EHA-1821

CPI-0610, A Bromodomain and Extra-terminal Domain (BET) Inhibitor, Reduces Proinflammatory Cytokines, Bone Marrow Fibrosis and the Number of Transfusions in Myelofibrosis Patients

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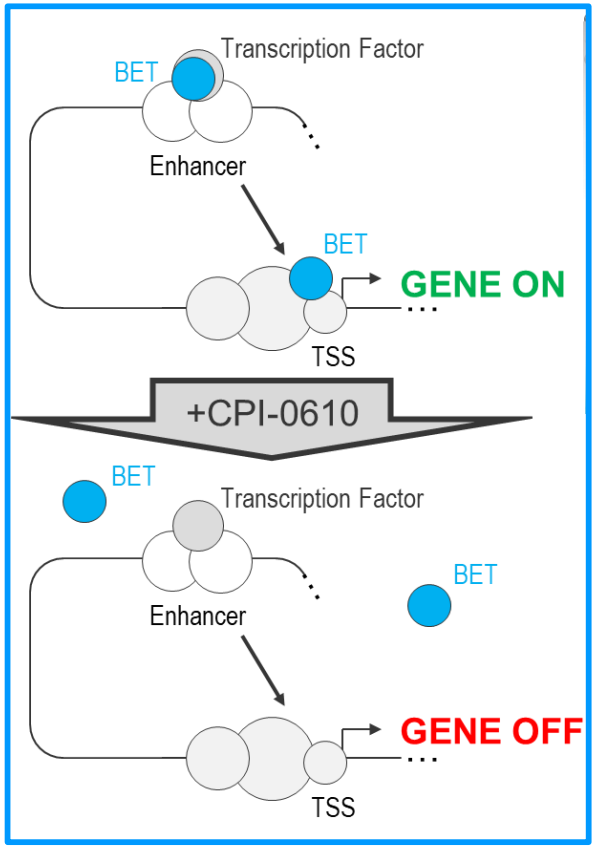
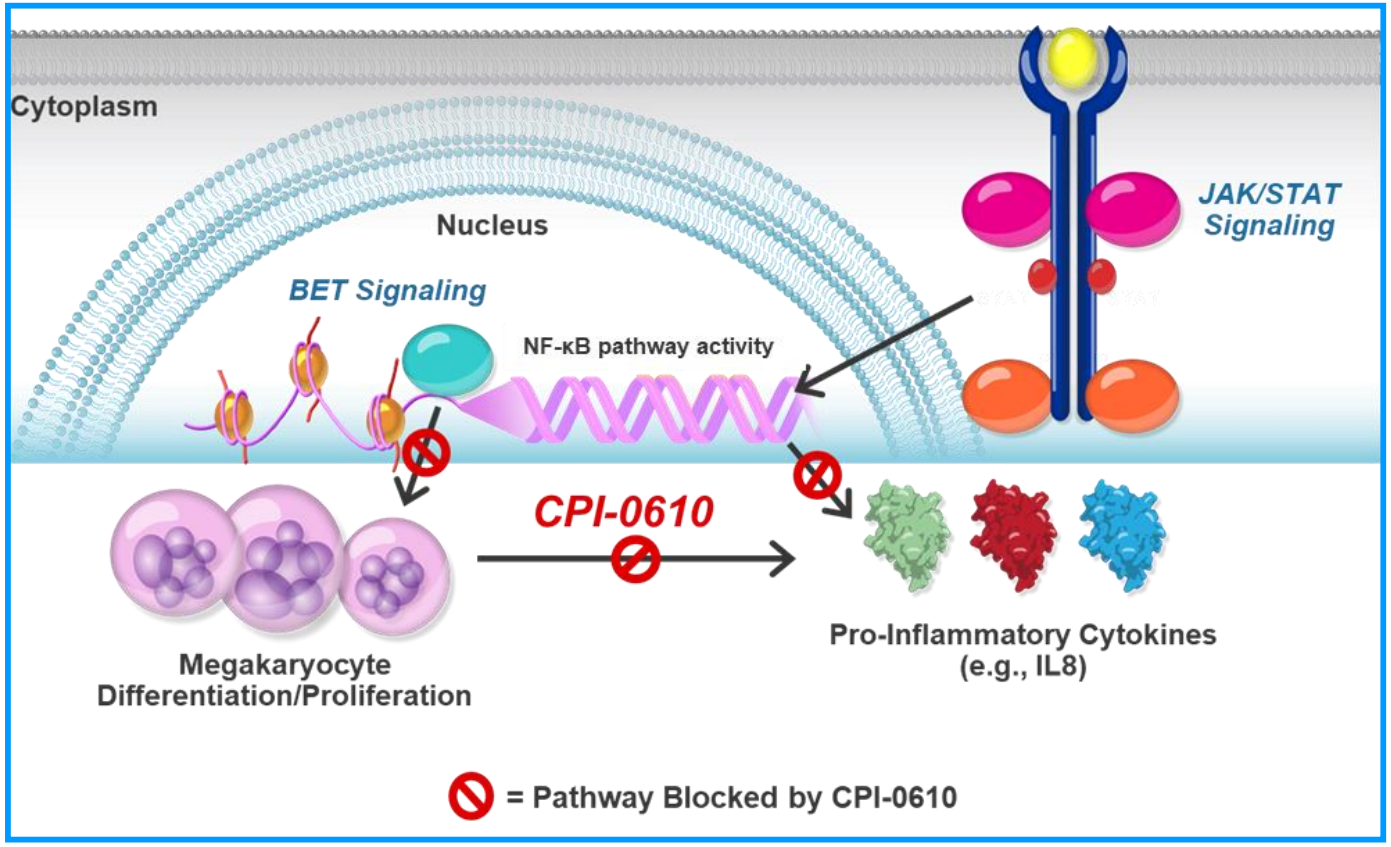
BET Plays an Important Role in Myelofibrosis



