A Phase 2 Study of CPI-0610, a Bromodomain and Extraterminal Protein Inhibitor (BETi) alone or with Ruxolitinib (RUX), in Patients with Myelofibrosis (MF)

Abstract #7056

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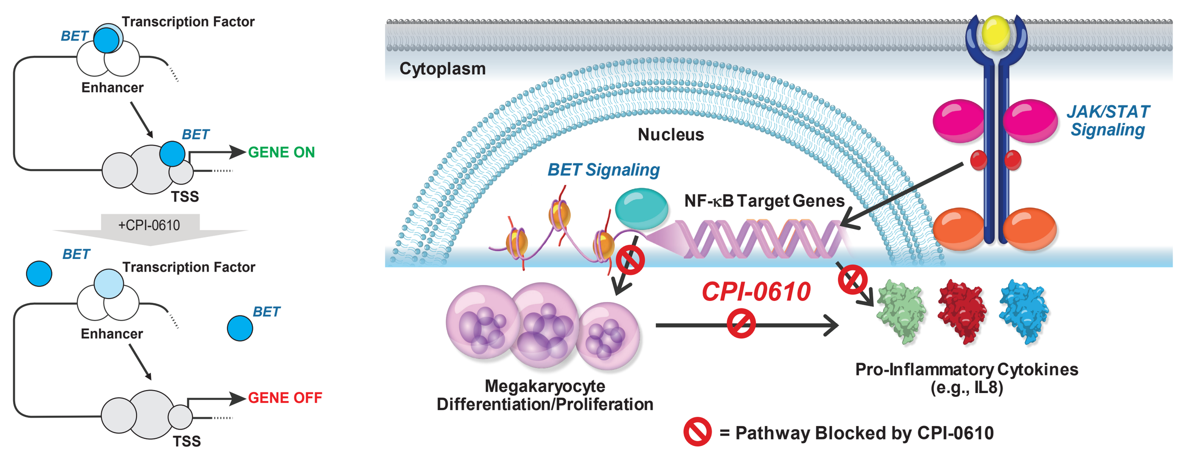
BACKGROUND

- CPI-0610 is an orally available small molecule inhibitor of Bromodomain and Extraterminal (BET) proteins that is potent, selective and potentially best in class[1]
- BET proteins are chromatin adaptor proteins that bind to acetylated lysines on histones and non-histone proteins via their bromodomains (commonly referred to as 'chromatin readers')
- BET proteins function as co-activators of gene expression at transcriptional start sites and gene enhancers
- CPI-0610 displaces BET proteins from target genes and has been shown to reduce gene expression of key oncogenic and immune signaling pathways (i.e., NF-κB target genes, *MYC*, TGF-β target genes) (**Figure 1**)
- Myelofibrosis (MF), an unmet medical need, is characterized by abnormal megakaryocytes and elevated pro-inflammatory cytokines due to dysregulated JAK/STAT and NF-κB signaling. Hallmarks of MF include clonal myeloproliferation, bone marrow fibrosis, anemia, splenomegaly, and constitutional symptoms
- In preclinical studies, BET inhibition has been shown to:
  - Downregulate pro-inflammatory cytokines through its effects on the NF-κB pathway and inhibit megakaryocyte differentiation
  - Combine with ruxolitinib to achieve a synergistic reduction of splenomegaly, BM fibrosis and the mutant allele burden in a mouse MF model[2]
- Phase I experience in lymphoma patients determined the MTD of CPI-0610 is 225 mg, given PO, once daily for 2 weeks on / 1 week off in a 21-day dosing cycle[3]
  - Antitumor activity was observed in different R/R NHL tumor types including ABC-DLBCL, FL among others at doses below the MTD
  - Adverse events included nausea, vomiting, diarrhea, fatigue, and dose-dependent, non-cumulative and reversible thrombocytopenia
  - Rapid suppression of blood *IL8* (an NF-κB target gene) and *CCR1* (a known direct target of BET) expression was observed in patients in a dose-dependent manner at doses below the MTD
- Patients with MF that progress on ruxolitinib treatment have few treatment options and have a poor prognosis, illustrating a significant unmet medical need
- Based on the strong preclinical and clinical rationale, a Phase 2 MANIFEST study of CPI-0610, either alone or in combination with ruxolitinib in MF patients resistant/refractory/intolerant to ruxolitinib, was initiated (ClinicalTrials.gov Identifier: NCT02158858)
- Preliminary clinical data (cut-off date: 17 April 2019) from the Phase 2 MANIFEST study are presented here

