













MANIFEST: Pelabresib in Combination With Ruxolitinib for Janus Kinase Inhibitor Treatment-Naïve Myelofibrosis

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ABSTRACT




PURPOSE Standard therapy for myelofibrosis comprises Janus kinase inhibitors (JAKis), yet spleen response rates of 30%-40%, high discontinuation rates, and a lack of disease modification highlight an unmet need. Pelabresib (CPI-0610) is an investigational, selective oral bromodomain and extraterminal domain inhibitor (BETi).

METHODS MANIFEST (ClinicalTrials.gov identifier: [NCT02158858](https://clinicaltrials.gov/ct2/show/study/NCT02158858)), a global, open-label, nonrandomized, multicohort, phase II study, includes a cohort of JAKi-naïve patients with myelofibrosis treated with pelabresib and ruxolitinib. The primary end point is a spleen volume reduction of $\geq 35\%$ (SVR35) at 24 weeks.

RESULTS Eighty-four patients received ≥ 1 dose of pelabresib and ruxolitinib. The median age was 68 (range, 37-85) years; 24% of patients were intermediate-1 risk, 61% were intermediate-2 risk, and 16% were high risk as per the Dynamic International Prognostic Scoring System; 66% (55 of 84) of patients had a hemoglobin level of < 10 g/dL at baseline. At 24 weeks, 68% (57 of 84) achieved SVR35, and 56% (46 of 82) achieved a total symptom score reduction of $\geq 50\%$ (TSS50). Additional benefits at week 24 included 36% (29 of 84) of patients with improved hemoglobin levels (mean, 1.3 g/dL; median, 0.8 g/dL), 28% (16 of 57) with ≥ 1 grade improvement in fibrosis, and 29.5% (13 of 44) with $> 25\%$ reduction in JAK2V617F-mutant allele fraction, which was associated with SVR35 response ($P = .018$, Fisher's exact test). At 48 weeks, 60% (47 of 79) of patients had SVR35 response. Grade 3 or 4 toxicities seen in $\geq 10\%$ patients were thrombocytopenia (12%) and anemia (35%), leading to treatment discontinuation in three patients. 95% (80 of 84) of the study participants continued combination therapy beyond 24 weeks.

CONCLUSION The rational combination of the BETi pelabresib and ruxolitinib in JAKi-naïve patients with myelofibrosis was well tolerated and showed durable improvements in spleen and symptom burden, with associated biomarker findings of potential disease-modifying activity.

ACCOMPANYING CONTENT

-  [Article, p. 5044](#)
-  [Data Supplement](#)
-  [Protocol](#)

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BACKGROUND

Myelofibrosis, a chronic, potentially life-threatening hematologic neoplasm, is characterized by clonal myeloproliferation, ineffective erythropoiesis, bone marrow (BM) stromal changes, extramedullary hematopoiesis, and aberrant cytokine expression.¹ Patients typically present with splenomegaly, systemic symptoms, anemia, and BM fibrosis.

Janus kinase (JAK) inhibitors (JAKis) ruxolitinib, fedratinib, and pacritinib have been approved by the Food and Drug

Administration for patients with myelofibrosis on the basis of demonstrated splenic responses and symptom improvement in phase III clinical studies.²⁻⁶ Although ruxolitinib is the current standard of care, progressive disease and toxicity frequently lead to ruxolitinib discontinuation (median time: approximately 3 years),⁷ which is associated with poor survival.⁸⁻¹⁰

Pelabresib (CPI-0610) is an investigational, oral, small-molecule bromodomain and extraterminal domain (BET) inhibitor (BETi). BET proteins regulate transcription of

CONTEXT

Key Objective

To assess the efficacy and safety of the combination of pelabresib and ruxolitinib in Janus kinase inhibitor treatment-naïve patients with myelofibrosis.

Knowledge Generated

In Arm 3 of the MANIFEST phase II study, the combination of pelabresib and ruxolitinib demonstrated clinically meaningful durable improvements in splenomegaly and symptoms, was associated with biomarker findings indicating potential disease modification, and demonstrated a generally favorable safety profile without clinically relevant added or limiting toxicity.

Relevance (C.F. Craddock)

Combined pelabresib and ruxolitinib is well tolerated and has the potential to improve the standard of care for Janus kinase inhibitor treatment-naïve patients with myelofibrosis and warrants further investigation in prospective trials.*

*Relevance section written by JCO Associate Editor Charles F. Craddock, MD.

specific genes integrating an array of oncogenic signals.¹¹ BET inhibition could modify critical components of myelofibrosis pathobiology, including megakaryocyte differentiation and proliferation,^{12,13} and reduce proinflammatory cytokine expression via the nuclear factor kappa B (NF- κ B) signaling pathway.^{14,15} In murine myelofibrosis models, BET inhibition reduced proinflammatory cytokine levels, spleen volume, and BM fibrosis.¹⁶ These benefits increased when BET inhibition was combined with the JAKi ruxolitinib, suggesting synergism by cooperated downregulation of JAK-driven oncogenic activity and BET-driven proinflammatory signaling.¹⁶ In a phase I study in patients with lymphoma, pelabresib demonstrated a wide therapeutic index, with a maximum tolerated dose approximately four times greater than the lowest active dose and an acceptable safety profile.^{17,18} In advanced myelofibrosis, pelabresib monotherapy demonstrated splenic responses and symptom improvement.¹⁹

We present results from JAKi treatment-naïve patients with myelofibrosis enrolled in the MANIFEST phase II study who were treated with pelabresib plus ruxolitinib.

