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Poster# **MPN-794**

Pelabresib in combination with ruxolitinib for Janus kinase inhibitor-naive patients with myelofibrosis: 72-week follow-up with long-term efficacy outcomes of the Phase III MANIFEST-2 study

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KEY FINDINGS & CONCLUSIONS

- In JAKi-naive patients with myelofibrosis, PELA+RUX compared with PBO+RUX at Week 72 data cutoff continues to demonstrate meaningful clinical benefits, with correlative biomarkers supporting potential evidence of ongoing disease modification, specifically:
  - Deep and sustained spleen reduction, with a higher proportion of patients maintaining response
  - Sustained numerical improvements in absolute change in TSS from baseline and TSS50 response
  - Nearly double the percentage of patients with dual SVR35 / TSS50 response
  - Higher rates of hemoglobin responses, fewer patients with transfusion requirement, and fewer anemia AEs
  - Continued improvement in bone marrow fibrosis
- Most frequent TEAEs were low grade (Grade <3)
- An early imbalance in cases of leukemic transformation was observed with PELA+RUX compared with PBO+RUX. Over time, the imbalance in proportion of patients with transformation to blast phase decreased. Overall, the observed frequency was in line with what is typically seen in MF
- Longer-term follow-up (Week 72 data cutoff) showed fewer deaths in the PELA+RUX arm compared with the PBO+RUX arm

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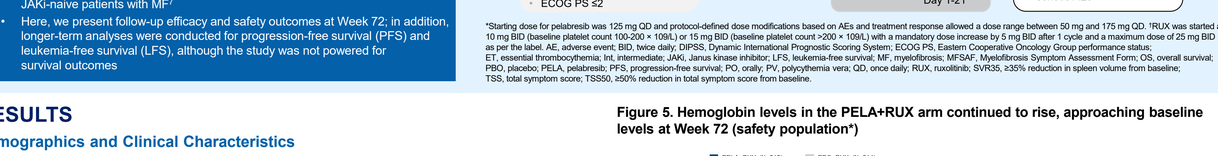
INTRODUCTION

- Dysregulation of the Janus kinase/signal transducer and activator of transcription pathway, and bromodomain and extraterminal domain (BET)-mediated gene modulation are associated with myelofibrosis (MF) pathophysiology[1,2]
- MF is a progressive and life-threatening disease, characterized by debilitating symptoms, cytopenias (e.g., anemia), splenomegaly, and impairment of the bone marrow microenvironment (including fibrosis)[3]
  - Reduction in spleen size is associated with improved OS[4]
- Janus kinase inhibitor (JAKi) monotherapy is the standard of care in intermediate- and high-risk MF[5]
- Pelabresib (CPI-0610/DAK539) is an investigational, oral, small molecule drug that inhibits BET proteins and alters BET-mediated expression of genes that contribute to the pathology of MF[6]
- The MANIFEST-2 study met its primary endpoint, showing a statistically significant improvement in SVR35 response at Week 24 with pelabresib-ruxolitinib (PELA+RUX) compared with placebo-ruxolitinib (PBO+RUX) in JAKi-naive patients with MF[7]
- Here, we present follow-up efficacy and safety outcomes at Week 72; in addition, longer-term analyses were conducted for progression-free survival (PFS) and leukemia-free survival (LFS), although the study was not powered for survival outcomes

METHODS

- The MANIFEST-2 study is a global, randomized, double-blind, Phase III trial (**Figure 1**) investigating the efficacy and safety of the combination therapy of PELA+RUX versus PBO+RUX in JAKi-naive patients with MF[7, 8]

Figure 1. Study population and design



*Starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD. †RUX was started at 10 mg BID (baseline platelet count 100-200 × 109/L) or 15 mg BID (baseline platelet count >200 × 109/L) with a mandatory dose increase by 5 mg BID after 1 cycle and a maximum dose of 25 mg BID as per the label. AE, adverse event; BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; Int, intermediate; JAKi, Janus kinase inhibitor; LFS, leukemia-free survival; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; OS, overall survival; PBO, placebo; PELA, pelabresib; PFS, progression-free survival; PO, orally; PV, polycythemia vera; QD, once daily; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

RESULTS

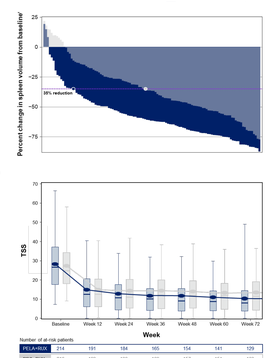
Demographics and Clinical Characteristics

