Review Article

JAK Be Nimble: Reviewing the Development of JAK Inhibitors and JAK Inhibitor Combinations for Special Populations of Patients with Myelofibrosis

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ABSTRACT

Myelofibrosis (MF) is a myeloproliferative neoplasm hallmarked by uncontrolled blood counts, constitutional symptoms, extramedullary hematopoiesis, and an increased risk of developing acute myeloid leukemia. Janus kinase (JAK) inhibitors are the most common treatment for MF due to their ability to reduce spleen size and improve disease-related symptoms; however, JAK inhibitors are not suitable for every patient and their impact on MF is limited in several respects. Novel JAK inhibitors and JAK inhibitor combinations are emerging that aim to enhance the treatment landscape, providing deeper responses to a broader population of patients with the continued hope of providing disease modification and improving long-term outcomes. In this review, we highlight several specific areas of unmet need within MF. Subsequently, we review agents that target those areas of unmet need, focusing specifically on the JAK inhibitors, momelotinib, pacritinib, itacitinib, and NS-018 as well as JAK inhibitor combination approaches using CPI-0610, navitoclax, parsaclisib, and luspatercept.

Keywords: JAK inhibitor, myelofibrosis, myeloproliferative neoplasm, rare disease

INTRODUCTION

Myelofibrosis (MF) is a chronic leukemia driven by somatic mutations that activate the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. Although clinically heterogeneous, patients often suffer from symptoms related to inflammatory cytokines, extramedullary hematopoiesis, and cytopenias, and have an increased risk of developing acute myeloid leukemia (AML). The current management of MF focuses on blunting the upregulated JAK/STAT signaling, which helps to control spleen volume and improve cytokine-driven constitutional symptoms.[1] Despite providing substantial benefit for many patients with MF, currently approved JAK inhibitors are limited in their ability to meaningfully address cytopenias, induce disease remission, or prevent clonal progression.[2,3] In an effort to meet these needs, novel JAK inhibitors have emerged; each with potential to address important gaps in our current care. In addition, novel combination strategies are being developed to provide more comprehensive disease control with aspirations of modifying the underlying disease.

In this review, we closely assess several subpopulations of patients with MF that are underserved by current therapies, focusing on patients with thrombocytopenia, anemia, a suboptimal or lack of response to JAK inhibitor therapy, and high-risk gene mutations. After addressing these areas of unmet need, we review the emerging JAK inhibitors, focusing of the impact of each on these special populations. Last, we review novel combination approaches that have demonstrated encouraging early results.

THROMBOCYTOPENIA

Thrombocytopenia, when defined as a platelet count $< 100 \times 10^9$/L, occurs in approximately 10 to 20% of patients with primary myelofibrosis (PMF) and is independently associated with high-risk *U2AF1* Q157 mutations and worse overall survival (OS).[4,5] In the pivotal COMFORT trials that led to the approval of ruxolitinib, patients with a platelet count $< 100 \times 10^9$/L

were excluded. Baseline platelet count directed initial ruxolitinib dosing with patients who had a baseline platelet count between 100 and 200×10^9/L receiving 15 mg twice daily (BID), whereas the remainder of patients (platelet count $> 200 \times 10^9$/L) received a starting dose of 20 mg BID.[6,7] Although the United States Food and Drug Administration (FDA) label for ruxolitinib extends to patients with platelet count $\geq 50 \times 10^9$/L, doses recommended for thrombocytopenic patients are associated with fewer clinical responses.[8,9] Beyond pretreatment thrombocytopenia, ruxolitinib treatment often leads to a decrease in platelet count and dose modification is frequently required.[9] Thrombocytopenia of any grade was seen in 69.7 and 60.0% on the COMFORT-I and COMFORT-II studies, respectively, with grade 3 or worse thrombocytopenia seen in 12.9 and 8.0%, respectively.[6,7] In patients who discontinue ruxolitinib, a platelet count $< 100 \times 10^9$/L at time of discontinuation is associated with inferior OS.[3]