METHODS

Study Design

MANIFEST, a global, open-label, nonrandomized, multicohort, phase II study (ClinicalTrials.gov identifier: [NCT02158858](https://clinicaltrials.gov/ct2/show/study/NCT02158858)), includes a cohort of JAKi treatment-naïve patients treated with pelabresib combined with ruxolitinib (Arm 3); enrollment for this cohort is complete (Data Supplement [Fig S1], online only). Pelabresib was administered in 21-day cycles at an initial dose of 125 mg once daily for 14 days, followed by a 7-day break, combined with continuous ruxolitinib (twice a day).²⁰ The maximum dose

permitted for this cohort was 175 mg once daily (additional dosing details are provided in the Data Supplement).

Patient Population

Eligible patients were JAKi and BETi treatment-naïve adults with confirmed diagnoses of primary myelofibrosis or postessential thrombocythemia or postpolycythemia vera myelofibrosis. Patients had to have a spleen volume of ≥ 450 cm³ determined by magnetic resonance imaging or computed tomography (CT), intermediate-2- or high-risk disease according to the Dynamic International Prognostic Scoring System (DIPSS) categories, and ≥ 2 measurable symptoms (score ≥ 3) or a total score of ≥ 10 using the Myelofibrosis Symptom Assessment Form version 4.0. Following a protocol amendment, patients with intermediate-1 DIPSS risk were excluded from the trial; this amendment ensured that the patient population reflected historical studies² and was independent of interim assessment of efficacy or adverse events. Patients were required to have a platelet count of $\geq 100 \times 10^9/L$, an absolute neutrophil count of $\geq 1 \times 10^9/L$, a peripheral blood blast count of $< 10\%$, and an Eastern Cooperative Oncology Group performance status of ≤ 2 . Patients evaluable for review of BM samples were defined as those with available baseline and ≥ 1 postbaseline assessment; those discontinuing without postbaseline assessment were defined as not improved/not stabilized.

End Points and Assessments

The primary end point was defined as $\geq 35\%$ reduction in spleen volume (SVR35) from baseline to 24 weeks, measured by imaging. The secondary end point was $\geq 50\%$ reduction in total symptom score from baseline to 24 weeks (TSS50) measured by Myelofibrosis Symptom Assessment Form v4.0 (Critical Path Institute, Tucson, AZ). BM biopsies were

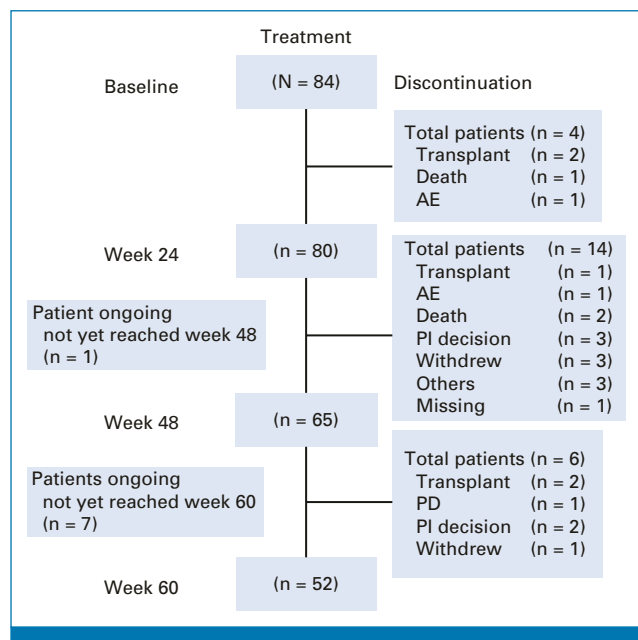


FIG 1. Patient disposition. AE, adverse event; PD, progressive disease; PI, principal investigator.

collected at baseline and every 24 weeks thereafter during treatment. Exploratory end points included BM fibrosis improvement according to blinded central hematopathologist review (two blinded pathologists and one blinded adjudicator) following European consensus criteria for reticulin fibrosis grading and improvement in anemia and transfusion requirements (per Gale criteria²¹). Safety analyses used National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Mean hemoglobin increase was assessed on the basis of the rolling average of at least a 1.5 g/dL increase from baseline over any 12-week period without red blood cell transfusions, and the absolute increase was assessed at week 24 (excluding assessments within 2 weeks after a red blood cell transfusion).

Eighty-six myelofibrosis-linked cytokines were measured by enzyme-linked immunoassay from plasma obtained at baseline and after 2, 6, 12, and 24 weeks of treatment (InflammationMAP, CustomMAP, Simoa only for IL-6, IFN- γ , and TNF- α ; RBM, Austin, TX). Mutational analyses from peripheral whole blood samples were performed as an exploratory end point by targeted sequencing using the amplicon-based Rapid Heme Panel assay.²²

Trial Oversight

The study was approved by the institutional review board or independent ethics committee at each participating site, conducted in accordance with the Declaration of Helsinki and overseen by a safety review committee. Written informed consent was obtained from each patient, their guardian, or

their legal representative before study entry. Data were collected by study investigators and analyzed by the study sponsor.

Statistical Analysis

This JAKi treatment-naïve cohort was planned to enroll 81 patients. On the basis of a Simon's two-stage design to allow the possibility of early stopping for futility, this yields a one-sided type I error rate of 0.05 and a power of 80% when the true splenic response rate was 45% versus 30% under the null hypothesis. In stage 1, 27 patients were enrolled; as > nine responses occurred in these patients, 57 additional patients were enrolled in stage 2. Week 24 spleen volume was imputed for six patients (four responders and two nonresponders) from scans at week 31 (n = 2) and weeks 32, 34, 37, and 39 (all n = 1); ability to perform radiographic assessment was affected by the COVID-19 pandemic. Patients who discontinued without week 24 assessment for any reason were included as nonresponders. The primary end point was analyzed on the basis of the intent-to-treat population. Spleen volume and symptoms were assessed using a 95% exact binomial confidence interval, whereas biomarker assessments included one-/two-sample tests, proportional tests, Fisher's exact tests, and linear mixed effect model for longitudinal analysis.