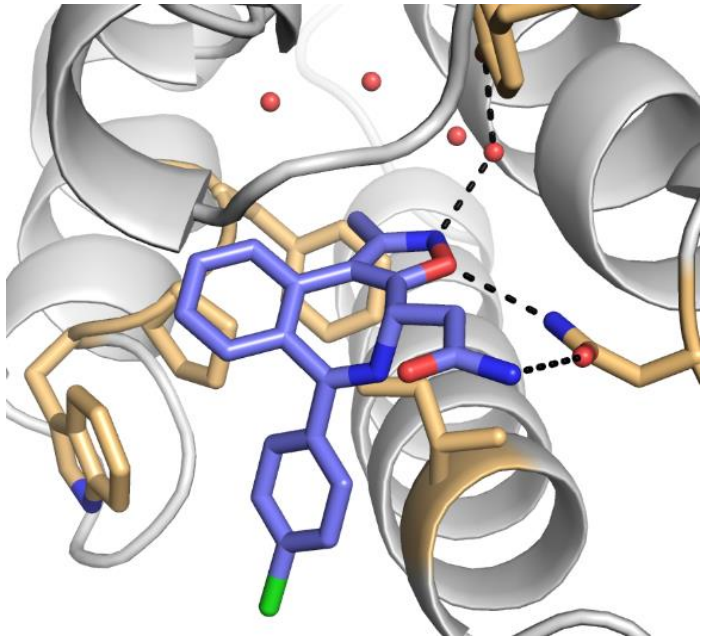


- BET proteins bind to acetylated histone lysine residues and function as co-activators of gene expression
- BET inhibition downregulate pro-inflammatory cytokines and inhibit megakaryocyte differentiation
- Significant combinatorial activity of BET inhibitor + JAK inhibitor ruxolitinib with respect to splenomegaly, bone marrow fibrosis and mutant allele burden[1]

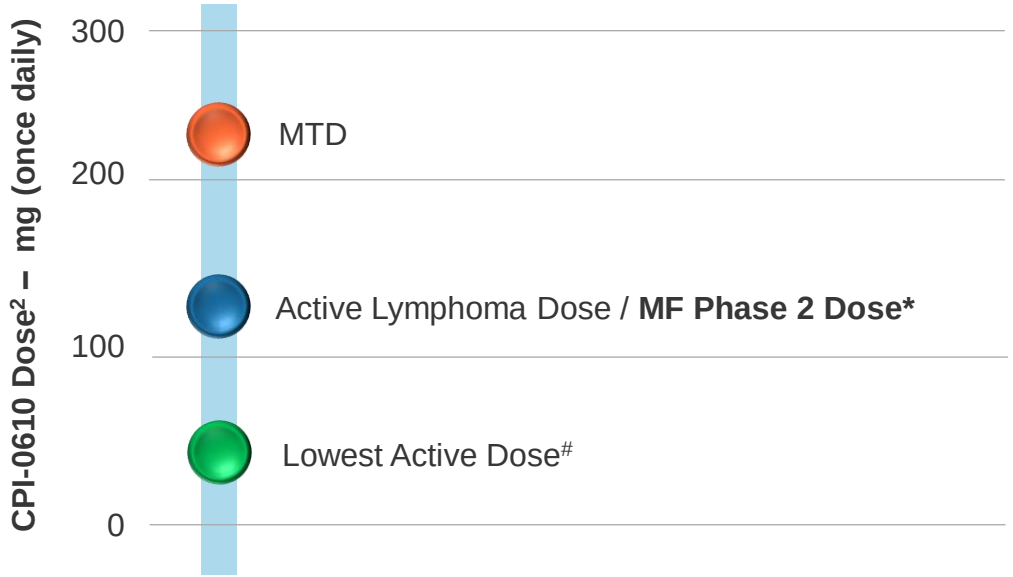
[1] Kleppe M *et al.* Cancer Cell (2018). 33:29-43

CPI-0610 is a Potential Best-in-Class BET Inhibitor

- CPI-0610 is a **potent** and **selective** oral BET inhibitor with favorable pharmaceutical properties[1]
  - Targets only BET family members (BRD2, BRD3, BRD4, BRDT); similar potency for all the tandem bromodomains
  - PK profile allows for once daily dosing

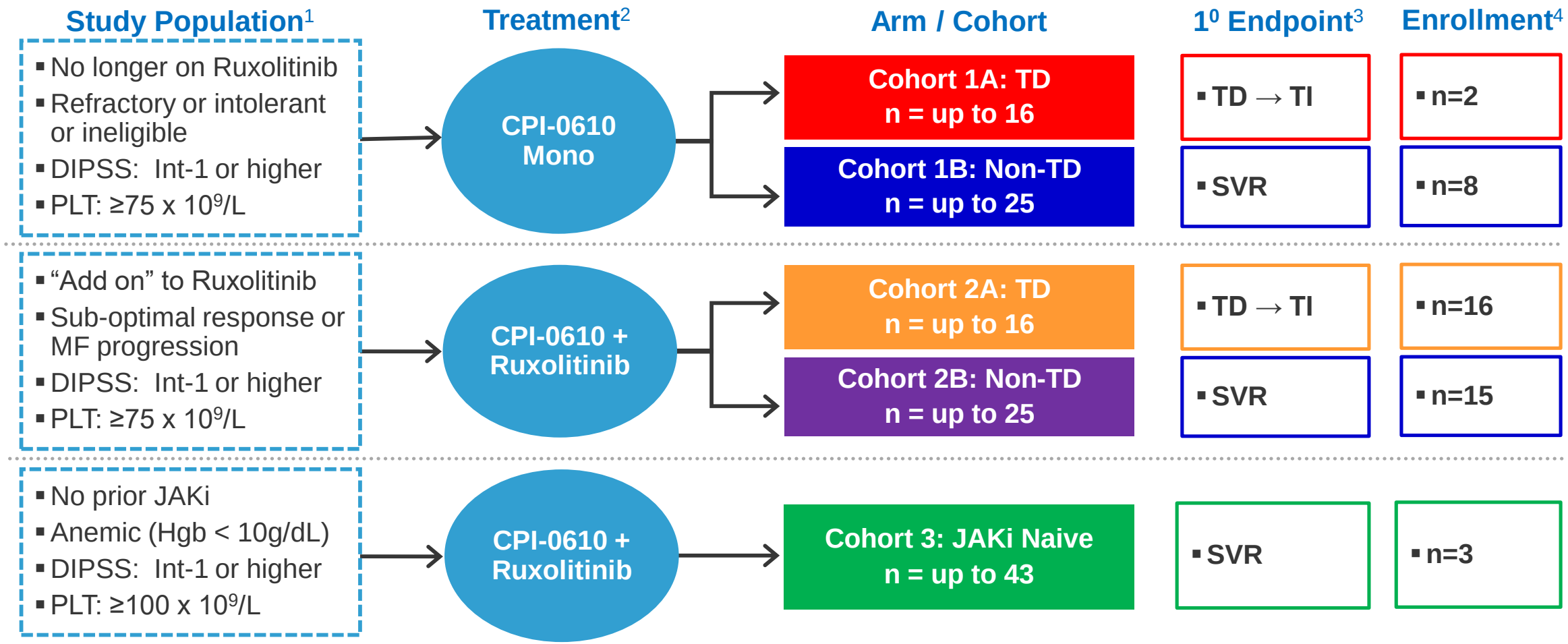


- Preliminary **Clinical Experience** with CPI-0610
  - **138 patients** treated in Phase 1 trials in various hematologic malignancies[1]
  - Safety signals of CPI-0610 potentially differentiates it from other BET inhibitors
    - Phase 1 data suggest that thrombocytopenia (DLT) is **dose dependent, reversible** and **non-cumulative** [1, 2]
    - Preliminary **clinical activity** observed **at range of doses below the MTD** in Phase 1 lymphoma patients[2]