Fig 1: BET Proteins: Function and Rationale for CPI-0610, a BET Inhibitor, in MF



STUDY DESIGN OVERVIEW

Study Population	Treatment	Arm/Cohort	1° Endpoint
▪ No longer on ruxolitinib ▪ Refractory, intolerant, or ineligible	CPI-0610 Mono	Cohort 1A: TD n = up to 16	▪ TD → TI
		Cohort 1B: Non-TD n = up to 25	▪ SVR
▪ "Add on" to ruxolitinib ▪ Sub-optimal response or MF progression	CPI-0610 + Ruxolitinib	Cohort 2A: TD n = up to 16	▪ TD → TI
		Cohort 2B: Non-TD n = up to 25	▪ SVR
▪ No prior JAKi ▪ Anemic (Hgb < 10g/dL)	CPI-0610 + Ruxolitinib	Cohort 3: JAKi Naive n = up to 43	▪ SVR

TD = Transfusion Dependent; TI = Transfusion Independent; SVR = Spleen Volume Response
Cohorts 1A/1B and Cohorts 2A/2B will apply a Simon-2 stage design

- Other endpoints include to evaluate changes in patient reported outcomes (PROs), i.e. total symptom score (TSS) per MFSAF v4.0 and PGIC, in response categories per the revised 2013 IWG-MRT response criteria, and in bone marrow morphology
- The starting dose of CPI-0610 is 125 mg, given PO, once daily for 2 weeks on / 1 week off in a 21-day dosing cycle – which is lower than the established MTD
  - Upward titration of CPI-0610 dose up to 225 mg is allowed based on predefined safety parameters
- Key inclusion criteria are:

Key Inclusion Criteria (Cohorts 1 and 2)

- Adult (aged ≥ 18 years)
- Patients with confirmed diagnosis of MF who meet all of the following criteria:
  - DIPSS risk category of intermediate-1 or higher
  - Platelet count ≥ 75 x 10^9/L
  - ANC ≥ 1 x 10^9/L
  - Palpable spleen ≥ 5 cm that is below the costal margin on physical examination for Cohorts 1B and 2B OR RBC transfusion dependent (defined as an average of ≥ 2 units of RBC transfusions per month over the 12 weeks prior to enrollment) for Cohorts 1A and 2A
  - Peripheral blood blast count <10%
  - At least 2 symptoms measurable (score ≥1) using the Myelofibrosis Symptom Assessment Form Version 4.0 (MFSAF v4.0)
- Monotherapy Arm (Arm 1): Previously treated with a JAK inhibitor and be intolerant, resistant, refractory or lost response to the JAK inhibitor; have not received the JAK inhibitor within 4 weeks prior to start of study drug, or are ineligible to be treated with a JAK inhibitor
- Combination Arm (Arm 2): Must have received single-agent ruxolitinib for at least 12 weeks and be on a stable dose for a minimum 8 weeks (prior to start of study drug)
- ECOG performance status ≤ 2
- No prior treatment with a BET inhibitor

Key Inclusion Criteria (Cohort 3)

- Adult (aged ≥ 18 years)
- Patients with confirmed diagnosis of MF who meet all of the following criteria:
  - DIPSS risk category of intermediate-1 or higher
  - Platelet count ≥ 100 x 10^9/L
  - ANC ≥ 1 x 10^9/L
  - Palpable spleen ≥ 5 cm that is below the costal margin on physical examination
  - Anemic, defined as a Hgb < 10g/dL
  - Peripheral blood blast count <10%
  - At least 2 symptoms measurable (score ≥ 3) or a total score of ≥ 10 using the MFSAF v4.0
  - No prior treatment with JAKi allowed
- ECOG performance status ≤ 2
- No prior treatment with a BET inhibitor

- Visit ClinicalTrials.gov Identifier: NCT02158858 for further details on the MANIFEST Phase 2 study