RESULTS

Patients

As of September 10, 2021, 84 JAKi treatment-naïve patients were enrolled and received pelabresib in combination with ruxolitinib (Fig 1). Of these, 53 remained on study treatment at the time of data cutoff. The median follow-up for time on treatment was 94 weeks (95% CI, 91 to 97), with 95%, 77%, and 62% of patients having completed ≥ 24 , ≥ 48 , and ≥ 60 weeks of study treatment, respectively. The median follow-up time for time on treatment was 94, 73, and 53 weeks for DIPSS intermediate-1-, intermediate-2-, and high-risk patients, respectively. All patients reached week 24 or discontinued earlier (primary end point analysis).

Patients were predominantly male (70%), had a median age of 68 years, and had primary myelofibrosis, with 24%, 61%, and 16% at intermediate-1, intermediate-2, or high risk, respectively, per DIPSS (Table 1). The median time since diagnosis was approximately 8.5 months. The most frequent mutations at baseline were *JAK2V617F* (74%), *ASXL1* (4.6%), *CALR* (21%), and *MPL* (8%).

Efficacy

Primary end point. At week 24, SVR35 responses were observed in 57 of 84 patients (68%; 95% CI, 57 to 78; Fig 2A and Data Supplement [Fig S2]; best SVR35 response at any time: 80% [67 of 84]). The median SVR was -50% (range,

–84% to 28%). Responses were consistent across all subgroups analyzed, including patient groups stratified by DIPSS and International Prognostic Scoring System (IPSS) risk category (Fig 3 and Data Supplement [Table S1]). SVR35 responses at week 24 were observed in 70% (14 of 20) and 67% (43 of 64) of patients with DIPSS intermediate-1- and intermediate-2-/high-risk disease, respectively, and 82% (9 of 11) and 66% (48 of 73) of those with intermediate-1- and intermediate-2-/high-risk disease, respectively, according to IPSS. No change in SVR35 was observed with imputation for missing values because of delays caused by the COVID-19 pandemic. At week 48, there were 47 (59.5%) SVR35 responders of 79 evaluable patients; the median SVR was –54.6% (range, –85.5% to 24.0%; Fig 2B). Kaplan-Meier estimates of patients with SVR35 response at any time point (n = 67) showed that 93.5% (95% CI, 87.4 to 99.7) of responders sustained their response 36 weeks after onset.

Secondary end points. Of 84 patients, 82 were evaluable for symptom scores. Two were excluded: one had a missing baseline value and one had a baseline TSS of 0 (both are ongoing with 52 and 96 weeks of treatment). TSS50 was observed in 46 of 82 (56%; 95% CI, 45 to 67) patients at week 24 (Fig 4A and Data Supplement [Fig S3]; best TSS50 response at any time: 83% [68 of 82]). The median change in TSS was –59% (range, –100% to 225%). At 48 weeks, 43% (34 of 79) had a TSS50 response; the median change in TSS was –54.8% (range, –100% to 307.1%), indicating sustained symptom responses over a 48-week treatment period (Fig 4B).

Pelabresib combined with ruxolitinib led to stabilization or improvements in hemoglobin levels (absolute change from baseline between –1 and + \geq 1.5 g/dL) in 55% (46 of 84) of patients at week 24 (Data Supplement [Table S2]). Hemoglobin levels improved in 36% (29 of 84) of patients (mean, 1.3 g/dL, median, 0.8 g/dL), whereas 30% (25 of 84) of patients experienced a worsening (decrease of \geq 1 g/dL from baseline). Over time, steady improvements in mean hemoglobin levels were observed in patients with baseline levels < 10 g/dL, and an initial decrease was observed in patients with baseline levels \geq 10 g/dL, with a return to or above baseline levels thereafter (Fig 5). Twenty-four percent (20 of 84) of patients achieved a mean hemoglobin increase of \geq 1.5 g/dL from baseline over any 12-week period without red blood cell transfusions. Ruxolitinib dose levels, spleen, and symptom responses in this group were similar to those of the overall study population.

Exploratory end points. Per blinded central pathology review of BM samples, 28% (16 of 57) of evaluable patients had \geq 1 grade improvement in reticulin fibrosis at week 24, including 7% (4 of 57) with improvements of two grades; 44% (25 of 57) had no change. Of 24 patients with Grade 1 or 2 reticulin fibrosis at baseline, four (17%) experienced worsening (two patients each with Grade 1 or Grade 2; Data

TABLE 1. Baseline Demographics and Clinical Characteristics

Variable	Safety Analysis Set (N = 84)
Age, years, median (min, max)	68 (37, 85)
Sex, No. (%)	
Male	59 (70)
DIPSS, No. (%)	
Int-1 ^a	20 (24)
Int-2	51 (61)
High	13 (16)
IPSS, No. (%)	
Int-1	11 (13)
Int-2	28 (33)
High	45 (53)
Myelofibrosis subtype, No. (%)	
Primary myelofibrosis	46 (55)
Postpolycythemia vera myelofibrosis	9 (11)
Postessential thrombocytopenia myelofibrosis	26 (31)
Missing	3 (4)
Mutations, No. ^b (%)	
JAK2V617F	59 (74)
CALR	17 (21)
MPL	6 (8)
Triple-negative	3 (4)
SRSF2	13 (16)
ASXL1	37 (46)
HMR ^c	46 (58)
Hemoglobin, g/dL	
Median (min, max)	9 (7, 17)
< 10, No. (%)	55 (66)
Platelets, $\times 10^9/L$	
Median (min, max)	293 (100, 1849)
≤ 200 , No. (%)	29 (35)
Spleen volume, cc	
Median (min, max)	1,698 (458, 4,782)
Spleen size by palpation below left costal margin (cm)	
Median (min, max)	10 (0.5, 23.0)
Bone marrow fibrosis, No. ^d (%)	
Grade 1/2	24 (46)
Grade 3	28 (54)
TSS	
Median (min, max)	16 (0, 38)

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; HMR, high-molecular risk; Int-1, intermediate-1; Int-2, intermediate-2; IPSS, International Prognostic Scoring System; TSS, total symptom score.