[1] Sims R *et al*. AACR Annual Meeting 2015; April 18-22, 2015; Philadelphia, PA
[2] Blum KA *et al*: Targeted Anticancer Therapies; March 5-7, 2018; Paris, France. Abstract 410
* Starting dose of CPI-0610 at 125 mg provides options for dose titration in MF patients
# CR also achieved at lower dose of 48mg OD capsule

Phase 2 MANIFEST Study: Design Overview



TD = Transfusion Dependent; TI = Transfusion Independent; SVR = Spleen Volume Response

[1] ClinicalTrials.gov Identifier: NCT02158858 for further details on study design and patient population

[2] 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

[3] Additional endpoints include to evaluate changes in patient reported outcomes (PROs), i.e. TSS and PGIC; response per the revised 2013 IWG-MRT response criteria; anemia response; and bone marrow morphology

[4] Enrollment as of 17 April 2019 data cut off

Phase 2 MANIFEST Study: Key Inclusion Criteria

Key Inclusion Criteria[1] (Cohorts 1 and 2)

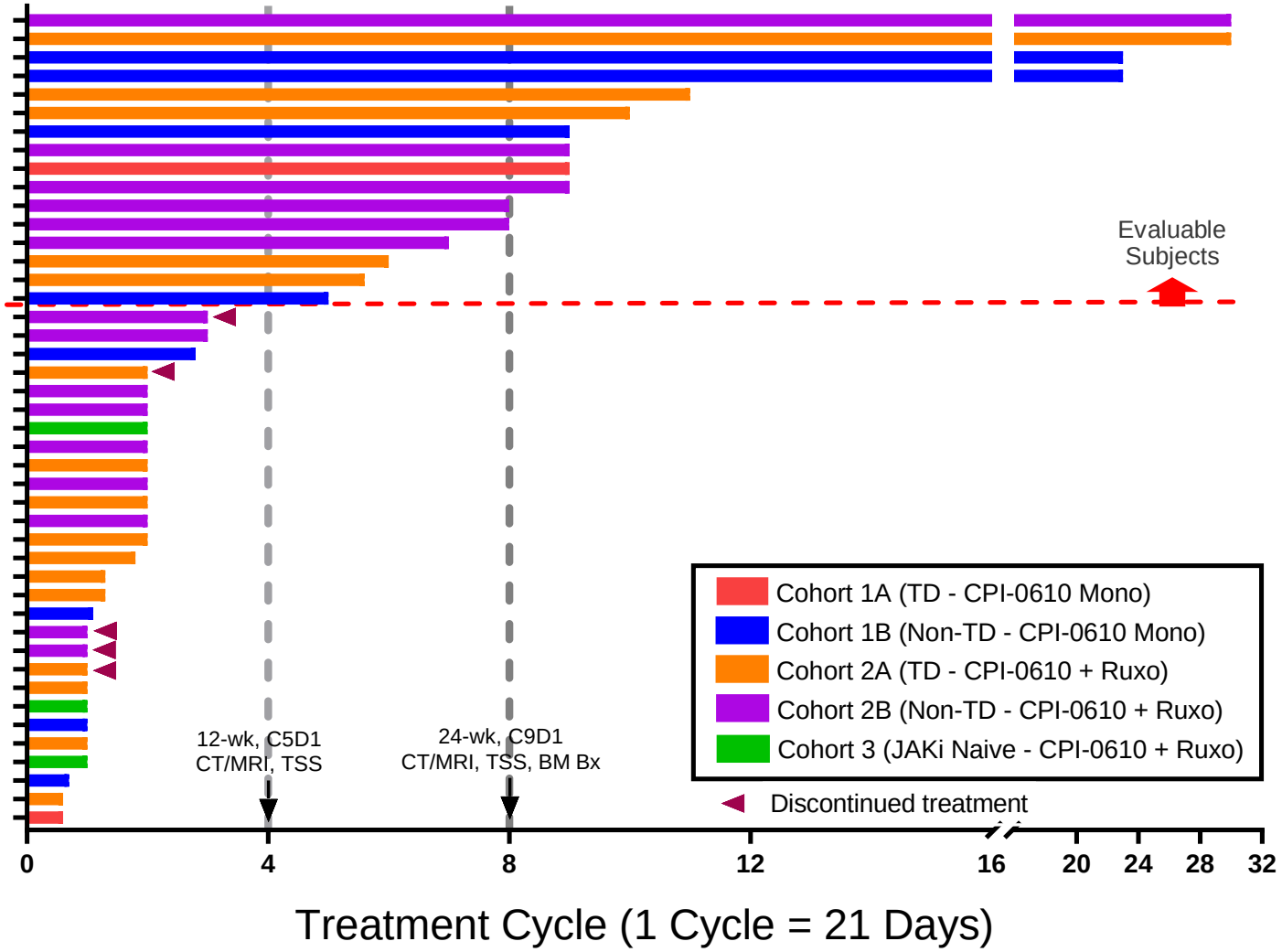
- Adult (aged ≥ 18 years)
- Patients with confirmed diagnosis of MF who meet all of the following criteria:
  - DIPSS risk category of intermediate-1 or higher.
  - **Platelet count ≥ 75 x 10^9/L**
  - ANC ≥ 1 x 10^9/L
  - **Palpable spleen ≥5 cm** that is below the costal margin on physical examination 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[1] (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

[1] ClinicalTrials.gov Identifier: NCT02158858 for further details on study design and patient population

Enrollment Status and Treatment Duration



As of April 17, 2019

- **44** patients **enrolled**
- **No** patient experienced **disease progression**
- First 2 combo patients **>20 months** treatment duration
- First 2 mono patients **>16 months** treatment duration
- **16** patients for at least **12 weeks**
- **12** patients for at least **24 weeks**