DEMOGRAPHY AND BASELINE

Baseline Demographics & Disease Characteristics

Parameter		Cohort 1A 0610 Mono TD (n=2)	Cohort 1B 0610 Mono Non -TD (n=8)	Cohort 2A 0610 + Rux TD (n=16)	Cohort 2B 0610 + Rux Non -TD (n=15)	Cohort 3 0610 + Rux JAKi Naïve (n=3)	TOTAL (n=44)
Age	Median (range)	68 (67, 69)	70 (46, 80)	72.5 (41, 83)	66 (49, 75)	71 (67, 76)	69 (41, 83)
Sex	Female (n, %)	1 (50.0)	5 (62.5)	6 (37.5)	6 (40.0)	0 (0.0)	18 (40.9)
	Male (n, %)	1 (50.0)	3 (37.5)	10 (62.5)	9 (60.0)	3 (100.0)	26 (59.1)
ECOG	≤1 (n, %)	2 (100.0)	7 (87.5)	14 (87.5)	14 (93.3)	2 (66.7)	39 (88.6)
	2 (n, %)	0 (0.0)	1 (12.5)	1 (6.3)	1 (6.7)	1 (33.3)	4 (9.1)
	Unknown (n, %)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (2.3)
DIPSS	Intermediate 1-2	2 (100.0)	5 (62.5)	13 (81.2)	12 (80.0)	3 (100.0)	35 (79.6)
	High	0 (0.0)	3 (37.5)	3 (18.8)	3 (20.0)	0 (0.0)	9 (20.4)
MF Subtype	Primary MF (n, %)	1 (50.0)	6 (75.0)	10 (62.5)	9 (60.0)	3 (100.0)	29 (65.9)
	Post PV MF (n, %)	0 (0.0)	1 (12.5)	3 (18.8)	3 (20.0)	0 (0.0)	7 (15.9)
	Post ET MF (n, %)	1 (50.0)	0 (0.0)	2 (12.5)	3 (20.0)	0 (0.0)	6 (13.6)
	Unknown (n, %)	0 (0.0)	1 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	2 (4.5)
Mutation Status	n	2	7	16	15	2	42
	≥3 mutations (n, %)	1 (50.0)	3 (42.9)	9 (56.3)	10 (66.7)	1 (50.0)	24 (57.1)
	ASXL1 (n, %)	1 (50.0)	4 (57.1)	8 (50.0)	12 (80.0)	1 (50.0)	26 (61.9)
Prior Ruxolitinib Tx Duration	<6 months	0 (0.0)	1 (12.5)	3 (18.8)	2 (13.3)	0 (0.0)	6 (13.6)
	≥6 months	0 (0.0)	6 (75.0)	12 (75.0)	13 (86.7)	0 (0.0)	31 (70.5)
	Unknown	1 (50.0)	1 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	3 (6.8)
	Not Applicable	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	4 (9.1)
Platelets	Median (range)	292.5 (157, 428)	548.0 (89, 895)	188.5 (77, 631)	224.0 (108, 673)	165 (112, 174)	211.5 (89, 895)
	<450 x 10^9/L	2 (100.0)	3 (37.5)	14 (87.5)	14 (93.3)	3 (100.0)	36 (81.8)
	≥450 x 10^9/L	0 (0.0)	5 (62.5)	2 (12.5)	1 (6.7)	0 (0.0)	8 (18.2)
Hemoglobin	Median (range)	7.55 (7.0, 8.1)	9.25 (7.9, 11.8)	8.35 (6.4, 9.4)	10.3 (8.1, 13.0)	8.7 (7.9, 8.9)	8.9 (6.4, 13.0)
	<10g/dL	2 (100.0)	6 (75.0)	16 (100.0)	6 (40.0)	3 (100.0)	33 (75.0)
	≥10g/dL	0 (0.0)	2 (25.0)	0 (0.0)	9 (60.0)	0 (0.0)	11 (25.0)
Spleen Volume	n	2	8	11	13	3	37
	Median (range)	1514.5 (452, 2577)	2114.5 (635, 3997)	1179.0 (167.9, 4007)	2409.0 (123, 4941)	1810.0 (1379, 2409)	2164.0 (123, 4941)
Total Symptoms Score (TSS)	n	0	6	13	13	3	35
	Median (range)	NA	22.2 (9.2, 42.6)	13.0 (1.4, 37.3)	28.0 (5.0, 56.0)	14.6 (9.1, 16.7)	17.0 (1.4, 56.0)