Fedratinib, a more selective JAK2 inhibitor, is also FDA-approved for the treatment of MF. The pivotal phase 3 JAKARTA study, which led to the approval of fedratinib, included patients with a platelet count $\geq 50 \times 10^9$/L; however, only 14 (15%) patients treated at the recommended 400 mg daily dose of fedratinib had a platelet count between 50 and 100×10^9/L.[10] In this study, treatment-emergent thrombocytopenia was common, occurring in 63% of patients, with grade 3 or 4 thrombocytopenia occurring in 17% of patients.[10] Gastrointestinal side effects are common in fedratinib-treated patients, with nausea and diarrhea occurring in 64 and 66% of patients treated at the approved dose. The vast majority of gastrointestinal adverse events were grade 1 or 2 in severity and may be modified by prophylactic antiemetics or administration with a high-fat meal.[10,11] Fedratinib holds a "black box warning" in the prescribing information highlighting the risk for serious or fatal encephalopathy, including Wernicke encephalopathy (WE), a condition caused by thiamine deficiency. Concern for fedratinib-induced encephalopathy emerged due to eight potential cases of WE reported in patients with MF and patients without MF being treated with fedratinib. Central review of these cases revealed only one definitive case of WE in a patient with non–treatment-related risk factors and two unconfirmed cases of WE in patients with confounding abnormalities. Ultimately, there is scant evidence of a link between fedratinib and encephalopathy, but a high index of suspicion is recommended.[12] For that reason, patients starting fedratinib should have thiamine levels checked before initiation and periodically during the course of treatment. Patients with evidence of thiamine deficiency should receive repletion before initiation.

Recently, increased attention has been paid to thrombocytopenic patients treated with approved JAK inhibitors. At the 2019 American Society of Hematology (ASH) annual meeting, Harrison et al.[13] presented an analysis of thrombocytopenic patients treated with fedratinib on the JAKARTA and JAKARTA-2 studies. Among patients with baseline platelet counts $< 100 \times 10^9$/L, spleen responses were seen in 36 and 36% of patients on JAKARTA and JAKARTA-2, respectively, with symptom responses occurring in 31 and 39% of patients. Dose modification and treatment discontinuation due to thrombocytopenia was rare, but occurred more commonly in patients with baseline thrombocytopenia.[13] Alternatively, the EXPAND study, a prospective trial aimed at determining the optimal ruxolitinib dosing strategy in thrombocytopenic patients with MF enrolled patients with a platelet count between 50 and 100×10^9/L, assigning them to two strata based on baseline platelet count of 75 to 99×10^9/L (stratum 1) and 50 to 74×10^9/L (stratum 2). In both strata, the maximum safe starting dose was found to be 10 mg BID and spleen responses were seen in 33.3 and 30.0% of patients on stratum 1 and 2, respectively, at 48 weeks. This study also reinforced the challenge in treating thrombocytopenic patients with MF as only 24.6% (17 of 69) of patients were still receiving treatment at the week 48 data cutoff.[14]

Although improving thrombocytopenia is rarely the primary focus of treatment in patients with MF, it often requires consideration. Danazol and thalidomide are two agents that have shown the potential to improve platelet counts in patients with MF while improving anemia. In patients with MF with anemia, danazol monotherapy has demonstrated an anemia response rate of 30% with an approximately 14 months' duration of response. In this study, among 13 patients with platelet counts $< 100 \times 10^9$/L treated with danazol, 3 (23%) experienced a platelet increase of $> 50 \times 10^9$/L.[15] Furthermore, danazol has demonstrated safety in combination with ruxolitinib; however, its impact on thrombocytopenia in this setting has not been adequately assessed.[16] Thalidomide, an immunomodulatory imide agent with antiangiogenic properties, offers an additional option for thrombocytopenic patients with MF. Poorly tolerated at doses > 100 mg per day, it has demonstrated tolerability and efficacy at a dose of 50 mg daily in combination with a corticosteroid taper. In a small phase 2 study, low-dose thalidomide led to anemia improvement in 62% of patients with MF. In addition, six (75%) of eight thrombocytopenic patients experienced a $\geq 50\%$ increase in platelet count.[17] Additional small studies have demonstrated similar impact on hemoglobin and platelets.[18,19] An ongoing study assessing the addition of thalidomide to ruxolitinib (NCT03069326) has shown its ability to improve platelet counts within this context as well.[20] The continued use of danazol and thalidomide in thrombocytopenic patients with MF despite relatively weak evidence highlights the need for the development of novel therapeutic agents in this subset of patients.