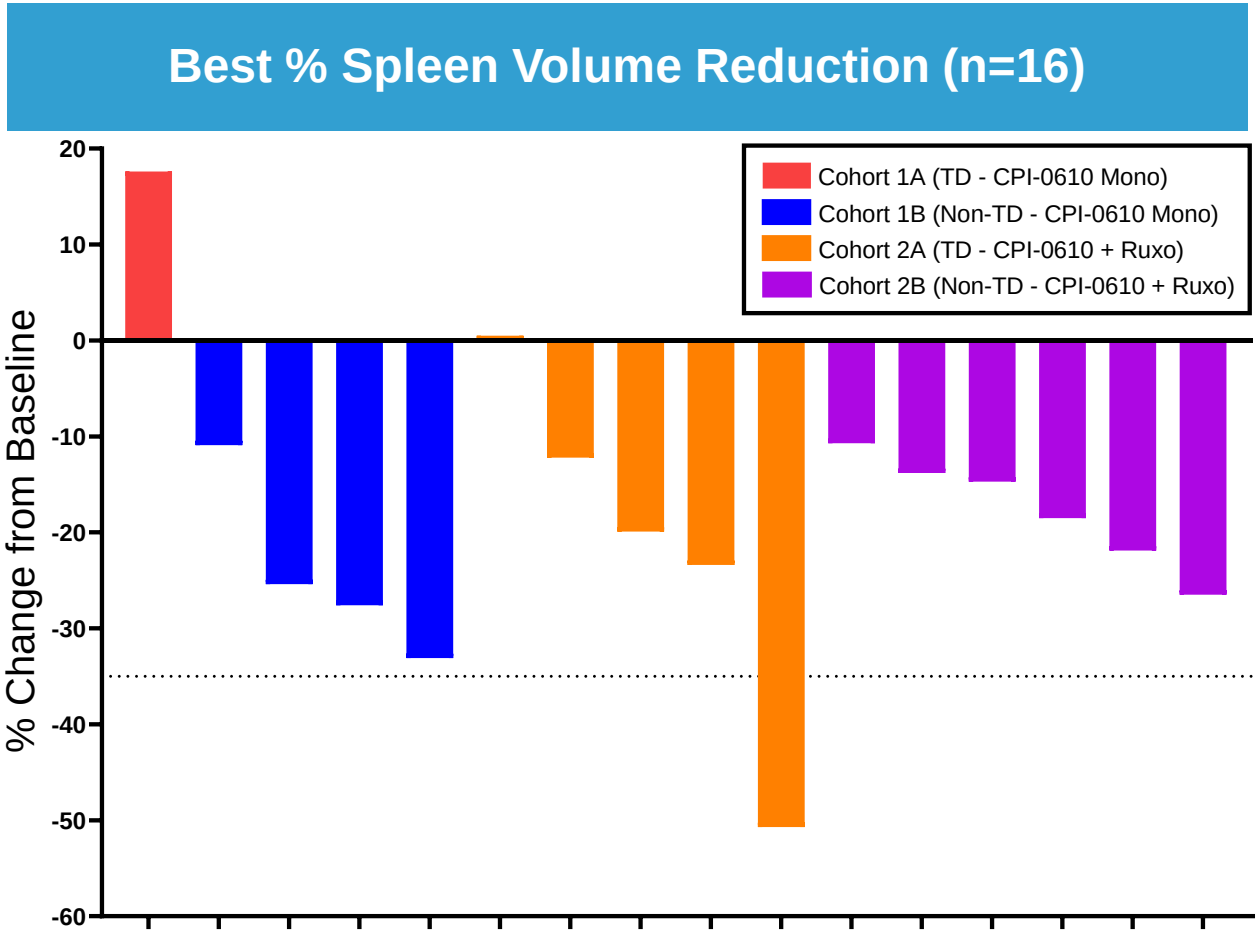
Baseline Demographics and Disease Characteristics

Parameter		TOTAL (n=44)
Age	Median (range)	69 (41, 83)
Sex	F/ M (n, %)	18 (40.9) / 26 (59.1)
ECOG	≤1 / 2 (n, %)	39 (88.6) / 4 (9.1)
DIPSS	Int 1-2 / High (n, %)	35 (79.6) / 9 (20.4)
MF Subtype	Primary MF (n, %)	29 (65.9)
	Post PV MF (n, %)	7 (15.9)
	Post ET MF (n, %)	6 (13.6)
Mutation Status	n	42
	≥3 mutations (n, %)	24 (57.1)
Prior Ruxolitinib Tx Duration	<6 months (n, %)	6 (13.6)
	≥6 months (n, %)	31 (70.5)
Platelet	Median (range)	211.5 (89, 895)
Hemoglobin	Median (range)	8.9 (6.4, 13.0)
	<10g/dL (n, %)	33 (75.0)
	≥10g/dL (n, %)	11 (25.0)
Spleen Volume (cm^3)	n	37
	Median (range)	2164.0 (123, 4941)
Total Symptoms Score (TSS)	n	35
	Median (range)	17.0 (1.4, 56.0)

		High Molecular Risk (HMR) Mutations						Driver Mutations		
	Mutation #	*ASXL1*	*EZH2*	*IDH1/2*	*SRSF2*	*U2AF1*	HMR	*CALR*	*JAK2*	*MPL*
Prevalence (%)	*Spiegel 2017*	33	8	4	7	10		14	79	6
	Pacilli 2018	36.6	8.5	0			42.2	16.9	76	4.2
	Guglielmelli 2014	25.6	5.5	3.5	9.7		35.3		59.7	6.1
	Vannucchi 2013	21.7	5.1	2.6	8.5			20.3	59.2	5.2
	MANIFEST	**61.9**	**9.5**	**2.4**	**9.5**	**11.9**	**71.4**	**28.6**	**54.8**	**14.3**

- **Majority** of the **patients** enrolled in the MANIFEST study
  - **Anemic**, had **large spleen** and **high symptom burden**
  - **High frequency of mutations** associated with **poor prognosis**
    - **71%** patients with **HMR genomic profile**
    - **62%** patients with ***ASXL1*** mutations
    - **57%** patients have **≥3 mutations** in commonly mutated genes
    - 1 patient is triple negative (*CALR*/*MPL*/*JAK2* WT)
  - **Driver mutations** observed
    - *JAK2* - 55% of patients
    - *CALR* - 29% of patients
    - *MPL* - 14% of patients