PV: polycythemia vera; ET: essential thrombocythemia

Baseline Mutation Status

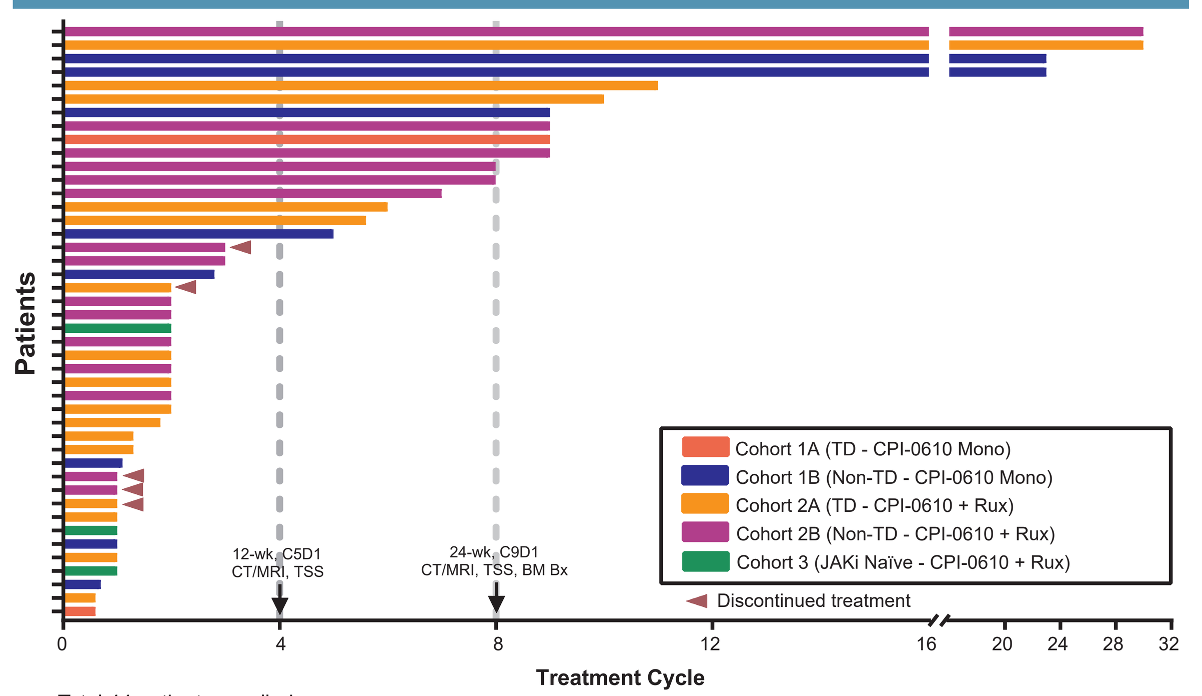
Prevalence (%)

Mutation	High Molecular Risk (HMR) Mutations: ASXL1	EZH2	IDH1/2	SRSF2	U2AF1	HMR	Driver Mutations: CALR	JAK2	MPL	CBL	CUX1	DNMT3A	EED	ETV6	GATA2	GNAS	NRAS	PHF6	PTPN11	SETBP1	SF3B1	TET2	TP53	ZRSR2
Spiegel 2017[4]	33	8	4	7	10		14	79	6	5	1	6		1	1	1	5	3	2	2	13	28	4	2
Pacilli 2018[5]	36.6	8.5	0			42.2	16.9	76	4.2	0	0	0									7	22.5	4.2	11.7
Guglielmelli 2014[6]	25.6	5.5	3.5	9.7		35.3		59.7	6.1															
Vannucchi 2013[7]	21.7	5.1	2.6	8.5			20.3	59.2	5.2	4.4		5.7										9.7		
MANIFEST	**61.9**	**9.5**	**2.4**	**9.5**	**11.9**	**71.4**	**28.6**	**54.8**	**14.3**	**11.9**	**7.1**	**11.9**	**4.8**	**4.8**	**0**	**2.4**	**2.4**	**4.8**	**0**	**4.8**	**4.8**	**19.1**	**0**	**4.8**