ANEMIA

Anemia is a diagnostic and prognostic feature of MF.[21,22] Often defined as a hemoglobin < 10 g/dL,

anemia is present in approximately 36 to 50% of patients, and its incidence increases throughout the course of the disease.[23,24] When defined less stringently, anemia is found in nearly 90% of patients with MF.[24] In patients younger than 65, anemia is the clinical factor that most strongly affects survival and has been weighted accordingly in prognostic models.[22,25] Therapy-related anemia is also common. Ruxolitinib induces a hemoglobin drop of 10 to 15% that nadirs between 8 and 12 weeks and recovers to near-baseline levels by 24 weeks.[9] Among 43 patients treated with ruxolitinib in the COMFORT-II study who did not have baseline anemia, 38 (88%) developed grade $\geq$ 1 anemia while on the study. Regardless of baseline hemoglobin, a change of at least two grades (i.e., grade 1 to $\geq$ 3 or grade 2 to 4) was demonstrated in 30% of patients.[6] Fedratinib had a similar impact on hemoglobin in the phase 3 JAKARTA study with a median 1.5 g/dL drop in hemoglobin nadiring at 12 to 16 weeks and showing a general trend toward recovery after week 20.[10] Interestingly and importantly, the anemia induced by JAK inhibitors does not appear to adversely impact survival.[26] Within the context of clinical trials, anemia is a rare cause of JAK inhibitor discontinuation; however, in the real-world setting this differs, with discontinuation being attributed specifically to anemia in approximately 10% of cases.[9,27,28]

The pathogenesis of anemia in MF is complex and incompletely defined. Genetically, mutations involving pre–messenger RNA (mRNA) splicing have been linked to anemia in MF, with the specific implication of *U2AF1* mutations.[5,24,29] Additional contributing factors include upregulation of inflammatory cytokines, increased plasma volume, and splenic sequestration.[30–32] Historically, treatment approaches have included erythropoiesis stimulating agents (ESA), androgens, corticosteroids, and immunomodulatory imide agents.[15,17,33–39] Despite the demonstration of clinical efficacy in several small, early-phase studies, it is important to note that none of these agents have demonstrated their benefit within the context of a randomized phase 3 clinical trial. In fact, pomalidomide, after demonstrating encouraging anemia-related benefits in phase 2 studies, failed to show improved responses compared with placebo in a randomized phase 3 study.[40–42] This cautionary experience highlights the flaws in deriving too much value from single-arm, phase 2 studies, while highlighting the desperate need for active agents for anemic patients with MF.

HIGH MOLECULAR RISK

Beyond phenotype-driving mutations in *JAK2*, *MPL*, or *CALR*, patients with MF often harbor somatic mutations in genes that regulate epigenetic control, transcription, cell signaling, and pre-mRNA splicing.[43] The mechanisms and specific clinical impact of mutations in these genes are being increasingly characterized. To this point, mutations in *ASXL1*, *SRSF2*, *U2AF1*, *IDH1/2*, *EZH2*, *TP53*, and the RAS-pathway have been linked to adverse outcomes.[44–47] The lack of a mutation in *JAK2*, *MPL*, or *CALR* also defines a high-risk MF subgroup, often referred to as "triple-negative."[48] At least one high-risk mutation occurs in up to 50% of patients with MF.[4,44] In patients treated with ruxolitinib, the presence of $\geq$ 3 mutations of any type correlated with shorter time to treatment discontinuation and inferior OS.[49] In addition, acquisition of a new mutation while on ruxolitinib is associated with inferior survival after ruxolitinib discontinuation.[3] Recently, the presence of RAS-pathway mutations was shown to be associated with a decreased probability of achieving a spleen response in patients treated with ruxolitinib.[46]

Within the field of myeloid malignancies, the presence of specific mutations at the time of allogeneic hematopoietic cell transplantation (AHCT) can inform the pretransplant conditioning regimen and has been linked to transplant-related outcomes.[50] In MF, the data addressing the impact of mutations on AHCT outcome have not been consistent. In one analysis that included 169 patients with PMF, secondary MF, and MF in transformation, the presence of an *ASXL1* or *IDH2* mutation was associated with worse progression-free survival, whereas the presence of a *CALR* mutation was associated with associated with favorable outcomes.[51] In contrast, a multivariate analysis of 101 chronic-phase patients with MF showed mutations in *U2AF1* and *DNMT3A* were associated with reduced relapse-free survival and *U2AF1* mutations were associated with reduced OS. A mutation in *ASXL1*, *SRSF2*, *IDH1/2*, *EZH2,* or *TP53* was not associated with posttransplant outcomes.[52]

