

JAK Inhibitors in the Treatment of Myelofibrosis

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Abstract: Myelofibrosis (MF) is a myeloproliferative neoplasm driven by constitutive activation of the JAK/STAT pathway, resulting in clonal hematopoiesis, fibrotic replacement of the bone marrow, extramedullary hematopoiesis, splenomegaly, and debilitating constitutional symptoms. The advent of JAK inhibitors has changed the landscape of treatment options for patients with MF, providing relatively tolerable drug options that control symptoms, reduce splenomegaly, and improve quality of life, but often at the expense of worsening cytopenias. JAK inhibitors do not appear to halt the progression of disease or prevent leukemic transformation, and their effect on survival is debated. Here, we review both the US Food and Drug Administration–approved JAK inhibitors and those in late-phase clinical trials, with a focus on clinical activity and unique adverse effects. We also provide a schema for choosing among these options for patients with MF.

Introduction

Myelofibrosis (MF) is a Philadelphia chromosome–negative (Ph–) myeloproliferative neoplasm (MPN) characterized by clonal hematopoiesis and replacement of the bone marrow by reticulin/collagen fibrosis.¹ MF can be idiopathic (primary myelofibrosis, or PMF) or a consequence of the other Ph– MPNs: polycythemia vera (PV) and essential thrombocythemia (ET).² The clinical manifestations of MF can include debilitating constitutional symptoms, splenomegaly resulting from extramedullary hematopoiesis, and abnormalities in peripheral blood cell counts. Depending on the type of imbalance between normal and malignant hematopoiesis, some patients present with a myeloproliferative phenotype characterized by leukocytosis and thrombocytosis, whereas in others, a myelodepletive phenotype develops that resembles a bone marrow failure state, often with transfusion-dependent anemia and thrombocytopenia, as well as neutropenia.³

Keywords

Clonal hematopoiesis, JAK inhibitor, myelofibrosis, myeloproliferative neoplasm

Hyperactive signaling of the Janus kinase/signal transducer and activator of transcription proteins (JAK/STAT) pathway is implicated in the molecular pathogenesis of MF, and mutations of crucial genes in this pathway are now part of the major criteria in the World Health Organization diagnostic criteria for primary MF.¹ Approximately 50% to 60% of patients with PMF harbor the somatic *JAK2* V617F gain-of-function mutation,^{4,5} 20% to 25% have a calreticulin (*CALR*) mutation,⁶ and 5% to 10% have a myeloproliferative leukemia protein (*MPL*) mutation.^{7,8} The pathogenic consequence of each of these mutations is due at least partially to activation of the JAK/STAT pathway. Even patients with “triple-negative” MPNs, who lack all 3 of these somatic mutations, appear to have hyperactive JAK/STAT signaling,⁹ which points again to the centrality of the JAK/STAT pathway in the development of MF. Recognition of the importance of JAK/STAT signaling in MF provided the rationale for the development of JAK inhibitors (JAKis) as a therapeutic option.

The treatments used historically for MF include erythropoiesis-stimulating agents (ESAs), androgens, prednisone, danazol, thalidomide (Thalomid, Celgene), lenalidomide, hydroxyurea, and pegylated interferon alfa-2a, but use of these agents is hampered by moderate response rates and intolerable side effects that lead to high rates of discontinuation.¹⁰⁻¹⁴

The 2005 discovery of *JAK2* V617F as a primary driver of clonal hematopoiesis in MPNs fostered interest in targeting the mutation for therapeutic benefit.^{5,15-17} The valine-for-phenylalanine substitution occurs in the pseudokinase domain of *JAK2*, resulting in impaired negative regulation of *JAK2*'s kinase. Most of the *JAK2* inhibitors developed, however, bind the unmutated adenosine triphosphate (ATP)-binding site of *JAK2* (type 1 inhibitor), with affinity for both wild-type and mutated *JAK2* proteins, leading to some of the myelosuppressive complications associated with these therapies.¹⁸

In the last decade, the landscape of MF treatment has been transformed by the introduction of JAKis, which are now first-line therapy for patients with high- or intermediate-risk disease or symptomatic low-risk disease. Here, we review the available JAKis approved by the US Food and Drug Administration (FDA), as well as several currently in clinical development, with a focus on clinical activity and unique adverse events (AEs).

FDA-Approved JAK Inhibitors

Ruxolitinib

Ruxolitinib (Jakafi, Incyte), a potent inhibitor of JAK1 (half-maximal inhibitory concentration [IC₅₀] of 3.3 nM) and JAK2 (IC₅₀ of 2.8 nM),¹⁹ first entered clinical

trials for MF in 2007 and quickly demonstrated unprecedented activity in reducing spleen volumes and decreasing MF-related constitutional symptoms.^{20,21} The landmark COMFORT-I (NCT00952289) and COMFORT-II (NCT00934544) trials subsequently compared ruxolitinib with placebo and with best available therapy (BAT) in patients who had International Prognostic Scoring System (IPSS) intermediate-2 (Int-2)-risk or high-risk disease.

In COMFORT-I,²² 309 adults were randomly assigned in a 1:1 ratio to either placebo or ruxolitinib at 1 of 2 doses, depending on baseline platelet count. The primary endpoint of spleen volume reduction (SVR) of at least 35% from baseline after 24 weeks was reached by 41.9% of patients in the ruxolitinib arm vs 0.7% of those in the placebo arm ($P < .001$). Virtually all the patients in the ruxolitinib arm had some degree of spleen response, with a median SVR of 33%, whereas only one-quarter of the patients in the placebo group had any degree of spleen reduction, and most had progressive splenomegaly. Spleen responses were maintained at 48 weeks in more than two-thirds of patients taking ruxolitinib. Constitutional symptoms associated with MF were significantly reduced in the ruxolitinib group, as measured by a reduction of 50% or more in the Myelofibrosis Symptom Assessment Form Total Symptom Score (MFSAF TSS), version 2.0, from baseline to week 24 (Table). Symptom responses occurred rapidly, with most occurring within 4 weeks of the initiation of treatment. The rates of SVR and TSS reductions were similar in the patients with and without the *JAK2* V617F mutation.