^aPrior versions of the protocol allowed patients with DIPSS intermediate-1–risk score to enroll in the study.

^bSamples from 80 patients were available for mutation analysis.

^cHMR mutations: ASXL1, EZH2, IDH1/2, SRSF2, and U2AF1Q157.

^dSamples from 52 patients were available for central pathology review.

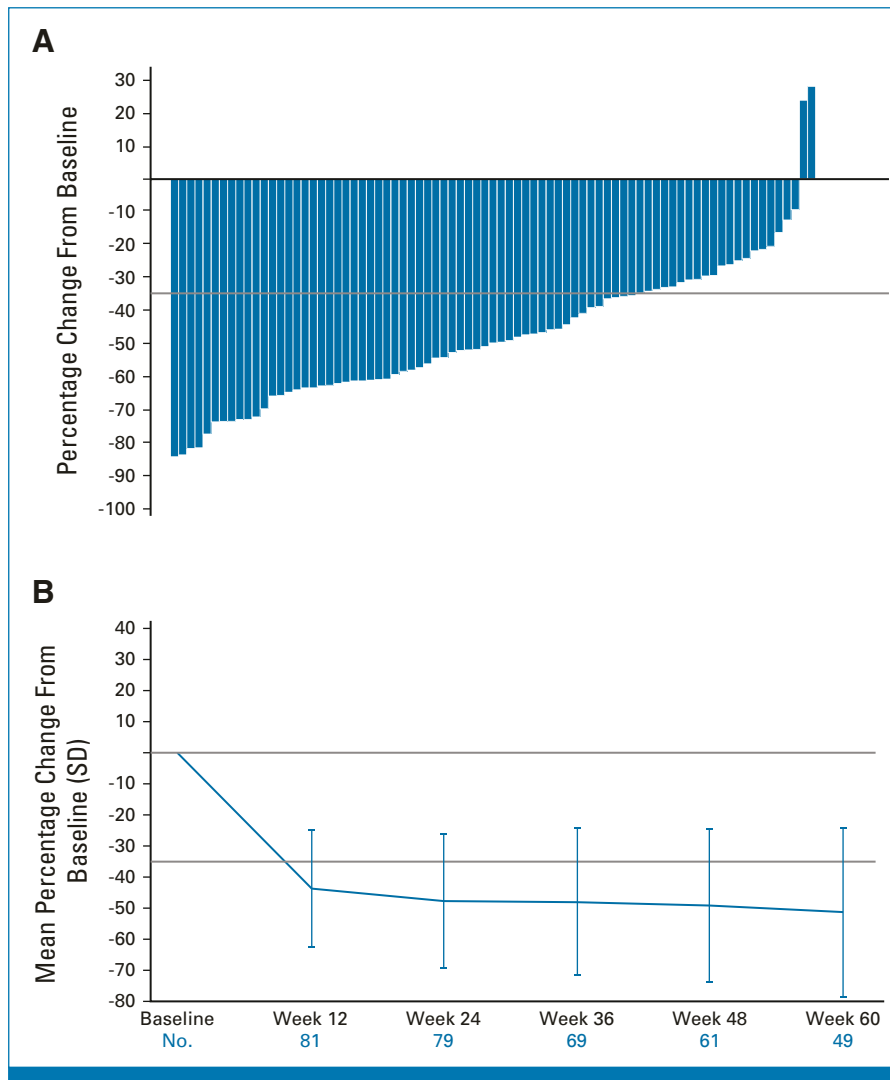


FIG 2. Change in spleen volume by local review after treatment with pelabresib and ruxolitinib. (A) Waterfall plot of percentage change from baseline spleen volume at week 24 by local review. (B) Mean percentage change from baseline spleen volume over time. Patients were evaluable for assessment of spleen volume reduction at week 24 if they had a week 24 assessment by the data cutoff or discontinued without a week 24 assessment at any time. Five patients who discontinued before week 24 spleen assessment were considered nonresponders. Spleen volume median percentage change includes patients with available spleen volume assessment for the corresponding time points. Five patients were nonevaluable at week 48 assessment as they had not yet reached week 48, and 18 patients who discontinued before week 48 were included as nonresponders. For SVR35 at week 24, 95% CIs were 57 to 78. SD, standard deviation; SVR35, $\geq 35\%$ reduction in spleen volume from baseline.

Supplement [Table S3]). No patients with Grade 1 reticulín fibrosis improved to Grade 0; 4 of 7 remained at Grade 1; and 2 of 7 worsened; data for one patient are missing. No significant associations were observed between reticulín fibrosis improvement and clinical end points.