Despite growing data, it is clear we do not yet fully understand how the presence of specific mutations in MF predict for treatment responses or transplant-related outcomes. But, it is also clear that the presence of specific gene mutations affects clinical phenotype, leads to upregulation of additional inflammatory pathways, and adds molecular complexity.[47,53,54] As a potential sign for optimism, targeted agents such as enasidenib and ivosidenib have been approved for the treatment of AML and are under investigation in myelodysplastic syndrome (MDS).[55,56] A recently published, small series of 12 post–myeloproliferative neoplasm (MPN) patients with AML with *IDH1* or *IDH2* mutations demonstrated favorable efficacy and tolerability of IDH1/2-inhibitor based therapies in this challenging patient population.[57]

SUBOPTIMAL RESPONSE TO JAK INHIBITION

Patients with MF who have either discontinued or experienced a suboptimal response to JAK inhibition have recently been identified as a prognostically adverse group. Despite the successes of ruxolitinib, most patients

will discontinue treatment by 3 years.[1] Reasons for discontinuation vary, but they include cytopenias, nonhematologic adverse effects, disease progression, pursuance of AHCT, or death.[1,27,28,58,59] Survival after ruxolitinib discontinuation has been estimated to be between 11 and 14 months; however, this varies according to the reason for discontinuation. Patients who lack or lose a spleen response have a median survival estimated at 32.4 and 27.9 months, respectively, whereas those who discontinue due to adverse events or blast phase have worse OS.[3,27,28,58]

Treatment options following discontinuation of ruxolitinib vary based on clinical need, but have historically included ESAs, androgens, immunomodulatory imide drugs, hydroxyurea, hypomethylating agents, and clinical trials.[27] These agents are associated with rare and short duration of benefit. More recently, fedratinib emerged as a therapeutic option after discontinuation of ruxolitinib, as its approval in 2019 was agnostic to line of therapy. The use of second-line fedratinib was assessed in the phase 2 JAKARTA-2 study, wherein 55% of patients who had previously been exposed to ruxolitinib were able to achieve a spleen response.[61] Interpretation of this study is challenging for a number of reasons, including a subjective definition of ruxolitinib resistance/intolerance, a required 14-day washout period of ruxolitinib, and early termination of the study.[60] For these reasons, a reanalysis of JAKARTA-2 was performed by Harrison and colleagues in 2020.[61] Using intention-to-treat analysis principles and a more stringent definition for ruxolitinib failure, spleen volume response at the end of six cycles was confirmed in 30% of patients.[61] Currently, fedratinib is the only FDA-approved agent that has demonstrated efficacy in the second-line setting. Momelotinib and pacritinib have demonstrated modest efficacy in patients with prior exposure to ruxolitinib. Emerging combination therapies hope to improve response rates in this patient population and multiple phase 3 combination studies are actively enrolling. For a summary of the efficacy of emerging agents in the post-ruxolitinib setting, see Table 1.

JAK INHIBITORS IN DEVELOPMENT

Pacritinib

Pacritinib, a JAK inhibitor with specificity to JAK2 in addition to FMS-like tyrosine kinase (FLT3), interleukin-1 receptor-associated kinase 1 (IRAK1), and colony-stimulating factor 1 receptor (CSF1R), has been extensively evaluated in MF, including two phase 3 clinical trials, PERSIST-1 and PERSIST-2. In PERSIST-1, higher-risk patients with MF were randomized (2:1) to receive pacritinib 400 mg daily or best available therapy (BAT), excluding JAK2 inhibitors. There was no exclusion criterion for platelet count. The most used treatments in the BAT arm were hydroxyurea (57%) and watchful waiting (25%). At week 24, in the intention-to-treat population, 42 (19%) of 220 patients treated with pacritinib achieved a spleen response compared with 5 (5%) of 107 treated with BAT ($p = 0.0003$). Encouraging activity was seen among thrombocytopenic patients ($< 100 \times 10^9$/L), with 12 (17%) of 72 experiencing a spleen response with pacritinib compared with 0 (0%) of 34 treated with BAT ($p = 0.0086$). Among 35 patients treated with pacritinib who had a baseline platelet count $< 50 \times 10^9$/L, 8 (23%) achieved a spleen response compared with 0 (0%) of 16 treated with BAT ($p = 0.045$). There was no difference in symptom responses, a key secondary endpoint, between pacritinib and BAT at 24 weeks (19 versus 10%, $p = 0.24$).[62]