Ruxolitinib appeared to have an overall favorable safety profile, but hematologic AEs were significantly more frequent in the ruxolitinib arm. Rates of high-grade anemia in ruxolitinib-treated patients were more than double those of patients in the placebo arm, and high-grade thrombocytopenia was 10 times more common in the ruxolitinib-treated patients than in the placebo group. However, cytopenias were manageable with transfusions and dose modifications or interruptions of therapy, and only one patient in each arm required treatment discontinuation because of hematologic AEs. By week 8, the rate of high-grade cytopenias in the ruxolitinib arm matched that in the placebo arm.

At the same time as COMFORT-I, COMFORT-II randomly assigned 219 patients in a 2:1 ratio to ruxolitinib or investigator's choice of BAT, which most frequently consisted of hydroxyurea, glucocorticoids, or no therapy.²³ None of the patients in the BAT group reached the primary endpoint of SVR of at least 35% by 48 weeks, vs 28% of the patients receiving ruxolitinib. Spleen responses were durable, with 80% of patients in the ruxolitinib group maintaining a response after a

Table. Major Late-Phase Trials of JAK Inhibitors

Primary Targets	Trial, Phase (No. Patients)	Treatment Arms (Randomization)	Key Inclusion Criteria ^a	SVR ≥35% at 24 Wk	Symptom Response	Significant Toxicities
<i>Ruxolitinib</i>						
JAK1/2	COMFORT-I, phase 3 (309)	Ruxolitinib 15 mg BID for PLT 100-200×10 ⁹ /L and 20 mg BID for PLT 200×10 ⁹ /L vs placebo (1:1)	≥Int-2–risk MF, PLT ≥100×10 ⁹ /L, intolerant of or refractory to other available therapies	41.9% (ruxolitinib) vs 0.7% (placebo), OR 134.4 (95% CI, 18.0-1004.9; <i>P</i> <.001)	≥50% TSS reduction on MFSAF TSS version 2.0: 45.9% (ruxolitinib) vs 5.3% (placebo), OR 15.3 (95% CI, 6.9-33.7; <i>P</i> <.001)	Discontinuation for AEs: 11% with ruxolitinib vs 11% with placebo; ecchymosis (18.7%), dizziness (14.8%), headache (14.8%), grade 3-4 anemia (45.2%), thrombocytopenia (12.9%), neutropenia (7.1%)
	COMFORT-II, phase 3 (219)	Ruxolitinib 15 mg BID for PLT 100-200×10 ⁹ /L and 20 mg BID for PLT >200×10 ⁹ /L vs BAT (2:1)	≥Int-2–risk MF, PLT ≥100×10 ⁹ /L	32% (ruxolitinib) vs 0% (BAT); <i>P</i> <.001	EORTC QLQ-C30 Global Health Status and Quality of Life score mean change from baseline: +9.1 (ruxolitinib) vs +3.4 (BAT) FACT-Lym total score mean change from baseline: +11.3 (ruxolitinib) vs -0.9 (BAT)	Discontinuation for AEs: 8% with ruxolitinib vs 5% with BAT; diarrhea (23%); grade 3-4 anemia (42%), thrombocytopenia (8%)
<i>Fedratinib</i>						
JAK2>JAK1, TYK2, JAK3	JAKARTA, phase 3 (289)	Fedratinib 400 mg daily vs fedratinib 500 mg daily vs placebo (1:1:1)	≥Int-2–risk MF, PLT ≥50×10 ⁹ /L, JAKi-naive	36% (fedratinib 400 mg, 95% CI, 27%-46%) vs 40% (fedratinib 500 mg, 95% CI, 30%-50%) vs 1% (placebo, 95% CI, 0%-3%) confirmed at 28 wk (<i>P</i> <.001)	≥50% MFSAF TSS reduction: 36% (fedratinib 400 mg) vs 34% (fedratinib 500 mg) vs 7% (placebo), <i>P</i> <.001	Discontinuation for AEs: 14% (fedratinib 400 mg) vs 25% (fedratinib 500 mg) vs 8% (placebo); diarrhea (56%-66%), vomiting (42%-55%), nausea (51%-64%); grade 3-4 anemia (43%-60%), thrombocytopenia (17%-27%), neutropenia (8%-18%); WE (4 patients, all in 500-mg arm, all women)
	JAKARTA2, phase 2 (97)	Fedratinib 400 mg daily (no comparator)	Int-1–risk MF with symptoms, Int-2–risk or high-risk MF, PLT ≥50×10 ⁹ /L, ruxolitinib-intolerant/resistant	55% (95% CI, 44%-66%)	≥50% MFSAF TSS reduction: 26%	Discontinuation for AEs: 19%; diarrhea (58%), vomiting (41%), nausea (56%); grade 3-4 anemia (38%), thrombocytopenia (22%)

