of adverse events

Treatment-Emergent Adverse Events[1]	All Grade N=46[2] n (%)	Grade 3 N=46[2] n (%)	Grade 4 N=46[2] n (%)
Hematological Events			
Thrombocytopenia[3]	14 (30)	7 (15)	0
Anemia	7 (15)	6 (13)	0
Non-hematological Events			
Gastrointestinal Events			
Nausea	18 (39)	0	0
Diarrhea	17 (37)	2 (4)	0
Constipation	10 (22)	1 (2)	0
Other Non-hematological Events			
Dysgeusia	14 (30)	0	0
Asthenic conditions[4]	14 (30)	0	0
Respiratory tract infection[5]	13 (28)	1 (2)	0
Cough	12 (26)	0	0
Weight decreased	10 (22)	1 (2)	0

[1] TEAEs of all grade that occurred in ≥20% of patients and TEAEs of special interest
[2] Safety evaluable population: Received at least one dose of study drug as of the data cut
[3] Includes TEAE platelet count decrease
[4] Include TEAEs of fatigue and malaise
[5] Includes TEAEs of upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, influenza, laryngitis, bronchitis, sinusitis, nasopharyngitis, pneumonia

- CPI-0610 as monotherapy in TD and non-TD cohort patients was generally well tolerated
- 45 pts (98%) reported at least one TEAE; 29 pts (63%) reported at least one ≥ Gr 3 TEAE
- The most common (≥20%) hematologic TEAE was thrombocytopenia
- The most common (≥20%) non-hematologic TEAEs were – nausea, diarrhea, taste changes, asthenic conditions, respiratory tract infections, cough, constipation and weight decreased
- 9 pts (20%) reported TEAEs that lead to CPI-0610 discontinuation
- Other G3/4 TEAEs (≥ 5%) include hyperuricemia (9%), hyperkalemia (7%) and dyspnea (7%).

Conclusions

- CPI-0610 monotherapy demonstrated evidence of clinical activity in heavily pretreated MF population
- SVR35 and TSS50 responses observed in MF patients who are refractory, intolerant or ineligible for ruxolitinib treatment
- Conversions to transfusion independence were observed with CPI-0610 monotherapy
- Improvements observed in hemoglobin levels in patients without any transfusions
- Improvements in bone marrow fibrosis were also observed
- CPI-0610 as monotherapy was generally well tolerated and thrombocytopenia was low grade, manageable, and reversible