- Majority of the patients enrolled are anemic, had large spleen and high symptom burden
- Enrolled patients have high frequency of mutations associated with poor prognosis
  - 71% patients with HMR genomic profile
    - shortened survival
  - 62% patients with *ASXL1* mutations
    - shortened survival, shorter time to ruxolitinib discontinuation
  - 57% of patients have ≥3 mutations in commonly mutated genes
    - shortened survival; significantly lower odds of a spleen response, more aggressive disease, less amenable to treatment with ruxolitinib and shorter time to ruxolitinib discontinuation
  - 1/42 patients is triple negative (*CALR/MPL/JAK2* WT)
    - shortened survival
- Driver mutations observed in MANIFEST study:
  - *JAK2* mutations in 55% of patients
  - *CALR* mutations in 29% of patients
  - *MPL* mutations in 14% of patients

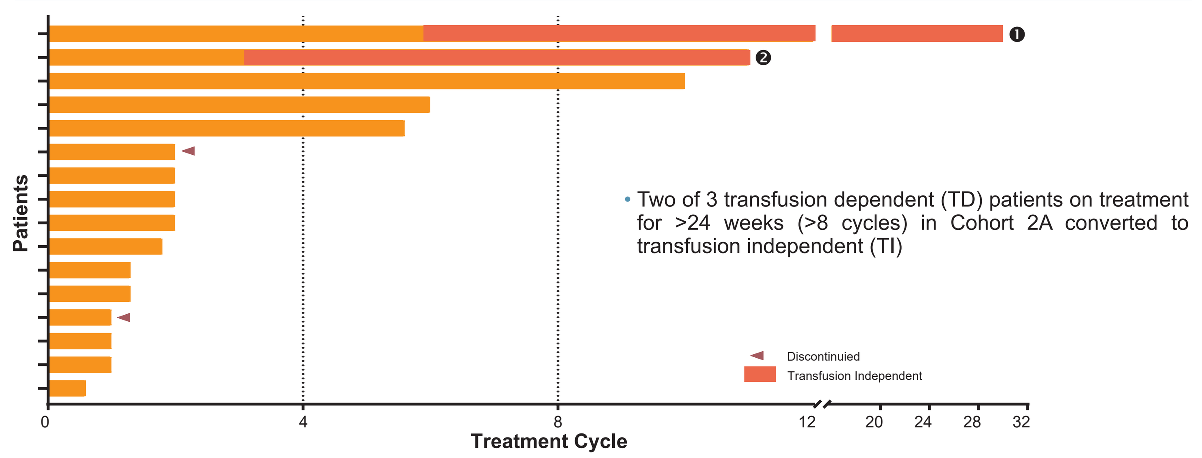
RESULTS

Treatment Duration



- Total 44 patients enrolled
  - 39 patients active on treatment; 5 patients discontinued
- Median duration on treatment (cycles)
  - All cohorts: 2 (range: 1, 30)
  - CPI-0610 monotherapy cohorts: 2 (range: 1, 23)
  - CPI-0610 + ruxolitinib combination therapy cohorts: 2 (range: 1, 30)
- Evaluable patient population
  - Safety: Received C1D1 treatment – n=44
  - SVR: Baseline and one post-baseline data available – n=16 @ 12 weeks; n=12 @ 24 weeks
  - TSS: Baseline TSS data available – n=11 @ 12 weeks
  - Bone marrow morphology: Baseline and one post-baseline data available – n=10 @ 24 weeks
- Reasons for treatment discontinuation
  - Depression Gr 4 and alcohol intoxication Gr 2 – n=1
  - Squamous cell ca Gr 3 (due to prior ruxolitinib therapy) – n=1
  - Acute renal failure Gr 5 (unlikely related) – n=1
  - Diarrhea Gr 2 (withdrew consent) – n=1
  - Diarrhea Gr 2 (pre-existing condition IBD, withdrew consent) – n=1

Two Transfusion Dependent Patients Treated with CPI-0610 Plus Ruxolitinib Converted to Transfusion Independent



- Two of 3 transfusion dependent (TD) patients on treatment for >24 weeks (>8 cycles) in Cohort 2A converted to transfusion independent (TI)