Table. (Continued) Major Late-Phase Trials of JAK Inhibitors

Primary Targets	Trial, Phase (No. Patients)	Treatment Arms (Randomization)	Key Inclusion Criteria ^a	SVR ≥35% at 24 Wk	Symptom Response	Significant Toxicities
<i>Pacritinib</i>						
JAK2, FLT3, IRAK1, CSF1R	PERSIST-1, phase 3 (327)	Pacritinib 400 mg daily vs BAT (2:1)	≥Int-1—risk MF, symptoms based on MPN-SAF TSS version 2.0, no exclusion criteria based on baseline Hgb or PLT, no prior treatment with JAKi	19% (pacritinib) vs 5% (BAT) (<i>P</i> =.0003)	≥50% MPN-SAF TSS reduction: 19% (pacritinib) vs 10% (BAT) (<i>P</i> =.24)	Discontinuation for AEs: 10%; diarrhea (55%), nausea (27%), vomiting (16%); grade 3-4 anemia (17%), thrombocytopenia (11%)
	PERSIST-2, phase 3 (311)	Pacritinib 400 mg daily vs pacritinib 200 mg BID vs BAT (1:1:1)	≥Int-1—risk MF, symptoms based on MPN-SAF TSS 2.0, PLT ≤100×10 ⁹ /L	18% (pacritinib) vs 3% (BAT) (<i>P</i> =.001)	≥50% MPN-SAF TSS reduction: 25% (pacritinib) vs 14% (BAT) (<i>P</i> =.08)	Discontinuation for AEs: 9%-14%; diarrhea (53%), nausea (33.3%), vomiting (22%); grade 3-4 anemia (22%-27%), thrombocytopenia (31%-32%)
<i>Momelotinib</i>						
JAK1/2, TYK2	SIM-PLIFY-1, phase 3 (432)	Momelotinib 200 mg daily vs ruxolitinib 20 mg BID (1:1)	Int-1—risk MF with symptoms, Int-2— or high-risk MF, JAKi-naive	26.5% (momelotinib) vs 29.0% (ruxolitinib) (noninferiority proportion difference, 0.09; 95% CI, 0.02-0.16; <i>P</i> =.011)	≥50% MFSAF TSS reduction: 28.4% (momelotinib) vs 42.2% (ruxolitinib) (noninferiority proportion difference, 0.00; 95% CI, -0.08 to 0.08; <i>P</i> =.98)	Discontinuation for AEs: 13.1% (momelotinib) vs 5.6% (ruxolitinib); diarrhea (17.8%), headache (17.3%), dizziness (15.9%), nausea (15.9%), peripheral neuropathy (10.3%); grade 3-4 anemia (5.6%), thrombocytopenia (7.0%)
	SIM-PLIFY-2, phase 3 (156)	Momelotinib 200 mg daily vs BAT (2:1)	Int-1—risk MF with symptoms, Int-2— or high-risk MF, ruxolitinib intolerant/resistant	7% (momelotinib) vs 6% (ruxolitinib) (noninferiority proportion difference, 0.01; 95% CI, -0.09 to 0.10; <i>P</i> =.90)	≥50% MPN-SAF TSS reduction: 26% (momelotinib) vs 6% (BAT) (<i>P</i> =.0006)	Discontinuation for AEs: 14%; diarrhea (14%), nausea (17%); grade 3-4 anemia (38%), thrombocytopenia (7%)
<i>Itacitinib</i>						
JAK1	Phase 2 (87)	Itacitinib 100 mg BID vs 200 mg BID vs 600 mg daily (Simon 2-stage design)	≥Int-1—risk MF, PLT ≥50×10 ⁹ /L, symptomatic	16.7% (among all doses)	≥50% TSS reduction: 20% (100 mg BID) vs 35.7% (200 mg BID) vs 32.3% (600 mg daily)	Discontinuation for AEs: 8%; upper respiratory tract infections (19.5%), fatigue (28.7%), nausea (18%); grade 3-4 anemia (32.5%), thrombocytopenia (29.1%), neutropenia (4.7%)

Table. (Continued) Major Late-Phase Trials of JAK Inhibitors

Primary Targets	Trial, Phase (No. Patients)	Treatment Arms (Randomization)	Key Inclusion Criteria ^a	SVR ≥35% at 24 Wk	Symptom Response	Significant Toxicities
<i>Jakinib</i>						
JAK1/2	Phase 2 (118)	Jaktinib 100 mg BID vs 200 mg daily (1:1 for first 104 patients, then 14 additional patients in 100-mg BID group)	Int-1–risk MF with symptoms, Int-2– or high-risk MF	51.5% (100 mg BID) vs 28.8% (200 mg daily) (<i>P</i> =.0151)	63.6% (100 mg BID) vs 53.8% (200 mg daily)	Discontinuation for AEs: 10.2%; thrombocytopenia (31.4%), anemia (22.0%), and neutropenia (8.5%)

^aAll studies required patients to be at least 18 years of age and have palpable splenomegaly at least 5 cm below the left costal margin. In addition, all studies included primary MF, post–polycythemia vera MF, and post–essential thrombocythemia MF.

AEs, adverse events; BAT, best available therapy; BID, twice daily; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; Int-1, intermediate-1; FACT-Lym, Functional Assessment of Cancer Therapy–Lymphoma; Hgb, hemoglobin; JAKi, JAK inhibitor; MF, myelofibrosis; MFSAF TSS, Myelofibrosis Symptom Assessment Form Total Symptom Score; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; OR, odds ratio; PLT, platelet count; SVR, spleen volume reduction; WE, Wernicke encephalopathy; wk, weeks(s).

median follow-up of 12 months. Reductions in MF-related symptoms and improvement in quality of life as assessed on several scales were observed more frequently in the ruxolitinib group. Anemia remained a significant AE (22.5% in the ruxolitinib arm at final analysis), although it rarely led to drug discontinuation.²⁴

More recently, the phase 3b expanded-access JUMP trial demonstrated that the efficacy and safety of ruxolitinib in patients with Int-1–risk MF and palpable splenomegaly are similar to the efficacy and safety demonstrated in those with higher-risk MF in the COMFORT studies.^{25,26} The National Comprehensive Cancer Network includes ruxolitinib as an option for low-risk, symptomatic MF.²⁷

Survival in ruxolitinib-treated patients has been correlated with the degree of reduction in spleen size.^{28,29} Additionally, it is inversely related to the number of myeloid mutations present on assessment with next-generation sequencing,³⁰ the presence of high-molecular-risk mutational profiles,³¹ and clonal evolution during treatment.³² Although baseline anemia before treatment is associated with a poorer prognosis, treatment-emergent transfusion dependence is not.³³

Follow-up studies also have shown that spleen responses to ruxolitinib are durable,³⁴⁻³⁷ and patient-reported decreases in symptoms with ruxolitinib are consistent on numerous scoring tools.³⁸ Subgroup analyses of the patients in COMFORT found no differences in SVR, symptom reduction, and survival benefits across subgroups,^{39,40} but retrospective analyses have implicated several factors as contributors to a poor response to

ruxolitinib, including pretreatment transfusion dependence, thrombocytopenia, and the use of doses of less than 10 mg twice daily.⁴¹

One important consideration when ruxolitinib is used is the risk for ruxolitinib withdrawal syndrome, which can occur suddenly on discontinuation of the drug. The syndrome has been characterized by the rapid recurrence of splenomegaly, cytopenias, and occasionally septic shock–like signs and symptoms, including hemodynamic instability, disseminated intravascular coagulation, hypoxia, and altered mentation.⁴² Careful downward titration of ruxolitinib is required to mitigate this potentially severe discontinuation syndrome.