Unfortunately, the study was placed on a full clinical hold at a median follow-up of 11.5 months due to concerns regarding cardiovascular events, bleeding, and interim survival results. Because of this clinical hold, only 171 (78%) pf 220 and 72 (77%) of 107 patients on pacritinib and BAT, respectively, completed 24 weeks of study treatment.[62]

In contrast to PERSIST-1, the PERSIST-2 study focused specifically on thrombocytopenic patients with MF, allowed prior JAK inhibitor use, and allowed ruxolitinib use in the BAT arm. Patients were randomized 1:1:1 to pacritinib 400 mg daily, pacritinib 200 mg BID, or BAT. Coprimary endpoints included spleen response and symptom response at week 24. Approximately half of enrolled patients had received prior ruxolitinib and 45% of patients in the BAT received ruxolitinib. In the pacritinib daily, BID, and BAT arms, 51, 42, and 44% had baseline platelet counts $< 50 \times 10^9$/L. Unfortunately, the clinical hold placed on pacritinib led to early discontinuation and limited results. The full clinical hold occurred at a median of 23, 25, and 21 weeks on therapy in the daily, BID, and BAT arms, respectively. Still, among evaluable patients, a pooled analysis of the pacritinib-treated patients compared with BAT demonstrated a superior spleen response rate (18 versus 3%, $p = 0.001$). Spleen responses in patients with prior ruxolitinib use were rare. Comparing both pacritinib arms with BAT, a difference in symptom response rate did not reach statistical significance (25 versus 14%, $p = 0.08$).[63] Interestingly, in transfusion-dependent patients at baseline, a decrease in red blood cell transfusions was more commonly seen in patients treated with pacritinib than BAT. Despite exhibiting safety in thrombocytopenic patients, there was no evidence suggesting pacritinib led to improvement in thrombocytopenia.[63]

In the PERSIST-1 and PERSIST-2 studies, the adverse event (AE) profile was consistent, with gastrointestinal complaints (diarrhea, nausea) being most frequently reported. Diarrhea was the only nonhematologic grade ≥ 3 AE that occurred in at least 5% of patients.[62,63] To address toxicity and dosing concerns, a randomized dose-finding study (PAC203) was subsequently undertaken. Patients who were either resistant to or intolerant of ruxolitinib were randomized 1:1:1 to pacritinib 100 mg daily, 100 mg BID, or 200 mg BID. The definition for ruxolitinib resistance/intolerance used in the PAC203

Table 1. Summary of efficacy demonstrated in the post-ruxolitinib setting with agents currently in late-stage clinical development

Trial	Agent	Phase	*n*	Patient Population	Spleen Response, %	Symptom Response, %
JAKARTA-2[61]	Fedratinib	2	97 (83 assessable)	Ruxolitinib resistant or intolerant based on investigator assessment	55 (30*)	27
PERSIST-2[63]	Pacritinib	3	311 (48 with prior ruxolitinib)	Thrombocytopenic patients with splenomegaly and total symptom score $\geq$ 13	10^	21^
PAC203[64]	Pacritinib	2	161	Ruxolitinib intolerant or resistant (protocol-defined) with splenomegaly and total symptom score $\geq$ 10	19#	17#
SIMPLIFY-2[67]	Momelotinib	3	156	Ruxolitinib treatment for $\geq$ 28 days complicated by hematologic toxicity, splenomegaly	7	26
IMbark[104]	Imetelstat	2	59 (at 9.4 mg/kg dose)	Relapsed/Refractory to ruxolitinib	10	32
MANIFEST[80]	CPI-0610 + Ruxolitinib	2	70	Suboptimal or lost response to ruxolitinib	21	42
REFINE[86]	Navitoclax + Ruxolitinib	2	34	Persistent splenomegaly while on ruxolitinib	27	30

*Stringent criteria for ruxolitinib resistance or intolerance without last observation carried forward analysis.
^Combined pacritinib 400 mg every day and 200 mg twice a day (BID) cohorts.
#Evaluable patients in pacritinib 200 mg BID cohort.

study has since become tenet. Among 161 enrolled patients, severe thrombocytopenia ($< 50 \times 10^9$/L) was present in 44%. Spleen responses were more common in patients treated with 200 mg BID and symptom responses occurred with similar frequency across all dose levels.[64] Therefore, a dose of 200 mg BID has been selected for a randomized phase 3 study of patients with MF with severe thrombocytopenia, disease-related symptoms, and splenomegaly (PACIFICA; NCT03165734).[65] In this study that aims to enroll 348 patients, participants will be randomized to either pacritinib or physician's choice of a single-agent therapy with a primary endpoint of spleen response at 24 weeks.