Best Spleen Volume Reduction

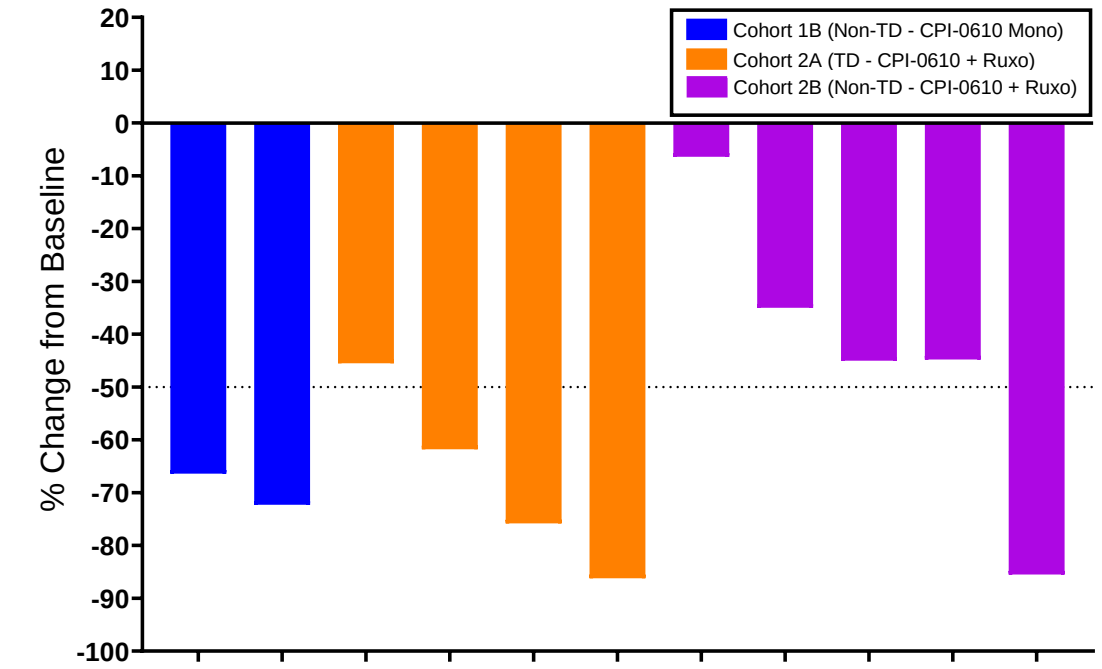


- **14 of 16** evaluable[1] patients had **spleen volume reductions**
- **Median** best change of **-19.2%**
- Spleen volume reduction observed in **4 of 4** evaluable non-TD **monotherapy** MF patients (depicted in blue)

[1] Spleen volume evaluable population: Baseline and one post-baseline data available – n=16 @ 12 weeks; n=12 @ 24 weeks

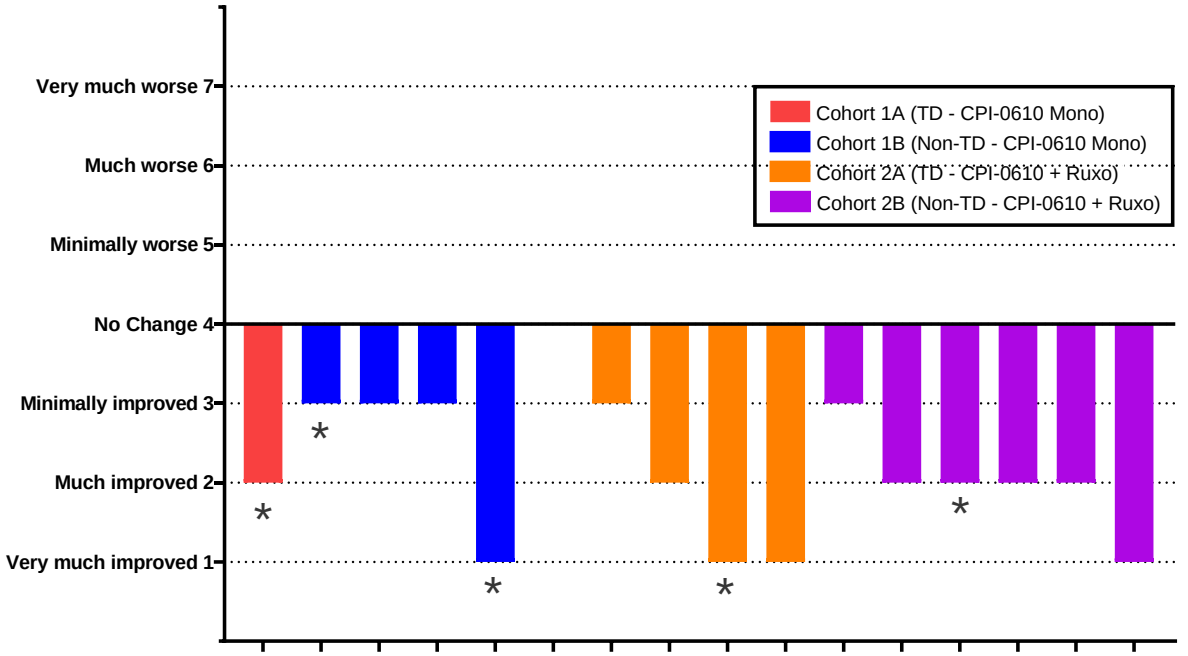
Improvements in Symptoms

Best % TSS Improvement (n=11)



- **≥50% improvement** in symptoms **in 6 of 11 patients** on treatment for ≥12 weeks and evaluable[1] for Total Symptoms Score (TSS)[2]

Best PGIC Observed (n=16)