Fedratinib

Fedratinib (Inrebic, Bristol Myers Squibb) was developed with the hope that it could provide an alternative treatment to patients with MF, especially those with ruxolitinib intolerance or resistance. In vitro studies of the tyrosine kinase specificity of fedratinib revealed that it inhibits up to 54 known kinases and has an exceptionally strong affinity for JAK2, with significantly lower affinity for JAK1, tyrosine kinase 2 (TYK2), and JAK3.⁴³ Fedratinib inhibits many kinases not targeted by ruxolitinib, including numerous proteins necessary for hematopoietic cell signaling and those expressed on nonhematopoietic cells. Molecular docking studies demonstrated that fedratinib has a unique ability to bind both the ATP- and substrate-binding sites of JAK2, and in vitro binding studies showed that it binds JAK2 even in the presence

of 211 amino acid substitutions that confer resistance to ruxolitinib in laboratory models.⁴⁴ Fedratinib received FDA approval for the treatment of MF in 2019, and it has been assessed both as first-line therapy and as second-line therapy after ruxolitinib in patients with Int-2- or higher-risk MF.

In the phase 3 JAKARTA trial (NCT01437787), 289 ruxolitinib-naïve patients with at least Int-2-risk MF were randomized 1:1:1 to receive fedratinib at 400 or 500 mg daily or placebo for 6 consecutive 4-week cycles.⁴⁵ The primary endpoint of SVR of at least 35% at 24 weeks and confirmed at 28 weeks was reached in only 1% of patients in the placebo group, whereas this endpoint was reached in 36% and 40% of patients taking fedratinib at 400 and 500 mg daily, respectively ($P < .001$). The percentage of patients with SVR was higher in the trial groups than in the placebo group regardless of baseline platelet count, JAK2 mutational status, or disease subtype (primary MF, post-PV MF, or post-ET MF). An MFSAF TSS reduction of at least 50% at 24 weeks was observed in just over one-third of patients in both fedratinib groups but in only 7% of those in the placebo group ($P < .001$). No significant changes were seen in *JAK2* V617F allele burdens, a finding that negates prior hypotheses that the clinical efficacy of fedratinib is directly related to a decrease in the mutant allele burden.⁴⁶

The rates of treatment discontinuation because of AEs were substantially higher in the fedratinib groups (25% and 14% in the 500- and 400-mg groups, respectively) than in the placebo arm (8%). The most common AEs were anemia, gastrointestinal toxicity, and heart failure. Thrombocytopenia occurred in more than half the patients in all study arms, and fedratinib discontinuation due to thrombocytopenia was most common in patients with a baseline platelet count of less than $100 \times 10^9/L$.

JAKARTA2 was a single-arm phase 2 trial of 97 patients with Int-1- or higher-risk MF in whom ruxolitinib resistance or intolerance was found after at least 14 days of therapy.⁴⁷ The trial was closed before completion because of concerns about the development of Wernicke encephalopathy (WE), resulting in a clinical hold on the drug in 2013. Use of a last observation carried forward method to evaluate data in the per-protocol population showed that 55% of evaluable patients achieved the primary endpoint of SVR, and just over one-quarter achieved an MFSAF TSS reduction of 50% or greater from baseline to the end of 24 weeks. A confirmatory analysis of the JAKARTA2 data, however, found SVR rates of 31% in the intention-to-treat (ITT) cohort, 30% in a cohort for which a more stringent definition of ruxolitinib failure was used, and 36% in a sensitivity analysis cohort.⁴⁸ Similar response rates were observed for patients who had baseline thrombocytopenia with a platelet count

of $50 \times 10^9/L$ to $100 \times 10^9/L$ and anemia with a hemoglobin level of less than 10 g/dL. Importantly, 91% of patients with baseline platelet counts of $50 \times 10^9/L$ to less than $100 \times 10^9/L$ received at least 80% of their intended fedratinib dose, and their SVR rates were comparable with those of patients who had higher baseline platelet counts, suggesting that fedratinib can be used in patients with thrombocytopenia without dose adjustment. These results indicated a role for fedratinib in patients with ruxolitinib resistance or intolerance.

Upon later review of the 8 cases of encephalopathy in the initial fedratinib trials, the affected patients were found either not to have WE or to have had other conditions predisposing them to encephalopathy, independently of fedratinib treatment.⁴⁹ Fedratinib eventually gained FDA approval in 2019 for use as a first-line agent in MF or as a second-line agent after ruxolitinib, with a Black Box Warning regarding the potential for WE, as well as a recommendation to assess for thiamine deficiency before initiation and periodically during treatment. Fedratinib is being evaluated further in the ongoing, single-arm phase 3b FREEDOM trial (NCT03755518), which has continued to show the safety and tolerability of the drug and has demonstrated improved AE rates with mitigation strategies (gastrointestinal prophylaxis and thiamine monitoring, plus plans to add luspatercept [Reblozyl, Bristol Meyers Squibb] for a subset of patients with anemia).⁵⁰ The efficacy of fedratinib in patients with ruxolitinib intolerance or resistance is also being compared with BAT in the phase 3 FREEDOM2 trial (NCT03952039).

Pacritinib

Pacritinib (Vonjo, CTI BioPharma) is the most recent JAKi to be approved by the FDA. It is a macrocyclic pyrimidine-based multikinase inhibitor that has specificity for JAK2, FLT3, IRAK1, and CSF1R but spares JAK1.⁵¹ After pacritinib had demonstrated an ability to reduce splenomegaly and constitutional symptoms in patients with MF in phase 1 and 2 trials,^{52,53} its efficacy was evaluated in 2 major randomized controlled trials, PERSIST-1 (NCT01773187) and PERSIST-2 (NCT02055781). Because early-phase trials revealed minimal hematologic AEs with pacritinib,⁵⁴ these studies did not exclude patients with baseline anemia or thrombocytopenia, and their inclusion set the trials apart from those conducted with the other JAK2 inhibitors. Early data raised concerns for increased mortality secondary to bleeding and cardiovascular events, including intracranial hemorrhage, cardiac arrest, and cardiac failure, and resulted in an FDA hold in February 2016 and treatment disruptions in both PERSIST trials. However, cardiovascular and bleeding events were rare among the patients who continued treatment under a compassionate use

authorization,⁵⁵ and more-mature data demonstrated that cardiac and bleeding events did not differ significantly between trial arms. With these data, as well as the submission of a dose-comparison study protocol, the FDA lifted the hold approximately 1 year after it had been placed.