Plasma cytokines were clustered into six groups on the basis of increased expression at baseline and reduced expression during treatment (Data Supplement [Fig S4]). At baseline, the majority of analyzed cytokines showed increased levels

(up to 10-fold) compared with healthy donors. In 51 patients with available data, rapid and durable (2–24 weeks) down-regulation was observed in a cluster of 19 cytokines (including CD40L, RANTES, TNF α , IL-6, CRP, and IL-18; median of -46% across cytokines and visits) and a second cluster of 24 cytokines (including TARC, ICAM-1, MMP-10, IP-10, and IL-8; median of -23% across cytokines and visits). These clusters were enriched in cytokines previously shown to be NF- κ B targets, inflammation-related, and/or elevated in myelofibrosis.^{23–27} Hepcidin, ferritin (FRTN),

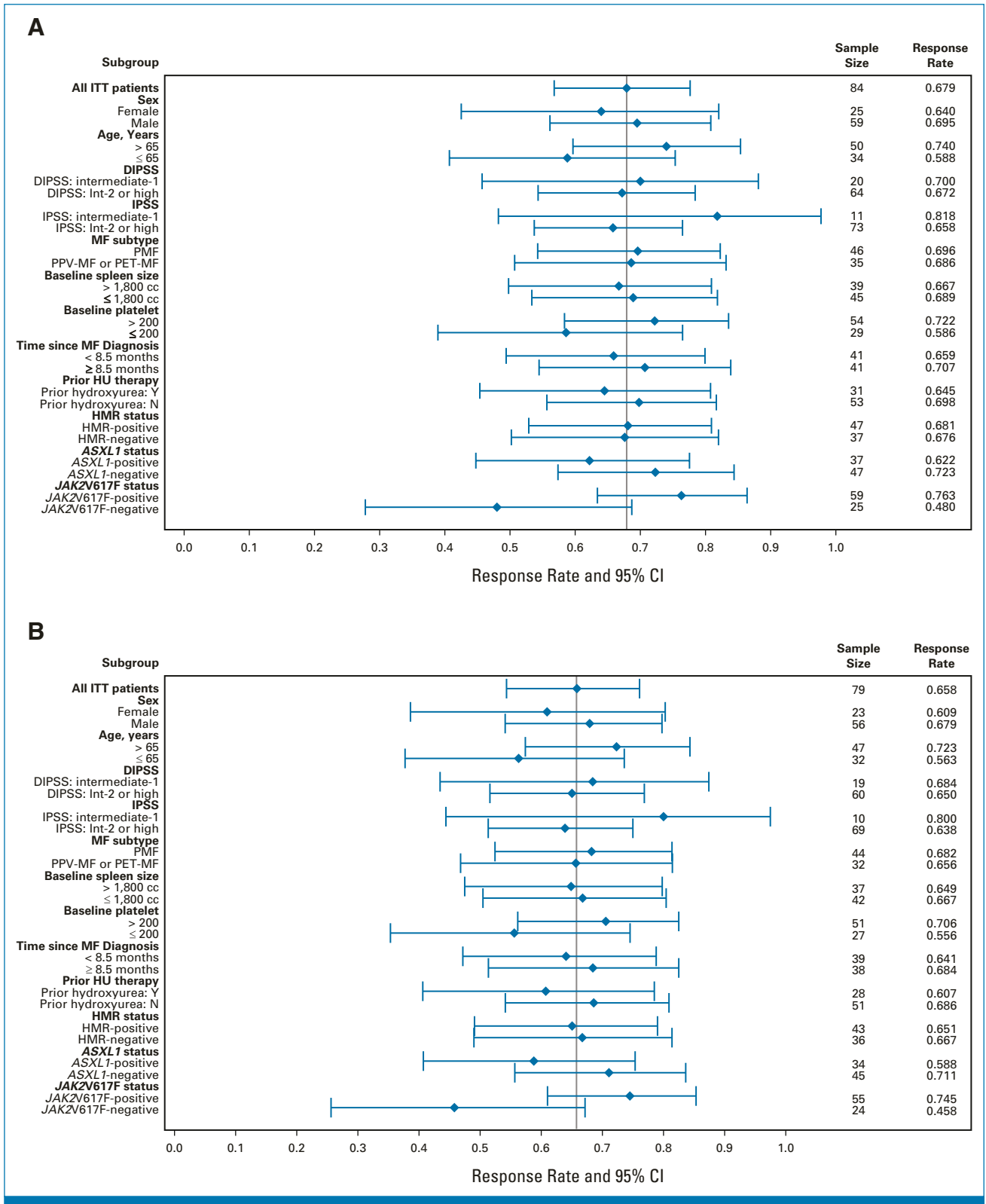


FIG 3. Subgroup analysis of SVR35 (ITT population). Subgroup analysis of SVR35 at (A) week 24 and (B) week 48. DIPSS, Dynamic International Prognostic Scoring System; HMR, high-molecular risk mutation; HU, hydroxyurea; Int-2, intermediate-2; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; MF, myelofibrosis; N, no; PET, postessential thrombocythemia; PMF, primary MF; PPV, postpolycythemia vera; SVR35; ≥ 35% reduction in spleen volume from baseline; Y, yes; yrs, years.