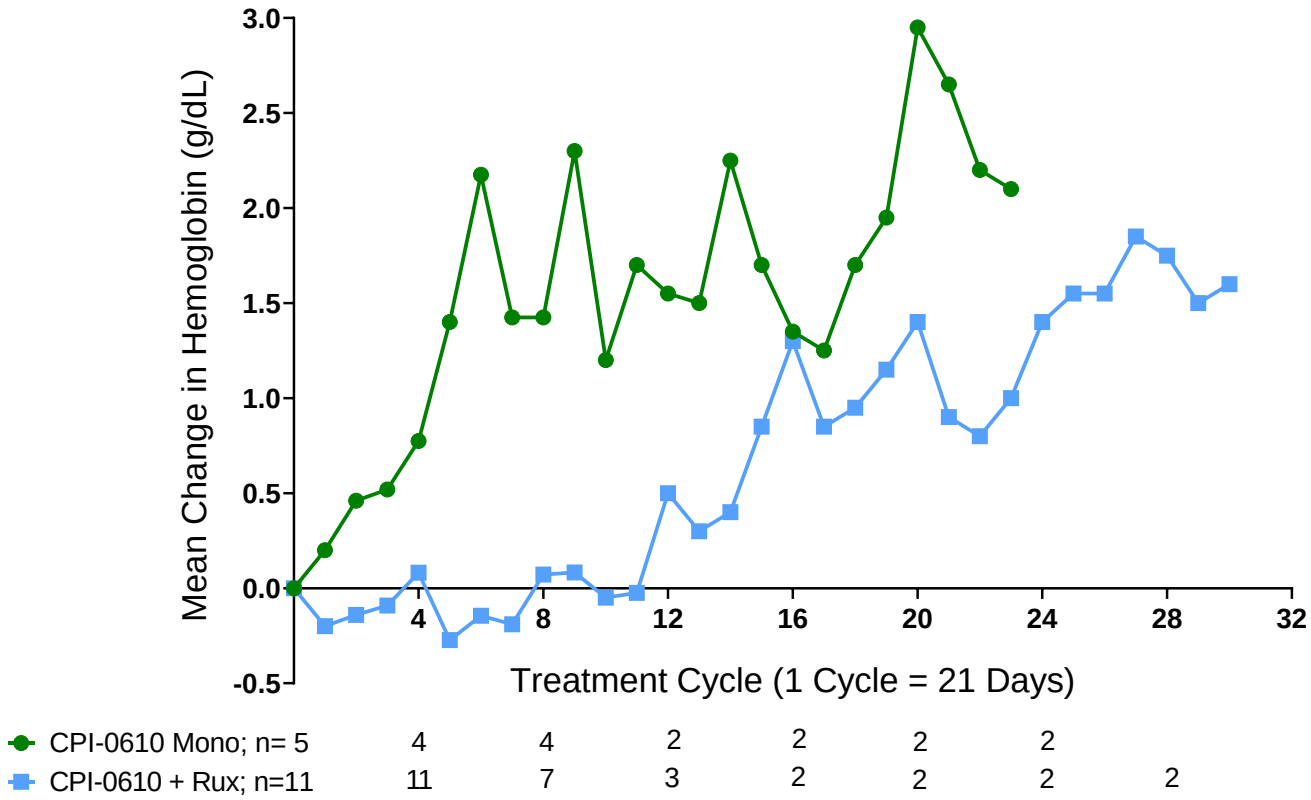


- **15 of 16 patients** reported **improvement in PGIC**[3] score, including the 5 patients for whom TSS could not be evaluated (depicted with *).

[1] TSS evaluable population: Baseline and one post-baseline data available – n=11 @ 12 weeks
[2] TSS measured by Myelofibrosis Symptom Assessment Form Version 4.(MFSAF v4)
[3] PGIC = Patient Global Impression of Change

Improvement in Hemoglobin

Mean Hemoglobin Change[1] by Treatment Regimen

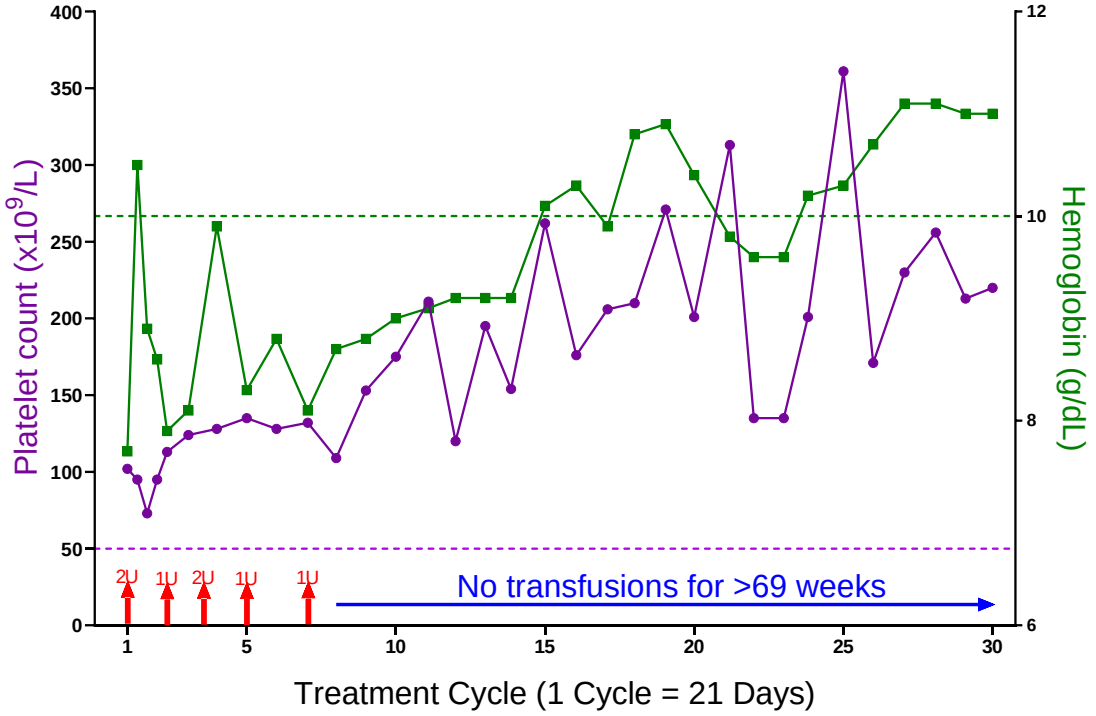


- Substantial **increase in hemoglobin** observed with CPI-0610 **monotherapy**
- With **CPI-0610 + ruxolitinib combo** therapy, observed **improvement in hemoglobin** is delayed
- Patients might need to **overcome effects of ruxolitinib** in JAK-2 signaling, a critical component of EPO pathway