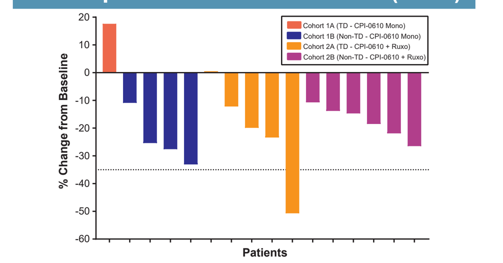
❶ Evidence of Durable Transfusion Independence with CPI-0610 Added to Ruxolitinib

- Patient with *CALR* mutation; transfusion dependent; resistant to ruxolitinib (spleen volume increased while on ruxolitinib); prior treatments include IFN, IMIDs, ESA.
- Patient started on CPI-0610 125 mg OD (upward titration- 175 mg at C6D1 and 200 mg at C26D1) and will continue on ruxolitinib 10 mg BID.
- Patient became transfusion independent, is continuing for >17 months, and no longer anemic (improvement in hemoglobin by ≥1.5 g/dL sustained for ≥12 weeks without any transfusion) - all suggesting a durable effect; improvement on platelets over time despite increase in CPI-0610 dose. The patient also showed improvement in the bone marrow fibrosis, increasing spleen volume reduction observed over time, (best reduction >50%), and resulted to be very much improved in PGIC.
- The patient showed improvement in all hallmarks of MF.

❷ Second Patient Converted to Transfusion Independence with CPI-0610 Added to Ruxolitinib

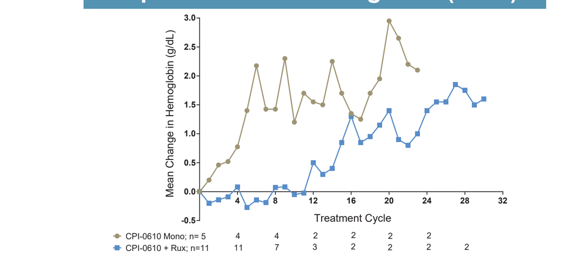
- Patient with *JAK2*, *TET2*, *SRSF2* and *U2AF1* mutations; transfusion dependent; resistant to ruxolitinib (spleen volume increased while on ruxolitinib); prior treatments include IFN and ESA.
- Patient on CPI-0610 125 mg OD and will continue on ruxolitinib 5 mg BID.
- Second patient who became transfusion independent, continuing for >6 months, and improvement in hemoglobin and platelets, all suggesting a durable effect. The patient also showed improvement in the bone marrow fibrosis and spleen volume reduction (best reduction 20%) and 45.5% improvement in TSS and in PGIC.
- The patient showed improvement in all hallmarks of MF.

Best Spleen Volume Reduction (n=16)



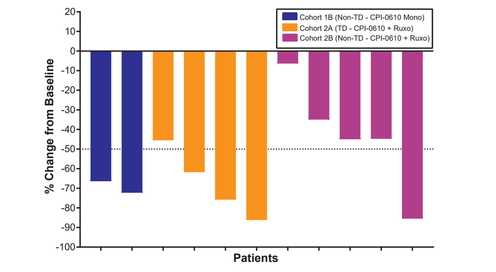
- 14 of 16 evaluable patients had spleen volume reductions from baseline measured by CT or MRI every 12-weeks. Overall, the median best spleen volume change from baseline was -19.2% with one patient achieving SVR >35% from baseline. Of note, reduction in spleen volume is observed in 4 of 4 evaluable non-TD refractory MF patients (depicted in blue) treated with CPI-0610 monotherapy.

Improvement in Hemoglobin (n=16)



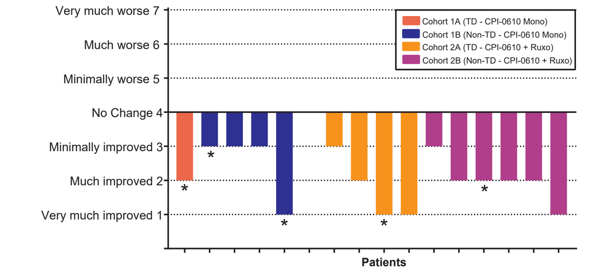
- A mean increase in hemoglobin was observed in CPI-0610 monotherapy patients who received treatment for >12 weeks (n=5). In patients treated with CPI-0610 and ruxolitinib combination (n=11), the observed improvement in hemoglobin is delayed as these patients potentially need to overcome the persistent intracellular effect of ruxolitinib in *JAK2* signaling, a critical component of EPO pathway.