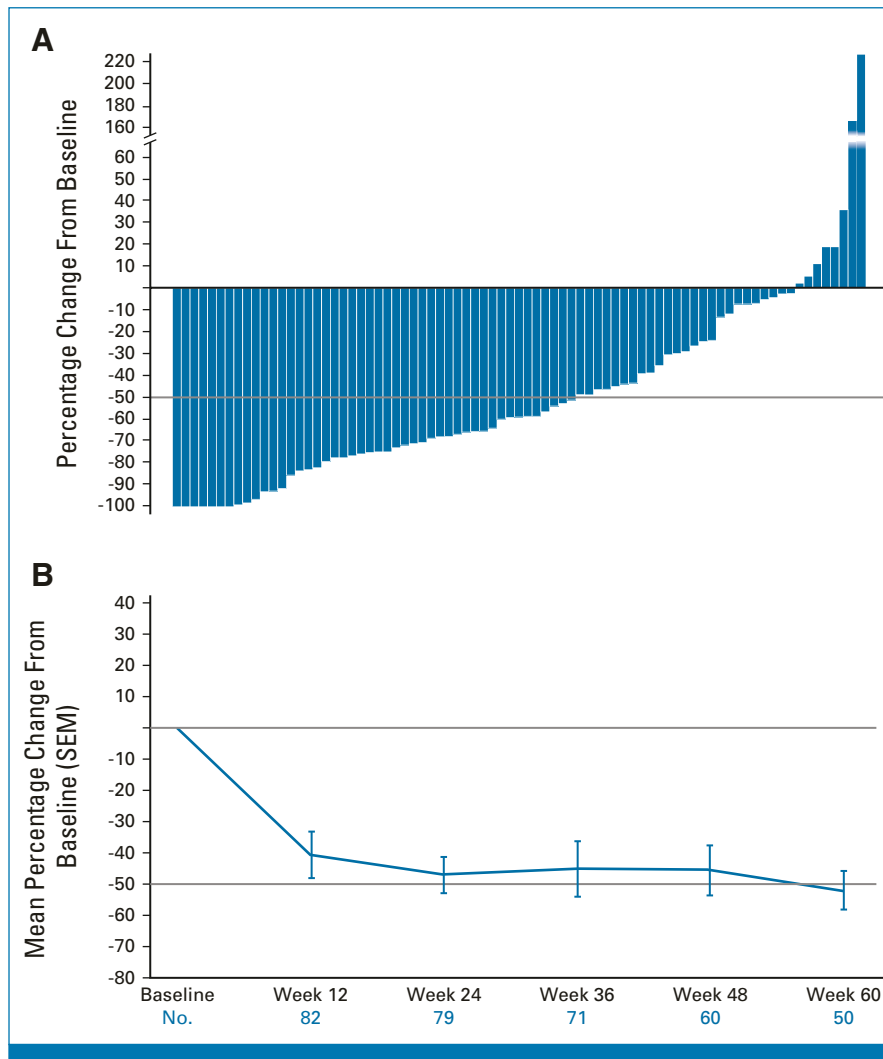


FIG 4. Change in total symptom score after treatment with pelabresib and ruxolitinib. (A) Waterfall plot of percentage change in TSS from baseline to week 24. (B) TSS mean percentage change over time. Patients were evaluable for change in total symptom score at week 24 if they had a week 24 TSS assessment by the data cutoff date or discontinued without a week 24 assessment at any time. Two patients with ongoing treatment were nonevaluable for TSS50 at week 24: one because of a missing baseline assessment and one because of a baseline TSS = 0. Long-term data are still maturing. For TSS50 at week 24, 95% CIs were 45 to 67. SEM, standard error of the mean; TSS, total symptom score; TSS50, $\geq 50\%$ reduction in TSS from baseline.

EPO, and IFN- γ were clustered together because of their upregulation at baseline and during treatment (median increase of 122% across cytokines and visits). Similar changes in plasma cytokines were observed in relapsed/refractory patients with myelofibrosis treated with pelabresib monotherapy¹⁹ and with pelabresib add-on treatment in patients with suboptimal response to ruxolitinib.²⁸

At baseline, the *JAK2V617F* variant was identified in 59 of 80 assayed patients with a mean mutant allele fraction (MAF) of 62.9%. In 44 patients with available blood samples, 29.5% achieved a reduction $> 25.0\%$ (allelic reduction was represented as the percentage change in MAF at week 24 compared with baseline). The mean reduction at week 24 was 13%

($P < .0001$; Data Supplement [Fig S5]). Longitudinal analysis across baseline and weeks 24, 48, and 72 showed significant MAF reduction over time ($P = .0028$), which correlated with spleen volume reduction ($P = .0044$). No association of transfusion-dependent status, sex, and age with reduction in MAF has been observed. Compared with patients with primary myelofibrosis, the MAF reduction in patients with post-polycythemia vera myelofibrosis was similar, whereas that of patients with postessential thrombocythemia myelofibrosis was greater ($P = .0036$)—likely because of the different distribution of MAF across subtypes.

MAF reductions were also observed for *CALR* and *MPL* at weeks 24 and 48, not reaching statistical significance with