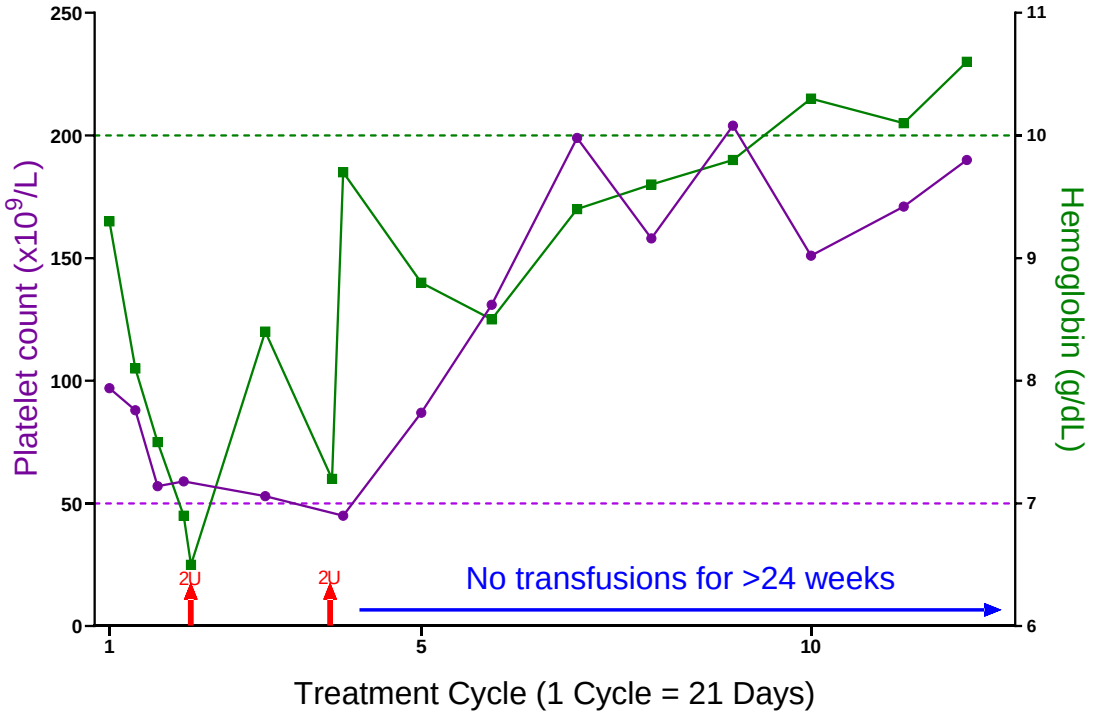
[1] Hemoglobin change in evaluable population: Received treatment for ≥12 weeks (n=16)

Two Transfusion-Dependent (TD) Patients Converted to Transfusion Independence (TI)

Patient 11-246: CPI-0610 + Ruxolitinib *CALR* Mutation



Patient 11-252: CPI-0610 + Ruxolitinib *JAK2, TET2, SRSF2* and *U2AF1* Mutations



- Evidence of **durable transfusion independence** in 2 patients treated with CPI-0610 added to ruxolitinib
- Patients **no longer anemic,** had evidence of **bone marrow fibrosis improvement**

TD = Transfusion dependent is defined as receiving an average of ≥ 2 RBC transfusions per month during the 12 weeks prior to enrollment
TI = Transfusion independent is defined as absence of RBC transfusions over any consecutive 12 week period

Improvement in Bone Marrow Fibrosis

Tx Arm / Cohort	Marrow Fibrosis Grading*				Reticulin Staining Grading*				Best % SVR	Best % TSS Improvement	HMR[1] Mutations
	Baseline	24 Wk	48 Wk	72 Wk	Baseline	24 Wk	48 Wk	72 Wk			
CPI-0610 Mono Non-TD Cohort 1B	3	3	2		3	3	2		-25.4	N/E	Y
	2	1	1		3	1	1		-10.9	N/E	Y
	2	2			No Data	No Data			-33.1	-72.3	
CPI-0610 + Rux Combo TD Cohort 2A	3	No Data	2	2	3	No Data	2	2	-50.7	N/E	
	2	2			2	1			-19.9	-45.5	Y
	3	1			No Data	No Data			-12.2	-87.4	Y
CPI-0610 + Rux Combo Non-TD Cohort 2B	3	3			No Data	3			-14.7	-45.0	Y
	3	2			No Data	2			-21.9	-44.8	Y
	3	3			No Data	No Data			-13.8	-6.4	Y
	3	3			No Data	No Data			-26.5	-85.5	Y

- **6 of 10** evaluable[2] patients had **improvement in bone marrow fibrosis***
- **Fibrosis score improvements** observed in both **monotherapy** and **combination** patients

[1] HMR = High Molecular Risk (patients with one of these mutations: *ASXL1, EZH2, IDH1/2, SRSF2* and *U2AF1*)
[2] Bone marrow evaluable population: Baseline Bx available and at least 1 marrow @ or after 24 weeks – 10 of 44
* Per the European consensus on grading bone marrow fibrosis and assessment of cellularity (Thiele J *et al*. Haematologica. 2005;90:1128)

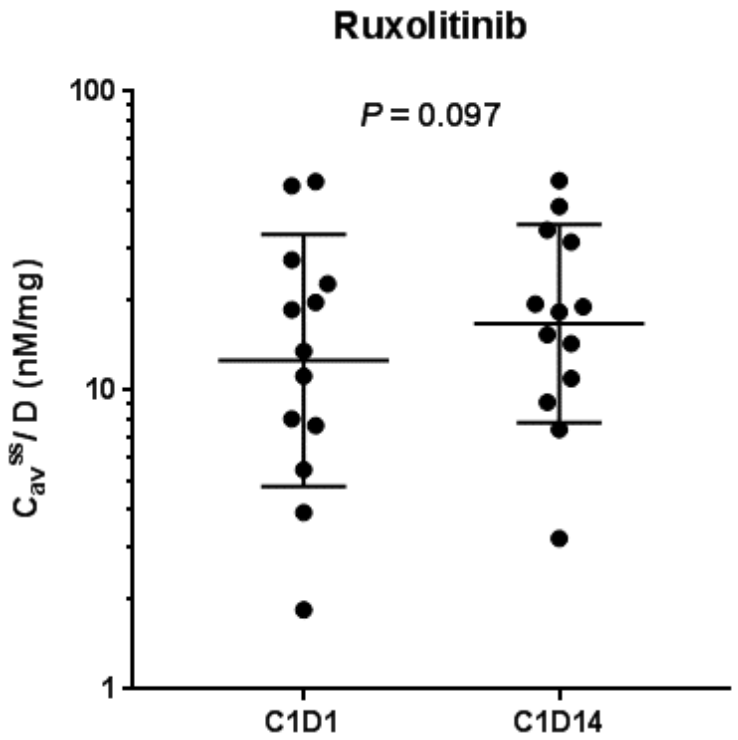
No Drug-Drug Interactions Observed with CPI-0610 and Ruxolitinib Combination Therapy

Mean PK parameters for CPI-0610 125 mg QD given in combination with ruxolitinib 5-25 mg BID[a]

	Regimen	Study day	T_{max} (h)	C_{max} (ng/mL)	AUC_{24} (ng•h/mL)
Phase 2 MANIFEST Data (n=10)	CPI-0610 + ruxolitinib	C1D1	1.47 (16.9)	1,585 (23.8)	10,160 (40.4)
	CPI-0610 + ruxolitinib	C1D14	2.23 (45.0)	1,350 (41.4)	9,057 (69.5)
Phase 1 Lymphoma Data (n=5)	CPI-0610 alone[b]	C1D1	1.23 (81.8)	1,451 (27.7)	10,744 (31.7)
	CPI-0610 alone[b]	C1D14	2.56 (77.4)	1,324 (15.7)	10,189 (20.4)