- The analysis included 214 and 216 randomized patients in the PELA+RUX and PBO+RUX groups, respectively, from the MANIFEST-2 study
  - 212 (99.1%) and 214 (99.1%) patients were treated in the PELA+RUX and PBO+RUX groups, respectively
  - Patients ongoing for study follow-up are 145 (67.8%) and 157 (72.3%), and those on double-blind treatment are 114 (53.3%) and 120 (55.6%), in the PELA+RUX and PBO+RUX groups, respectively
- Patient characteristics were balanced as previously reported[7]
- Splenic response rates continued to be greater at Week 72 with PELA+RUX versus PBO+RUX (**Figure 2**)
- A greater number of patients maintained SVR35 responses with PELA+RUX (80%) versus PBO+RUX (73%) at Week 72 data cutoff (**Figure 3**)
- Nearly twice as many patients achieved both SVR35 and TSS50 responses with PELA+RUX versus PBO+RUX at Week 72 (**Figure 4**)
- A numerically greater proportion of patients had a hemoglobin response, and fewer patients required red blood cell (RBC) transfusions with PELA+RUX versus PBO+RUX over 72 weeks (**Figure 5**)
- A greater proportion of patients had improvements in bone marrow fibrosis at Week 72 with PELA+RUX versus PBO+RUX (**Figure 6**)
- Treatment-emergent adverse events were similar between treatment arms at Week 72 data cutoff (**Figure 7**)
- An early imbalance in cases of leukemic transformation was observed with PELA+RUX compared with PBO+RUX. Over time, the imbalance in proportion of patients with transformation to blast phase decreased. Overall, the observed frequency was in line with what is typically seen in MF (**Table 1**)
- Longer-term follow-up (Week 72 data cutoff) showed fewer PFS events in the PELA+RUX arm compared with the PBO+RUX arm; LFS outcomes were similar between both arms (**Figure 8**)

Safety

- 98 (45.8%) and 94 (43.5%) patients discontinued double-blind treatment in the PELA+RUX and PBO+RUX groups, respectively
- Treatment-emergent adverse events (TEAEs) were similar between treatment arms and most frequent were Grade <3
- By Week 72 data cutoff, there were fewer deaths in the PELA+RUX arm compared with the PBO+RUX arm

Figure 2. Sustained improvements in spleen volume (a) and TSS (b) with PELA+RUX versus PBO+RUX at Week 72

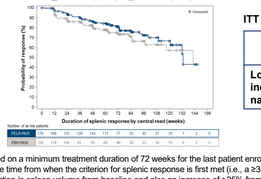


ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
SVR35 response at Week 72	46.3	29.2
Difference‡ (95% CI)	16.7 (7.9-25.4)	
Mean % change in spleen volume at Week 72§	−57.2 (n=114)	−34.9 (n=119)
95% CI	−61.0, −53.3	−39.0, −30.7
Absolute change in TSS¶ at Week 72, LSM	−15.42	−13.19
LSM difference (95% CI) at Week 72	−2.23 (−4.73, 0.27)	
TSS50 response at Week 72, %	42.1	35.2
Difference¶ (95% CI) at Week 72	6.3 (−2.6, 15.3)	

Spleen volume assessed by central read. *Waterfall plots represent patients who have baseline and Week 72 data. †Calculated by stratified Cochran-Mantel-Haenszel test. ‡Patients without Week 72 assessment are considered non-responders. §TSS assessed by MFSAF v4.0 and using an MMRM analysis of absolute change from baseline in TSS. ¶Difference in treatment groups analyzed by stratified Cochran-Mantel-Haenszel test (weighted 95% CI adjusted across strata).
CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

Figure 3. Durable splenic response persists with PELA+RUX versus PBO+RUX at Week 72 data cutoff

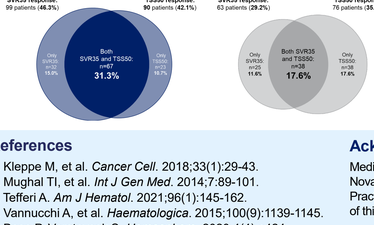


ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
Loss of SVR35 response and >25% increase in spleen volume from nadir, % (n/N)	22.7 (40/176)	25.8 (34/132)

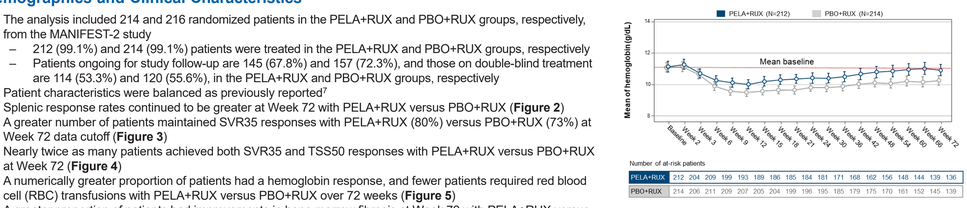
Based on a minimum treatment duration of 72 weeks for the last patient enrolled. Spleen volume assessed by central read. Duration of the splenic response is defined as the time from when the criterion for splenic response is first met (i.e., a ≥35% reduction from baseline spleen volume) until the time at which there is a <35% reduction in spleen volume from baseline and also an increase of >25% from nadir as measured by MRI or CT is first documented. ITT, intent-to-treat; MRI, magnetic resonance imaging; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline.

Figure 4. Dual SVR35 / TSS50 responders at Week 72



PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline; TSS50, ≥50% reduction in total symptom score from baseline.