From this extensive experience, pacritinib has shown the unique ability to safely induce spleen and symptom responses in severely thrombocytopenic patients with MF who are otherwise ineligible for JAK inhibitor therapy. Often, these patients have high molecular risk mutations (e.g., *U2AF1*) and have experienced suboptimal responses to prior JAK inhibitor therapy due to an inability to receive optimal doses. Approval of pacritinib would represent a significant leap forward for patients who currently lack standard treatment options.

Momelotinib

Momelotinib is a JAK1/2 inhibitor with additional inhibitory activity against activin receptor type-1 (ACVR1)-mediated expression of hepcidin in the liver. Momelotinib has been evaluated in two phase 3 studies, with a third ongoing. SIMPLIFY-1 was a noninferiority study in which 432 JAK inhibitor naïve patients were randomized to receive momelotinib 200 mg daily or ruxolitinib per label. The primary endpoint was a spleen response at 24 weeks with symptom response rate and change in transfusion requirement as secondary endpoints. At week 24, spleen response rates in the two arms were similar (26.5 versus 29% in the momelotinib and ruxolitinib arms, respectively), but momelotinib was inferior to ruxolitinib in terms of symptom responses (28.4 versus 42.2%). Notably, momelotinib appeared to have a beneficial effect on transfusion requirements. At baseline, 24.7 and 24.0% of patients were transfusion dependent in the momelotinib and ruxolitinib arms, respectively. At week 24, fewer momelotinib-treated patients were transfusion dependent compared with ruxolitinib (30.2 versus 40.1%, nominal $p = 0.019$). Treatment-emergent anemia was more common in patients treated with ruxolitinib compared with momelotinib (38.0 versus 13.6%, respectively). In addition, thrombocytopenia occurred more commonly with ruxolitinib than momelotinib (29.2 versus 18.7%). Despite a more favorable hematologic profile, momelotinib appeared to be more challenging to tolerate with more frequent treatment discontinuation, most of which was attributed to AEs. Peripheral neuropathy was more common in patients treated with momelotinib (19.3%) compared with those treated with ruxolitinib (4.6%), with most cases being grade 1 or 2 in severity and no patient discontinuing therapy as a result.[66]

The phase 3, open-label, SIMPLIFY 2 study evaluated patients with MF with splenomegaly who had previously received at least 28 days of ruxolitinib and had experienced red blood cell transfusions or dose reduction due to significant thrombocytopenia, anemia, or bleeding. Patients were randomized 2:1 to momelotinib or BAT with 46 (89%) of 52 patients receiving ruxolitinib as BAT. Importantly, this study lacked a washout period for prior therapy and had a primary endpoint of spleen response. At 24 weeks, there was no difference in spleen responses between patients treated with momelotinib and BAT (7 versus 6%, respectively, $p = 0.90$), meaning secondary endpoints could be assessed only for nominal significance. Nevertheless, more patients receiving momelotinib achieved symptom responses at 24 weeks

(26%) than those receiving BAT (6%) (nominal $p = 0.0006$), and, despite similar baseline rates of transfusion independence between groups (31 versus 37%), patients treated with momelotinib were more likely to be transfusion independent at week 24 (43 versus 21%; nominal $p = 0.0012$). AEs occurred more commonly in patients treated with momelotinib than BAT, leading to discontinuation of momelotinib in 21% of patients. Peripheral neuropathy only occurred in momelotinib-treated patients (11%), with three patients discontinuing therapy as a result. A "first-dose effect," that had been reported in phase 2 studies with momelotinib, was reported in 4 (4%) of momelotinib-treated patients and was defined as dizziness, flushing, hot flush, headache, hypotension, nausea, or a combination of these events that occur on the first dosing day and resolved by the following day.[67]