- [a] Results are presented as the geometric mean (geometric %CV), except for T_{max} which is the arithmetic average (%CV)
- [b] Data from the 0610-01 study patients receiving single agent treatment with CPI-0610 125 mg OD

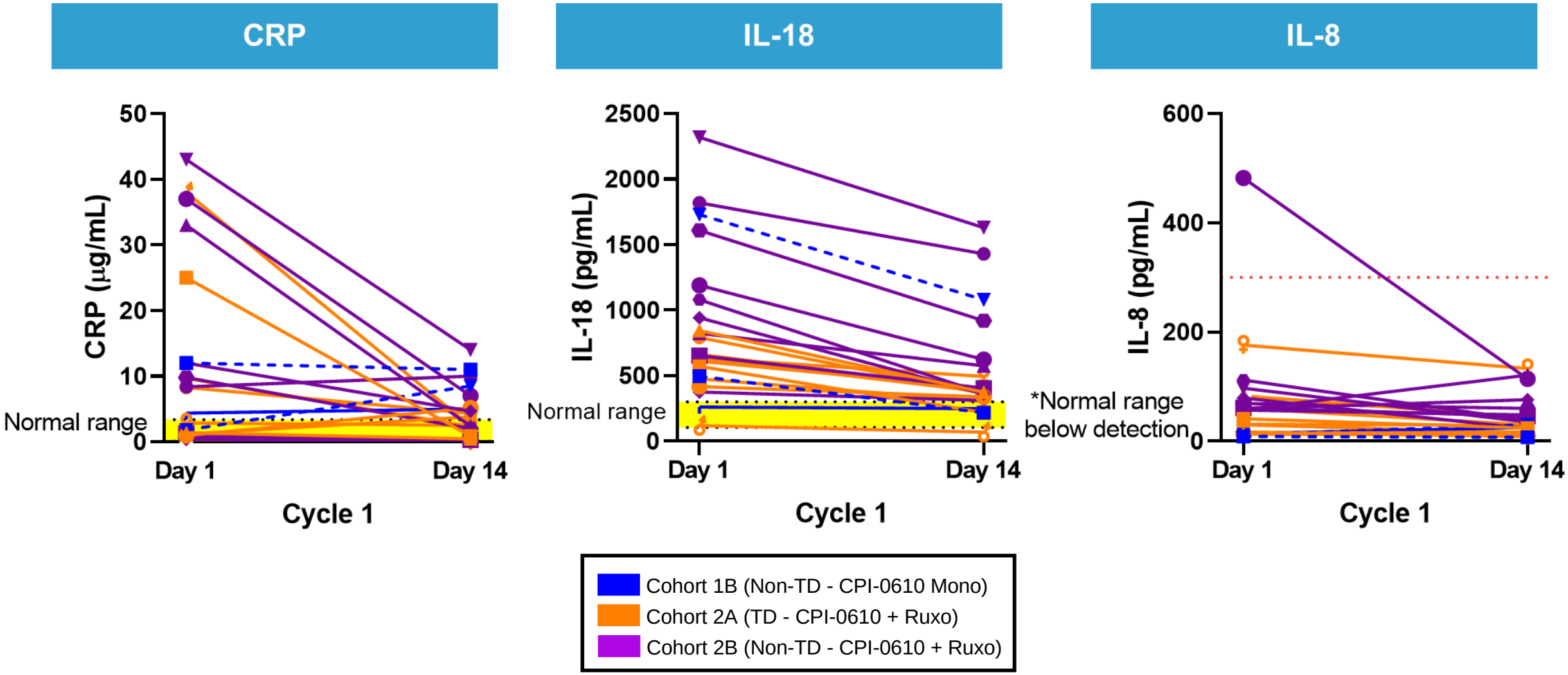
Average steady state concentration of ruxolitinib / dose is not changed from C1D1 to C1D14



- Data points are the C_{av}^{ss}/D values for individual patients shown with the geometric mean and standard deviation error bars
- The two tailed paired t-test of log-transformed data was used for the statistical comparison of data on C1D14 to C1D1

Reduction in Pro-Inflammatory Cytokine Levels

- **Cytokines reductions** observed in MF patients with **CPI-0610 monotherapy** or **combo with ruxolitinib**



Summary of Safety Profile

TEAE (≥10%) and AESI	All Grade n=44 (n, %)[1]	≥3 Grade* n=44 (n, %)[1]
Diarrhea	10 (22.7)	1 (2.3)
Vomiting	6 (13.6)	1 (2.3)
Upper respiratory tract infection	6 (13.6)	0 (0.0)
Epistaxis	6 (13.6)	0 (0.0)
Headache	6 (13.6)	0 (0.0)
Dysgeusia	5 (11.4)	0 (0.0)
Cough	5 (11.4)	0 (0.0)
Pruritis	5 (11.4)	0 (0.0)
Nausea	4 (9.1)	1 (2.3)
Rash	3 (6.8)	0 (0.0)
Decreased appetite	3 (6.8)	0 (0.0)
Thrombocytopenia	3 (6.8)	2 (4.5)
Platelet Count Decreased	3 (6.8)	2 (4.5)
Anemia	2 (4.5)	2 (4.5)
Neutropenia	1 (2.3)	1 (2.3)
Acute Kidney Injury	1 (2.3)	1 (2.3)
Pneumonia	1 (2.3)	1 (2.3)
Depression	0 (0.0)	1 (2.3)

TEAE = Treatment Emergent Adverse Event
AESI = Adverse Event of Special Interest
[1] Safety evaluable population: Received C1D1 treatment (n=44)

- CPI-0610 **monotherapy** or in **combination** with ruxolitinib in MF was **generally well tolerated**
- * **No ≥3 grade TEAE** with CPI-0610 **monotherapy**
- 4 of 44 patients treated showed **≥3 grade platelet count decrease** or thrombocytopenia
  - **All 4 patients** treated with CPI-0610 + ruxolitinib **combination**

Overall Summary of CPI-0610 in Myelofibrosis

- CPI-0610 monotherapy or in combination with ruxolitinib was generally well tolerated
  Observed thrombocytopenia is non-cumulative, generally reversible and manageable
- Evidence of BET-driven monotherapy activity
  Additive benefit in combination with JAK inhibitor (ruxolitinib)
- Improvements in symptoms, spleen volume, bone marrow fibrosis, and anemia
- Clinical effects of CPI-0610 were not immediate and emerged after ≥3 cycles of therapy
- Evidence of potential effects on bone marrow fibrosis and function
- Taken together the preliminary Phase 2 clinical data and FDA Fast Track designation of CPI-0610, the MANIFEST study warrants further investigation