In PERSIST-1,⁵⁶ patients with Dynamic International Prognostic Scoring System (DIPSS) int-1-, int-2-, or high-risk MF were randomly assigned to receive pacritinib or BAT, which consisted mostly of hydroxyurea or watchful waiting, and other JAKis were excluded. In an ITT analysis for the primary endpoint, SVR of at least 35% was achieved in 19% of patients in the pacritinib arm at 24 weeks, in comparison with 5% in the BAT arm ($P=.0003$). These patients maintained a spleen response through week 108. In prespecified subgroups of patients in the pacritinib group with baseline thrombocytopenia of less than $100 \times 10^9/L$ and less than $50 \times 10^9/L$, SVR of at least 35% was seen in 17% and 23% of patients, respectively, whereas this outcome was not reached in any of the patients receiving BAT in those subsets ($P=.0072$ and $P=.037$, respectively). Although no significant difference was found between the rates of reduction of at least 50% in MPN-SAF TSS 2.0 in the 2 groups at 24 weeks in the ITT analysis, the difference was significant when the entire evaluable population was included (36% for pacritinib vs 14% for BAT; $P=.029$). When considering responses to the 6 common questions on the MPN-SAF TSS 2.0 and an earlier version of the MPN-SAF TSS, the difference in TSS reduction was even more pronounced (41% with pacritinib vs 10% with BAT in the evaluable population). An ITT analysis showed no difference in overall survival (OS) at 24 weeks between the 2 arms but did reveal a nonsignificant trend toward improved OS in the BAT group after week 24 (hazard ratio [HR], 1.36; 95% CI, 0.89-2.09; $P=.16$). These results were confounded by the fact that 84% of patients in the BAT group crossed over to receive pacritinib.

Platelet and hemoglobin trends during the trial were more favorable in the pacritinib arm. Patients in the pacritinib group with baseline severe thrombocytopenia exhibited a nonsignificant trend toward improved platelet counts ($P=.055$), those with a baseline hemoglobin level of less than 10 g/dL had a significant improvement with pacritinib ($P=.017$), and significantly more transfusion-dependent patients in the pacritinib arm than in the BAT arm achieved transfusion independence (25% vs 0%; $P=.043$). The most frequent nonhematologic AEs were diarrhea, nausea, and vomiting, which were significantly more common in the pacritinib group but were all grades 1 to 3. No significant difference between the rates of leukemic transformation was found in the 2 groups, and no transformations were observed after crossover.

PERSIST-2⁵⁷ evaluated the efficacy of pacritinib

once or twice daily vs BAT including ruxolitinib (45%), in patients with baseline thrombocytopenia (platelet count $<100,000/\mu L$). As in PERSIST-1, significantly more participants in the pacritinib arm in PERSIST-2 achieved SVR of at least 35% by week 24 (18% in the 2 pacritinib arms combined vs 3% in the BAT arm; $P=.001$). A nonsignificantly greater percentage of patients in the combined pacritinib arms had an MPN-SAF TSS reduction of at least 50% (25% vs 14%; $P=.08$), but this difference was found to be significant when the twice-daily pacritinib dosing was compared with BAT (32% vs 14%; $P=.01$). The improved SVR and TSS reduction were similarly observed in patients with baseline platelet counts of less than $50,000/\mu L$ and in the fewer than 40% of patients previously treated with ruxolitinib.

Red blood cell transfusion requirements were lower in the 2 pacritinib groups than in the BAT group. Clinical and pharmacokinetic results in the study as well as in a phase 2 dose-finding study supported the use of pacritinib at a dosage of 200 mg twice daily.⁵⁸ A retrospective analysis of the data in PERSIST showed significantly better SVR and symptom responses in the patients who received pacritinib, even those with baseline severe thrombocytopenia, than in the patients who received BAT, with a tolerable safety profile.⁵⁹ Overall, pacritinib has shown promising results as an option to fill the unmet clinical needs of patients with baseline or treatment-emergent cytopenias.

No significant difference between the HRs for OS were found in a comparison of the pacritinib arms and the patients who received BAT, but the overall death rate within the BAT arm was substantially lower in those who crossed over to pacritinib (8% vs 20%). In a post hoc analysis of the combined PERSIST-1 and PERSIST-2 trials, spleen responses were observed regardless of the *JAK2* V617F allele burden or presence of the mutation. Spleen and symptom responses in patients with a *JAK2* V617F allele burden of less than 50% were significantly higher in the pacritinib arm than in the BAT arm, suggesting a unique role for pacritinib in patients with the myelodepletive phenotype.⁶⁰

In February 2022, on the basis of PERSIST-2, the FDA granted accelerated approval of pacritinib at a dose of 200 mg twice daily for patients with intermediate- or high-risk MF and a platelet count of less than $50,000/\mu L$.⁶¹ As a condition of the approval, the phase 3 PACIFICA trial (NCT03165734), which is currently enrolling patients, will be completed to confirm clinical the benefit of pacritinib vs physician's choice of therapy, including low-dose ruxolitinib, in patients with a baseline platelet count of less than $50,000/\mu L$.⁶² In response to these results, pacritinib is now recommended as first-line treatment for higher-risk MF patients with platelet counts

less than 50,000/L who are not transplant candidates, or in the second-line for patients with platelet counts of 50,000/L or greater who had an inadequate response to a prior JAKi.²⁷

JAK Inhibitors in Clinical Trials

Momelotinib

Momelotinib is a highly potent ATP-competitive inhibitor of JAK1/2 and TYK2^{63,64} that was initially identified as a potential therapeutic option after screening of a host of phenylaminopyrimidine compounds for their JAK2 inhibitory capabilities.⁶⁵