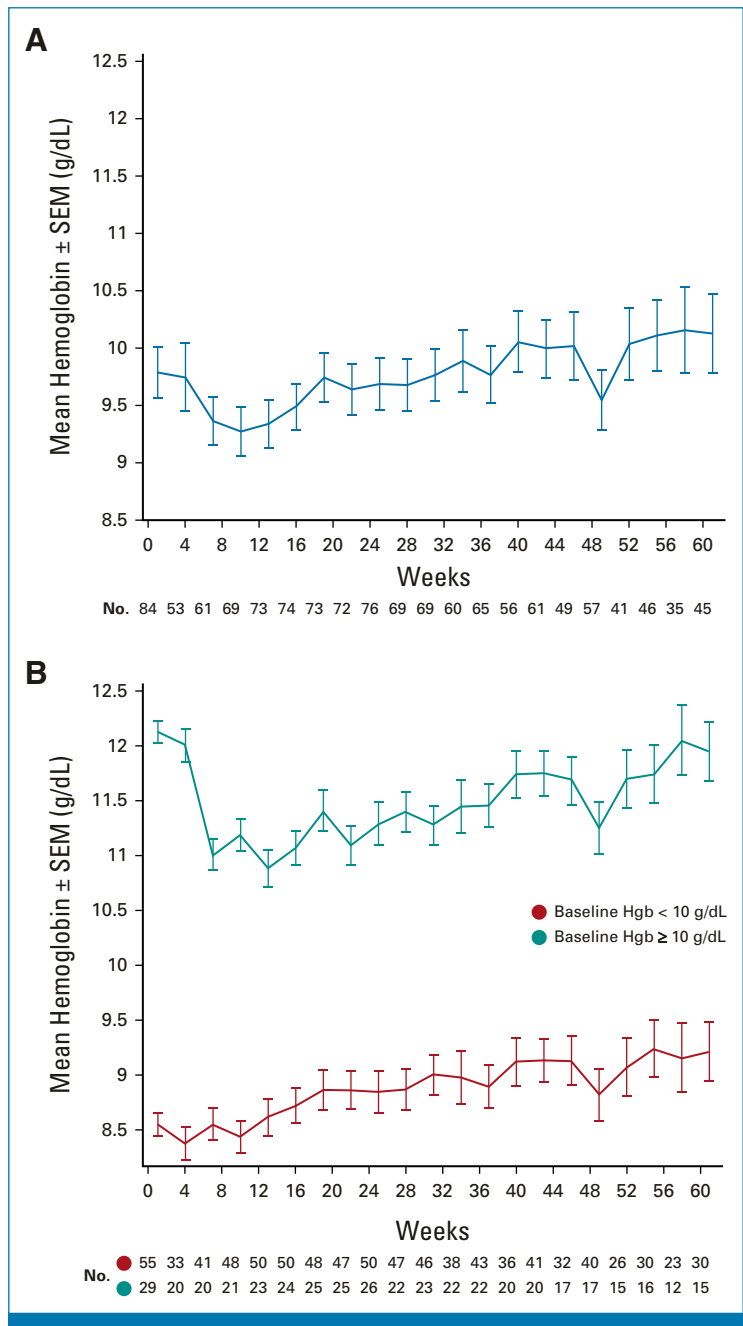


FIG 5. Mean hemoglobin levels over time. (A) Mean hemoglobin levels over time in all patients and (B) in patients on the basis of baseline levels of < 10 g/dL or ≥ 10 g/dL. Hemoglobin values within 2 weeks after transfusions are excluded. Hgb, hemoglobin; SEM, standard error of the mean.

the relatively small sample size. No reduction in MAF was observed for *ASXL1* at week 24 or 48.

Exposure

The starting dose of ruxolitinib was 5 mg twice a day in 4 (5%) patients, 10 mg twice a day in 32 (38%) patients, 15 mg twice a

day in 44 (52%) patients, and 20 mg twice a day in 4 (5%) patients. The median ruxolitinib dose for the first 24 weeks and at 36 and 48 weeks was 10 mg twice a day (min, max: 5, 25 mg). The median pelabresib dose for the first 24 weeks and at 36 and 48 weeks was 125 mg once daily. The ruxolitinib dose was increased (to 15 or 20 mg twice a day) for four patients (5%) because of not achieving an SVR35 at week 12.

TABLE 2. Summary of Most Common ($\geq 20\%$ of Patients) TEAEs Regardless of Relationship to Study Drug

TEAE ^a	All Grade (N = 84)	Grade 3 (N = 84)	Grade 4 (N = 84)
Hematologic events, No. (%)			
Thrombocytopenia ^b	44 (52)	7 (8)	3 (4)
Anemia	35 (42)	28 (33)	1 (1)
Nonhematologic events, No. (%)			
Gastrointestinal events			
Diarrhea	29 (35)	1 (1)	0
Constipation	21 (25)	0	0
Nausea	20 (24)	0	0
Abdominal pain ^c	19 (23)	0	0
Other nonhematologic events			
Fatigue ^d	28 (33)	1 (1)	0
Musculoskeletal pain ^e	25 (30)	0	0
Respiratory tract infections ^{f,g}	24 (29)	3 (4)	3 (4)
Dizziness ^h	22 (26)	0	0
Dysgeusia	18 (21)	0	0
Dyspnea	17 (20)	4 (5)	0

Abbreviation: TEAE, treatment-emergent adverse event.

^aTEAEs of all grades that occurred in $\geq 20\%$ of patients in the safety-evaluable population: received at least one dose of study drug.

^bIncludes TEAEs of platelet count decrease.

^cIncludes TEAEs of upper abdominal pain.

^dIncludes TEAEs of asthenia and fatigue.

^eIncludes TEAEs of myalgia, bone pain, arthralgia, and back pain.

^fInclude TEAEs of upper respiratory tract infection, influenza, bronchitis, sinusitis, rhinitis, nasopharyngitis, pneumonia, and pulmonary sepsis.

^gGrade 3 or higher respiratory infections were confounded by COVID-19 disease in the context of a global pandemic.

^hIncludes TEAEs of vertigo.

Safety

Ninety-six percent of patients (81 of 84) experienced \geq one treatment-emergent adverse event (TEAE), and 63% of patients (53 of 84) experienced \geq one TEAE of Grade 3 or higher. Thrombocytopenia (52%) and anemia (42%) were the most frequent hematologic TEAEs (Table 2). Of these, 12% and 34% were Grade 3/4 thrombocytopenia and anemia, respectively. These cytopenias were manageable and generally reversible with dose modifications or interruptions, with a low discontinuation rate: three (4%) patients discontinued pelabresib and ruxolitinib, two because of Grade 3 thrombocytopenia and one because of Grade 3 anemia.

The most frequent ($\geq 25\%$ of patients) nonhematologic TEAEs (Table 2) were diarrhea (35%), fatigue (33%), musculoskeletal pain (30%), respiratory tract infection (29%), and constipation (25%). These events were Grade 1 or 2, with the exception of Grade 3 diarrhea (1%), Grade 3 fatigue (1%), Grade 3 dyspnea (5%), and Grade 3 (4%) and Grade 4 (4%) respiratory tract infections; all were managed with appropriate supportive care or dose modification. No events of tuberculosis or hepatitis B reactivation were observed. Herpes zoster was reported in nine (10.7%), Herpes simplex in three (3.6%), and Varicella zoster in three (3.6%) patients;

however, these were mostly lower grade and nonserious events, with only one patient experiencing Grade 3 Herpes zoster. One patient each had pulmonary nocardiosis, bacterial endocarditis, cytomegalovirus infection, and *Achromobacter* infection.