Figure 5. Hemoglobin levels in the PELA+RUX arm continued to rise, approaching baseline levels at Week 72 (safety population*)

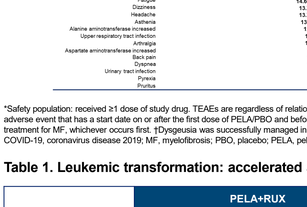


ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
Hemoglobin response,†,‡ % (n/N) (95% CI)	16.4 (35/214) (11.4-21.31)	9.3 (20/216) (5.39-13.12)
Hemoglobin response,†,‡ in patients with anemia (baseline <10 g/dL), % (n/n) (95% CI)	20.9 (14/67) (11.16-30.63)	16.9 (12/71) (8.18-25.62)

*Safety population received ≥1 dose of study drug. †Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the prior 12 weeks in the ITT population. ‡Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RBC, red blood cell; RUX, ruxolitinib.

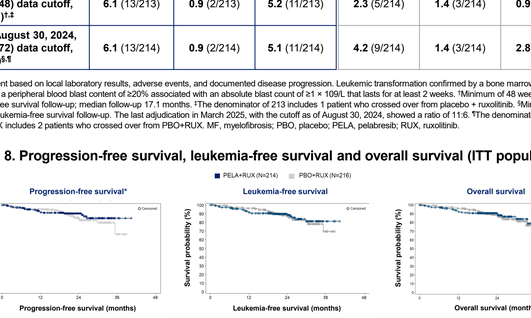
Figure 6. Improvement of reticulin fibrosis grade* with PELA+RUX versus PBO+RUX at Week 72



	PELA+RUX (N=74†)	PBO+RUX (N=71†)
Improved by ≥1 grade at Week 72, %	51.4	28.2
Worsened by ≥1 grade at Week 72, %	12.2	36.6

*By central read. †(n=145 evaluable patients (patients with non-missing baseline and non-missing Week 72 BMF data); n=74 in the PELA+RUX arm and n=71 in the PBO+RUX arm. n=285 (66%) missing data. BMF, bone marrow fibrosis; CI, confidence interval; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib.

Figure 7. The most frequent TEAEs in both treatment arms were low grade (Grade <3)



*Safety population: received ≥1 dose of study drug. TEAEs are regardless of relationship to study drug. A TEAE for the double-blind treatment period is defined as an adverse event that has a start date on or after the first dose of PELA/PBO and before 30 days after the last dose of PELA/PBO or before the start of alternative (off-study) treatment for MF, whichever occurs first. †Dysgeusia was successfully managed in most patients by dose reductions of pelabresib.
COVID-19, coronavirus disease 2019; MF, myelofibrosis; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; TEAE, treatment-emergent adverse event.

Table 1. Leukemic transformation: accelerated and blast-phase progression

	PELA+RUX			PBO+RUX		
	Accelerated and blast phase*	Accelerated phase	Blast phase	Accelerated and blast phase*	Accelerated phase	Blast phase
As of March 29, 2024, (Week 48) data cutoff, % (n/N)†,‡	6.1 (13/213)	0.9 (2/213)	5.2 (11/213)	2.3 (5/214)	1.4 (3/214)	0.9 (2/214)
As of August 30, 2024, (Week 72) data cutoff, % (n/N)§,¶	6.1 (13/214)	0.9 (2/214)	5.1 (11/214)	4.2 (9/214)	1.4 (3/214)	2.8 (6/214)

*Assessment based on local laboratory results, adverse events, and documented disease progression. Leukemic transformation confirmed by a bone marrow blast count of ≥20% or a peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 109/L that lasts for at least 2 weeks. †Minimum of 48 weeks of leukemia-free survival follow-up; median follow-up 17.1 months. ‡The denominator of 213 includes 1 patient who crossed over from placebo + ruxolitinib. §Minimum of 72 weeks of leukemia-free survival follow-up. The last adjudication in March 2025, with the cutoff as of August 30, 2024, showed a ratio of 11/6. ¶The denominator of 214 for PELA+RUX includes 2 patients who crossed over from PBO+RUX. MF, myelofibrosis; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib.

Figure 8. Progression-free survival, leukemia-free survival and overall survival (ITT population)



	PELA+RUX (N=214)	PBO+RUX (N=216)
Total events, n (%)	21 (9.8)	27 (12.5)
Hazard ratio (95% CI)	0.87 (0.49-1.56)	

	PELA+RUX (N=214)	PBO+RUX (N=216)
Total events, n (%)	25 (11.7)	28 (13.0)
Hazard ratio (95% CI)	0.99 (0.57-1.72)	

	PELA+RUX (N=214)	PBO+RUX (N=216)
Total events, n (%)	23 (10.7)	27 (12.5)
Hazard ratio (95% CI)	0.93 (0.53-1.66)	

*Defined as time from randomization until documented progression or until death from any cause for patients without documented progression, whichever comes first. Progression was defined as progressive splenomegaly (enlargement of spleen volume by MRI or CT of ≥25% vs baseline by central radiology review) or leukemic transformation (confirmed by blast of ≥20%), whichever comes first. CI, confidence interval; CT, computed tomography; ITT, intent-to-treat; LFS, leukemia-free survival; MRI, magnetic resonance imaging; PBO, placebo; PELA, pelabresib; PFS, progression-free survival; RUX, ruxolitinib.

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Disclosures

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