Best Improvement in TSS (n=11)



- 6 of 11 patients on treatment for >12 weeks and evaluable for Myelofibrosis Symptom Assessment Form Version 4.0 (MFSAF v4.0) for TSS showed ≥50% improvement in symptoms. Of note, both non-TD refractory MF patients (depicted in blue) treated with CPI-0610 monotherapy showed TSS responses greater than 50%.

Best Patient Global Impression Change (n=16)



- The majority of patients reported improvement in Patient Global Impression Change (PGIC) score, including the 5 patients for whom TSS could not be evaluated (depicted with *). The data suggest that CPI-0610 monotherapy or in combination with ruxolitinib may have effects on symptom improvement in refractory MF patients.

Bone Marrow Morphology Improvement* (n=10)

Tx Arm / Cohort	Mutation: ≥3	*ASXL1*	HMR	Best % TSS Improve	Best % SVR	Marrow Fibrosis Grading: Baseline	24 Wk	48 Wk	72 Wk	Reticulin Staining Grading: Baseline	24 Wk	48 Wk	72 Wk
CPI-0610 Mono Non-TD 1B		Y	Y	NE	-25.4	3	3	2		3	3	2	
	Y	Y	Y	NE	-10.9	2	1	1		3	1	1	
				-72.3	-33.1	2	2			ND	ND		
CPI-0610 + Rux TD 2A				NE	-50.7	3	ND	2	2	3	ND	2	2
	Y		Y	-45.5	-19.9	2	2			2	1		
	Y	Y	Y	-87.4	-12.2	3	1				ND		
CPI-0610 + Rux Non-TD 2B	Y	Y	Y	-45.0	-14.7	3	3			ND	3		
	Y	Y	Y	-44.8	-21.9	3	2			ND	2		
	Y	Y	Y	-6.4	-13.8	3	3			ND	ND		
		Y	Y	-85.5	-26.5	3	3			ND	ND		

HMR = High Molecular Risk (patients with one of these mutations: *ASXL1, EZH2, IDH1/2, SRSF2* and *U2AF1*);
NE = Not evaluable, no baseline measurement available; ND = No data. * Assessment based on local lab

- 6 of 10 patients evaluable had evidence of morphological improvement in bone marrow fibrosis, 5 patients show improvements in bone marrow fibrosis and 1 additional patient in reticulin staining. Bone marrow effects occurred as early as 24 weeks after initiation of therapy, in both CPI-0610 monotherapy and combination with ruxolitinib, and are associated with improvement in bone marrow functions- suggesting that CPI-0610 may have disease modifying effects in MF.

SAFETY RESULTS

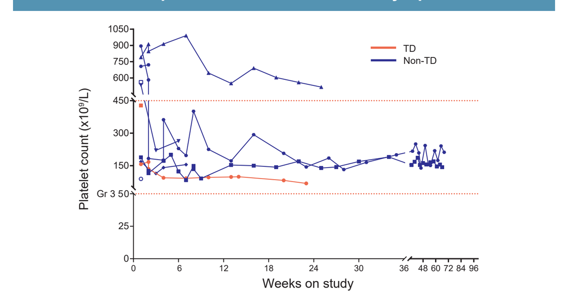
Treatment Emergent Adverse Event (TEAE): Summary of TEAE by ≥10% Frequency and AESI

Treatment Emergent Adverse Event	All Grade n=44 (n, %)	≥3 Grade* n=44 (n, %)
Blood and Lymphatic System Disorders		
Anemia	2 (4.5)	2 (4.5)
Thrombocytopenia	3 (6.8)	2 (4.5)
Neutropenia	1 (2.3)	1 (2.3)
Investigations		
Platelet Count Decreased	3 (6.8)	2 (4.5)
Blood Creatinine Increased	1 (2.3)	1 (2.3)
Gastrointestinal Disorders		
Diarrhea	10 (22.7)	1 (2.3)
Vomiting	6 (13.6)	1 (2.3)
Nausea	4 (9.1)	1 (2.3)
Metabolism and Nutrition Disorders		
Decreased appetite	3 (6.8)	0 (0.0)
Dehydration	1 (2.3)	1 (2.3)
Hyponatremia	1 (2.3)	1 (2.3)
Renal and Urinary Disorders		
Acute Kidney Injury	1 (2.3)	1 (2.3)
Proteinuria	1 (2.3)	1 (2.3)
General Disorders and Administration Site Conditions		
Fatigue	5 (11.4)	1 (2.3)
Infections and Infestations		
Upper respiratory tract infection	6 (13.6)	0 (0.0)
Pneumonia	1 (2.3)	1 (2.3)
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	6 (13.6)	0 (0.0)
Cough	5 (11.4)	0 (0.0)
Skin and Subcutaneous Tissue Disorder		
Pruritis	5 (11.4)	0 (0.0)
Rash	3 (6.8)	0 (0.0)
Psychiatric Disorder		
Depression	0 (0.0)	1 (2.3)
Alcohol Withdrawl Syndrome	1 (2.3)	0 (0.0)
Nervous System Disorders		
Headache	6 (13.6)	0 (0.0)
Dysgeusia	5 (11.4)	0 (0.0)