Momelotinib was evaluated in several clinical trials, and FDA approval is now pending through a fast-track designation process. In the initial phase 1/2 trials, a striking and unexpected anemia response that had not been seen with other JAKis was observed in the patients who received momelotinib; 70% of the transfusion-dependent patients became transfusion-independent during the 12-week assessment period.⁶⁶ Subsequent studies in animals elucidated that momelotinib inhibits activin A receptor type 1, decreasing hepcidin production; the subsequent mobilization of sequestered iron from cellular stores fosters erythropoiesis.⁶⁷

In the phase 3 SIMPLIFY-1 trial, momelotinib was compared with ruxolitinib in JAKi-naïve patients, with mixed results.⁶⁸ Although momelotinib met the primary endpoint of noninferiority to ruxolitinib in achieving SVR of at least 35% at 24 weeks, it failed to establish an improvement vs ruxolitinib in achieving a reduction of at least 50% in the MFSAF TSS. Momelotinib treatment did, however, result in a numerically higher composite clinical improvement rate and improvements in anemia endpoints. A subsequent survival analysis demonstrated that patients who became transfusion-independent on momelotinib had an OS advantage vs those who remained transfusion-dependent (median OS not reached; 3-year OS, 80%; HR, 0.30; $P < .0001$).⁶⁹ Rates of anemia were substantially higher in the ruxolitinib group, peripheral neuropathy was more common in the momelotinib group, and the number of AEs leading to discontinuation of the study drug was higher in the momelotinib group.

SIMPLIFY-2 enrolled patients in whom previous treatment with ruxolitinib had resulted in adverse hematologic effects requiring red blood cell transfusions or dose reduction and compared momelotinib with BAT, which included ruxolitinib in 89% of cases. Momelotinib was found to be nonsuperior to BAT for the primary endpoint of SVR of at least 35%, thus precluding statistical significance for the secondary endpoints; however, the secondary endpoints were nonetheless tested for nominal significance. An MPN-SAF TSS reduction of at least

50% was noted in more patients in the momelotinib arm than in the BAT arm (26% vs 6%; $P = .0006$), which was a reversal of the results from SIMPLIFY-1. The patients on ruxolitinib in SIMPLIFY-2 received lower doses than those in SIMPLIFY-1, which the investigators speculate may have contributed to this finding. Secondary transfusion endpoints were also better in the trial arm. Compared with patients in the BAT arm, those treated with momelotinib had higher rates of transfusion independence (43% vs 21%; nominal $P = .0012$) and lower rates of transfusion dependence (50% vs 64%; nominal $P = .10$) over 24 weeks, and their transfusion requirements overall were less during course of treatment (40% vs 27%). Surprisingly, the rates of grade 3 anemia were identical in the 2 groups.⁷⁰

Long-term follow-up data of momelotinib suggest durable spleen responses and extended periods of transfusion independence, but high rates of treatment discontinuation (91% at 1.4 years), a high incidence of potentially irreversible peripheral neuropathy (47%), and no effect on leukemia-free survival or OS.^{71,72} Currently, the MOMENTUM trial (NCT04173494) is seeking to compare momelotinib with danazol in JAKi-pretreated subjects with symptomatic MF and anemia.⁷³ Results of this trial may lead to regulatory approval of momelotinib, which would address the currently unmet need for therapy options for patients with myelodepletive MF.

Other JAK Inhibitors in Clinical Trials

Several other JAKis are progressing through early stages of trial evaluation, including itacitinib⁷⁴ (NCT04640025, NCT04629508, NCT03144687) and jaktinib⁷⁵ (NCT04851535, NCT03886415, NCT04617028, NCT04217993) (Table).

Limitations of JAK Inhibitors

Although JAKis have led to significant advances in MF symptom control, the use of these agents is limited by tolerability issues, and treatment does not appear to alter the natural history of MF for most patients. As previously discussed, the hematologic side effects are often dose-limiting and lead to discontinuation. In the COMFORT trials, 50% to 70% of patients discontinued treatment prematurely by the time of the 5-year data collection cutoff as a consequence of AEs, including cytopenias, disease progression, and unsatisfactory therapeutic effect.⁷⁶ However, in a post hoc analysis of the 13 patients in COMFORT-II who received ESAs concomitantly with ruxolitinib, the majority had substantial improvements in their hemoglobin levels within 6 weeks of ESA administration without any decrease in the effectiveness ruxolitinib for spleen reduction.⁷⁷ The observational Ruxo-EPO trial