Overall, 37% of patients had pelabresib dose reduction, and 36% had ruxolitinib dose reduction because of TEAEs; 19% required dose reduction of both agents because of TEAEs (additional details on dose reductions, interruptions, and discontinuations are provided in the Data Supplement). Five deaths occurred during study treatment or within 30 days after the last pelabresib dose: four were assessed by the investigator as unrelated to pelabresib and are described in the Data Supplement. One patient died from multiorgan failure because of sepsis secondary to pneumonia deemed as related to pelabresib.

Transformation to acute myeloid leukemia was observed in two (2%) patients on the basis of blast count in BM.

DISCUSSION

In MANIFEST Arm 3, pelabresib combined with ruxolitinib was well tolerated and showed durable spleen and symptom responses, with potential disease-modifying activity as

indicated by biomarker findings, in JAKi treatment-naïve patients with myelofibrosis.

The SVR35 response rate at week 24 was 68%; 94% of patients with an SVR35 response at any time point ($n = 67$) sustained their response 36 weeks after its onset. Symptom improvement was also reported by a substantial proportion of patients (56%). Pivotal studies of JAKi monotherapy have previously demonstrated SVR35 response rates of 29%–42%^{2–5} and TSS50 rates of 34%–46% at week 24.^{2,3,5} In general, the MANIFEST patient population was comparable with populations in other studies of JAKis, such as COMFORT-I²; 77% of patients had IPSS intermediate-2- or high-risk disease, and 56% had high-molecular risk mutations.^{5,9,29} Although baseline hemoglobin levels were lower, time from diagnosis to treatment was shorter, and rate of pretreatment with hydroxyurea was lower compared with historic controls, these parameters did not significantly affect the achievement of SVR35 (Fig 3). A high proportion of patients (46%) harbored adverse prognostic *ASXL1* mutations³⁰; however, this did not affect SVR35, TSS50, duration of response, or treatment duration (data not shown), indicating potential for this combination to improve outcomes across subgroups, including those harboring high-risk molecular profiles. The median time since diagnosis of approximately 8.5 months is shorter than that reported in historical studies of JAKi monotherapy; longer time from diagnosis to start of therapy has been associated with poor response.³¹

Pelabresib combined with ruxolitinib showed high clinical activity without clinically relevant added or limiting toxicity. Discontinuation of ruxolitinib in the real world is frequent, with 1-, 2-, and 3-year rates reported to be 49%, 71%, and 86% ($n = 51$), respectively, because of loss of therapeutic effect, lack of response, and drug-induced cytopenia.^{10,29} In the JUMP phase IIb, expanded-access study, 43% of patients discontinued ruxolitinib within 2 years.³² In this study, 37% (31 of 84) of patients discontinued treatment within 2 years, whereas treatment for 50% (42 of 84) of patients was still ongoing without reaching a 2-year follow-up despite adverse baseline characteristics. Hematologic adverse events, most commonly anemia and thrombocytopenia, were manageable, and two patients discontinued treatment because of Grade 3 thrombocytopenia. Herpes zoster and bacterial infections were mostly low grade and occurred at similar rates to those previously observed with ruxolitinib monotherapy, which is known to have immunosuppressive activity.³³

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Results of a matching-adjusted indirect comparison analysis to adjust for baseline characteristics and enable a cross-trial comparison focusing on Arm 3 of the MANIFEST trial versus phase III ruxolitinib (COMFORT-I and-II), fedratinib (JAKARTA), and momelotinib (SIMPLIFY-1) trials provide further evidence to support a potentially higher efficacy rate of pelabresib combined with ruxolitinib versus JAKi monotherapy.³⁴

Clinical and preclinical studies have demonstrated that BET proteins are key coactivators of NF- κ B-controlled gene expression, including inflammatory target genes such as *IL-8*.^{16,18,35} Pelabresib combined with ruxolitinib resulted in early and sustained reduction in levels of cytokines linked to inflammation and NF- κ B. We previously reported³⁶ that pelabresib, with or without ruxolitinib, downregulates several cytokines (eg, DKK1, CD27, and TIMP3) that have not previously been demonstrated to be regulated by JAKis^{37,38} and that the decrease with pelabresib and ruxolitinib treatment was higher than that observed after ruxolitinib monotherapy.² Centrally reviewed BM samples showed improved (≥ 1 grade) or stable BM fibrosis in 31% and 48% of patients, respectively (Data Supplement [Table S3]). Mutational analysis showed reductions in the mean *JAK2V617F* MAF, which were associated with SVR35 response. The observed effects on *JAK2V617F* MAF appear to be comparable with ruxolitinib monotherapy effects in the COMFORT-I study³⁹; however, limitations of cross-trial comparisons and differences in mutation assay methodology constrain comparative analyses.

To our knowledge, the MANIFEST trial in JAKi treatment-naïve patients is the first study with a rational combination of BETi pelabresib and ruxolitinib that showed clinically meaningful durable improvements in splenomegaly and symptoms, was associated with biomarker findings indicating potential disease modification, and demonstrated a generally favorable safety profile. This combination has the potential to improve the standard of care for treatment-naïve patients with myelofibrosis and warrants further investigation. A randomized, double-blind, phase III study (MANIFEST-2) compares safety and efficacy of pelabresib in combination with ruxolitinib with those of ruxolitinib monotherapy in JAKi treatment-naïve patients (ClinicalTrials.gov identifier: [NCT04603495](https://clinicaltrials.gov/ct2/show/study/NCT04603495)).

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

Data sharing requests by qualified researchers pertaining to Arm 3 of the MANIFEST study will be considered only for noncommercial use on a case-by-case basis (to be approved by MorphoSys; Delphine.EIMehdi@morphosys.com), starting 12 months from acceptance of the

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**MANIFEST: Pelabresib in Combination With Ruxolitinib for Janus Kinase Inhibitor Treatment-Naïve Myelofibrosis**

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