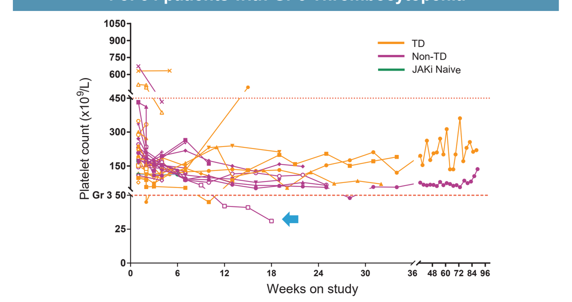
AESI: Adverse Event of Special Interest
*All ≥3 grade TEAEs were observed in patients treated with CPI-0610 + ruxolitinib therapy; no ≥3 grade TEAE was observed with CPI-0610 monotherapy

Effects on Platelet Levels

CPI-0610 Monotherapy (n=10)
No patients with Gr 3 Thrombocytopenia



CPI-0610 + Ruxolitinib (n=34)
4 of 34 patients with Gr 3 Thrombocytopenia



- In advanced MF, thrombocytopenia is a potential concern for both ruxolitinib and BET inhibitors. CPI-0610 monotherapy (left figure) demonstrated minimal non-cumulative and manageable thrombocytopenia. The combination therapy of CPI-0610 and ruxolitinib showed a non-cumulative, manageable and generally reversible asymptomatic Gr 3 thrombocytopenia (right figure). Of the 4 of 34 patients with Gr 3 thrombocytopenia, 3 patients recovered without any CPI-0610 or ruxolitinib dose modification, the 4th patient was on ruxolitinib 25 mg BID and is active on treatment with ruxolitinib dose modification (see ⇨)

OVERALL SUMMARY: CPI-0610 IN MYELOFIBROSIS

- In this preliminary analysis for the Phase 2 MANIFEST study of CPI-0610, a novel oral inhibitor of BET, in resistant/refractory/intolerant MF patients
  - CPI-0610 alone has demonstrated encouraging BET-driven monotherapy activity (Cohort 1)
  - There is potential additive benefit to patients when CPI-0610 is added to ruxolitinib (Cohort 2)
- Across the hallmarks of MF, CPI-0610 monotherapy or in combination with ruxolitinib interim data showed spleen volume reduction, and improvements in patient symptoms, anemia and transfusion dependence as well as bone marrow fibrosis
  - Evidence of durable transfusion independence was demonstrated in two patients
  - The majority of evaluable patients achieved spleen volume reductions
  - The majority of patients demonstrated improvement in symptoms as demonstrated by MFSAF v4.0 (≥50% TSS improvement) and PGIC
  - Bone marrow improvements were observed as early as 6 months
  - Most patients showed increased hemoglobin levels as well as normalization of platelets in thrombocytosis patients, suggesting an improvement in bone marrow function due to improvement in bone marrow fibrosis
- Overall, CPI-0610 monotherapy or in combination with ruxolitinib was generally well tolerated in patients with advanced MF and suggests that the observed thrombocytopenia is non-cumulative and manageable
- Taken together, with the early clinical data in patients with advanced MF and FDA Fast-track designation of CPI-0610, the MANIFEST study warrants further investigation to better characterize the potential efficacy and safety of CPI-0610 in resistant or refractory MF patients as well as in 1L JAKi-naïve patients

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