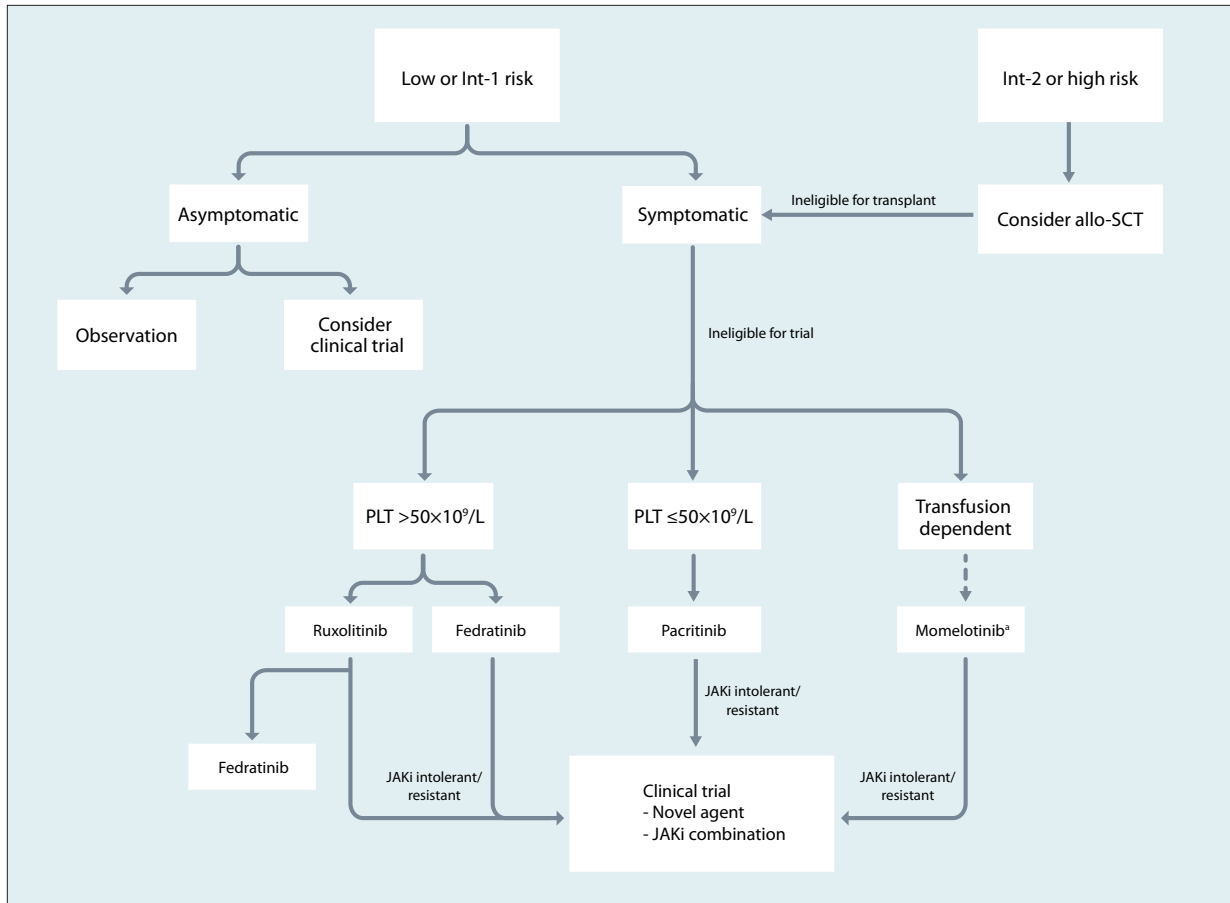


Figure. Approach to JAK inhibitor therapy by risk stratification in patients with myelofibrosis.

*Potential future therapeutic option.

Allo-SCT, allogeneic stem cell transplant; JAKi, JAK inhibitor; PLT, platelet count.

(NCT03208803) is attempting to collect more information about the effect of combining JAKis and ESAs.

Predicting a poor response to ruxolitinib is an area of active investigation. Several retrospective analyses have observed shorter times to treatment discontinuation and reduced spleen responses in patients with *JAK2* V617F allele burden of no more than 50% or with additional co-mutations, with the poorest spleen response in those with 3 or more co-mutations^{30,58,78} Outcomes in patients after the cessation of ruxolitinib are notoriously poor; these patients rarely respond to salvage therapy and have a median post-ruxolitinib survival of 13 to 14 months.^{33,79} The high rates of ruxolitinib discontinuation and unacceptable outcomes once ruxolitinib is stopped underscore the importance of alternative therapeutic options for patients with MF. Recently, ruxolitinib dose, spleen response, and transfusion requirement after 6 months of treatment have been integrated into a prognostic model, Response to Ruxolitinib After 6 Months (RR6), which aims to identify those patients who would benefit from

alternative treatments (eg, clinical trials, transplant).⁸⁰

JAKis do not reliably eradicate MPN clones, offer a realistic likelihood of disease remission, or prevent disease progression. Among 236 *JAK2* V617F-positive patients in the COMFORT trials, only 11% achieved partial or complete molecular remission, as defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT)/European LeukemiaNet (ELN) consensus criteria, after 2 years on therapy.⁴⁰ Fedratinib showed some promise in reducing *JAK2* V617F allele burden in phase 1 trials,⁴⁶ but this result was not replicated in the later-phase trials.^{45,47} Whole-exome sequencing in patients taking ruxolitinib at multiple times within their treatment showed that clonal evolution occurs despite JAKi treatment.⁸¹ Both ruxolitinib and fedratinib can stabilize or decrease morphologic bone marrow fibrosis, but the effects are fairly modest.⁸²⁻⁸⁴ None of the JAKi trials previously discussed demonstrated a significant reduction in the progression of MF to MPN blast phase, and leukemia transformation

can in fact develop in patients treated with ruxolitinib in an atypical manner.⁸⁵

There is substantial controversy regarding whether ruxolitinib improves OS. In the final 5-year analysis of COMFORT-I, median OS was not reached in the ruxolitinib group vs 3.8 years in the placebo group, with an HR for death of 0.69 (95% CI, 0.50-0.96; $P=.025$).⁷⁵ A pooled ITT analysis of the patients in COMFORT-I and COMFORT-II showed a 30% survival advantage with the use of ruxolitinib (HR, 0.70; 95% CI, 0.54-0.91), but a rank-preserving structural failure time model intended to correct for the high crossover rates from placebo or BAT to ruxolitinib suggests that the survival advantage derived from ruxolitinib is much more significant, at 65% (HR, 0.35; 95% CI, 0.23-0.59).³⁴ Interestingly, these studies have also shown a survival advantage in those initially randomized to ruxolitinib vs those who later crossed over to the trial arm, indicating that the longer a patient is exposed to ruxolitinib, the more profound its effect on survival.²⁴ When ruxolitinib-treated patients in phase 1/2 and phase 3 trials are compared with matched historical controls, ruxolitinib continues to show an association with improved survival.^{29,86}

Critics of the preceding survival data, however, take issue with the fact that the COMFORT studies were underpowered to assess survival outcomes, much of the data used takes advantage of methodological caveats within the studies, the survival analyses employ historical controls that are subject to multiple forms of bias, and the quality of evidence for a survival advantage from ruxolitinib is considered low.⁸⁷⁻⁸⁹

Approach to JAK Inhibitors in the Patient With Myelofibrosis

Despite the limitations of JAKi therapy, the approved JAKis remain first-line treatments for patients with symptomatic Int-1/low-risk MF or with Int-2/high-risk MF, regardless of *JAK2* V617F mutation status. With the expected introduction of additional JAKis, such as momelotinib and itacitinib, the question remains of how to decide among these agents. One proposed algorithm suggests using the degree of patients' cytopenias to determine which JAKi to choose for first-line treatment (Figure).⁹⁰ Still, referral to a center that hosts clinical trials of novel agents or JAKi combinations should be considered for most patients to improve the standard of care. Fit patients at relatively high risk should always be evaluated for allogeneic stem cell transplant, which remains the only curative treatment for MF.⁹¹

For patients who are started on frontline JAKi therapy, the choice of the initial agent is limited by the availability of only 3 approved agents. Ruxolitinib and

fedratinib are both contraindicated in patients with severe thrombocytopenia (platelet count $<50 \times 10^9/L$), but pacritinib is now an option for patients with significant thrombocytopenia (platelet count $<50 \times 10^9/L$). If momelotinib gains approval, it can also be an option for transfusion-dependent patients.

Patients whose disease fails to respond to the first JAKi can be trialed on a second JAKi, but, as discussed previously, a large portion of patients do not respond to salvage use of a second JAKi. Clinical trial options should again be discussed with those patients who cannot tolerate or whose disease is refractory to frontline JAKi monotherapy.

Conclusions and Future Directions

JAKis are the greatest advance in the treatment of MF in the past decade, and they have provided durable symptom relief with overall tolerable side effects for many patients. Determining the most appropriate way to position these agents will require both retrospective and prospective studies once more agents receive FDA approval.

Unfortunately, the evidence that JAKis alter the course of MF by meaningfully reducing bone marrow fibrosis, preventing leukemic transformation, and improving OS is slim. In addition, the provision of treatment options for patients who cannot tolerate JAKis remains an unmet need. Combination strategies are being investigated in an effort to further decrease MF-related symptoms while overcoming dose-limiting cytopenias, especially in patients who cannot tolerate or whose disease is refractory to JAKi monotherapy (see the eTable at www.hematologyandoncology.net). Further research investigating these combinations and monotherapy with other novel agents is imperative to change the course of this often-devastating disease.

Disclosures

Dr Hoffman serves as a consultant for Ionis Pharmaceuticals, Silence Therapeutics, and Protagonist Therapeutics; serves on the data safety monitoring boards of Novartis and AbbVie; and receives research support from Incyte. Drs Levavi and Marcellino declare no competing financial interests.

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Supporting Online Material

eTable. Novel JAK Inhibitor Combination Strategies Currently Under Clinical Investigation

Combination Agent	MOA	Ongoing Trial(s)	Phase	Study Population	Primary Out-come
<i>JAKi, Ruxolitinib +</i>					
Pevonedistat	NEDD8 inhibitor	NCT03386214	1	On RUX at time of enrollment	Safety, MTD
PIM 447	Pan-PIM kinase inhibitor	NCT02370706	1	Expansion cohort includes only RUX-naive patients and patients with relapse or disease refractory to RUX	DLT
LEE011	CDK4/6 inhibitor				
CPI-0610a (pelabresib)	BET inhibitor	NCT02158858	1/2	Separate cohorts for patients who are JAKi-naive, are resistant/refractory/intolerant to JAKi therapy, or had inadequate response to RUX; cohorts of transfusion-dependent and transfusion-independent patients	SVR, transfusion dependence, rates of CHR, depending on cohort
		NCT04603495	3		
Itacitinib	JAKi	NCT03144687	2	On RUX at time of enrollment or prior RUX intolerance/resistance	SVR
PEG-IFN α -2a	Immune modulator, pro-apoptotic promoter, among other MOAs	NCT02742324	1/2	JAKi-naive	DLTs (phase 1), ≥50% spleen length reduction
PU-H71 ^a	Hsp90 inhibitor	NCT03935555	1b	On RUX at time of enrollment	Safety, MTD
Pomalidomide	IMiD	NCT01644110	1b/2	Anemia (Hgb <10 g/dL) or transfusion-dependent anemia; no RUX within 14 days	Best response rate
9-ING-41	GSK-3 β inhibitor	NCT04218071	2	Inadequate response to RUX	ELN response rate
Azacitidine	Hypomethylating agent	NCT01787487	2	RUX-naive	ORR
Luspatercept	Activin receptor ligand trap	NCT03194542	2	Hgb ≤9.5 g/dL on ≥3 occasions; includes patients on a JAKi before enrollment	Anemia response
Thalidomide	IMiD	NCT03069326	2	On RUX at time of enrollment	Best ORR
Navitoclax	BCL-2/BCL-xL inhibitor	NCT204472598	3	JAKi-naive	≥35% SVR
Parsaclisib	PI3K δ inhibitor	NCT04551053	3	Prior RUX treatment	SVR
		NCT04551066	3	JAKi-naive	SVR
Panobinostat	HDAC inhibitor	NCT02386800	4	Rollover trial for patients enrolled in trials of panobinostat who are still experiencing clinical benefit	Safety and tolerability
<i>JAKi, Fedratinib +</i>					
Luspatercept ^b	Activin receptor ligand trap	NCT03755518	3b	Hgb ≤9.5 g/dL on ≥3 occasions or RBC transfusion-dependent; prior RUX treatment	Safety and tolerability

^aThese agents are also being evaluated as monotherapy in MF.

^bLuspatercept is being evaluated with fedratinib in a substudy of the FREEDOM trial in patients with anemia.

BCL-2, B-cell lymphoma 2; BCL-xL, B-cell lymphoma-extra large; BET, bromo- and extra-terminal domain; CDK4/6, cyclin-dependent kinase 4/6; CHR, complete hematologic response; DLT, dose-limiting toxicity; ELN, European LeukemiaNet; HDAC, histone deacetylase; Hgb, hemoglobin; Hsp90, heat shock protein 90; IMiD, immunomodulatory imide drug; JAKi, JAK inhibitor; MF, myelofibrosis; MOA, mechanism of action; MTD, maximum tolerated dose; ORR, objective response rate; PEG-IFN α -2a, pegylated interferon alfa-2a; PI3K δ , phosphoinositide 3-kinase δ ; RBC, red blood cell; RUX, ruxolitinib; SVR, spleen volume reduction.