Momelotinib's favorable impact on transfusion requirements has been attributed to its inhibition of ACVR1, a member of the transforming growth factor beta (TGF-β) superfamily of receptors. ACVR1 signaling leads to upregulation of hepcidin production, resulting in iron restriction and anemia of inflammation. In a phase 2 study of transfusion-dependent patients with MF, momelotinib treatment resulted in a rapid and sustained decrease in hepcidin levels. Patients achieving transfusion independence with momelotinib treatment were found to have lower baseline inflammatory markers and hepcidin levels.[68]

Despite favorable impacts on transfusion requirements, failure to meet primary and key secondary endpoints has prevented momelotinib from gaining regulatory approval. The ongoing, phase 3 MOMENTUM study (NCT04173494) hopes to remedy this situation by enrolling patients previously treated with ruxolitinib who have anemia, splenomegaly, and disease-related symptoms. Patients are randomized 2:1 to momelotinib or danazol, an androgen that is often used for MF-related anemia in the salvage setting, with a primary endpoint of symptom response at week 24. For patients with MF who have anemia in addition to symptomatic splenomegaly and/or constitutional symptoms, momelotinib represents an exciting therapeutic option, whereby patients may not have to accept worsening hematologic parameters in a trade-off for relief from disease-related symptoms. Momelotinib also represents a potential option for severely thrombocytopenic patients ineligible for standard JAK2 inhibitors because the MOMENTUM is open to patients with a baseline platelet count $\geq 25 \times 10^9$/L.[69]

Itacitinib

Itacitinib is a potent and selective JAK1 inhibitor that has been evaluated in acute graft-versus-host disease, cytokine release syndrome associated with chimeric antigen receptor (CAR)–T-cell therapy, chronic plaque psoriasis, and MF. In an open-label phase 2 study, itacitinib was evaluated at doses of 100 mg BID, 200 mg BID, and 600 mg once daily, although only the latter two doses met criteria for expansion. In these two cohorts, the primary endpoint of symptom response at 12 weeks was met in 35.7 and 32.3% of patients, respectively. Most patients experienced an improvement in symptoms, the magnitude of which appeared dose dependent. Spleen response, a secondary endpoint, rarely occurred; however, most patients achieved improvement in spleen volume that did not meet criteria for a response. Median spleen volume reduction at week 12 was 14.2 and 14.5% in patients treated with dosages of 200 mg BID and 600 mg daily, respectively. Hemoglobin and platelet levels remained relatively stable throughout the study at all doses.[70]

Considering the promising role of JAK1 inhibition in managing disease-related symptoms, a new clinical trial is being planning to study an immediate-release formulation of itacitinib (NCT04629508).[71] This formulation offers improved JAK2 inhibition while maintaining substantial JAK1 inhibition. In this study, itacitinib will be assessed at two different dose levels in patients who have previously been treated with either ruxolitinib or fedratinib. To date, the four JAK inhibitors that have been extensively studied in MF (ruxolitinib, fedratinib, pacritinib, and momelotinib) are either dual JAK1/2 inhibitors or are selective for JAK2. Continued study of itacitinib will shed light on the clinical relevance of the relative inhibition of JAK1 and JAK2 as it pertains to symptom improvement, spleen reduction, and hematologic toxicity.

NS-018

NS-018 is a selective JAK2 inhibitor that has been studied in a phase I/II study with a recommended phase 2 dose of 300 mg daily. Among 36 evaluable patients, a spleen response by palpation was observed in 20 (56%) patients with a median duration of splenic response of 5.5 cycles. The most common nonhematologic adverse events were due to neurologic or gastrointestinal complaints. Grade 3/4 anemia or thrombocytopenia occurred in 6 and 17% of patients, respectively.[72] Further development of this agent in patients with thrombocytopenia is being pursued.

JAK INHIBITOR COMBINATIONS

As a direct result of being first to market, the vast majority of ongoing or planned JAK inhibitor combinations use ruxolitinib. Undoubtedly, this will change over the next half-decade as additional JAK inhibitors are approved, given that each has unique properties that may allow for more optimal matching with other agents. Although there are a host of ongoing combination trials in early-phase development,[73] we address four combinations that have entered or are entering later stage development.

Ruxolitinib + CPI-0610

Bromodomain and extraterminal domain (BET) proteins regulate transcription of critical genes involved in fibrogenesis, making them an intriguing target in MF. Preclinically, BET inhibition induces apoptosis of MPN cell lines and primary MPN cells, has demonstrated synergism with JAK2 inhibitors, and can overcome JAK2 inhibitor resistance.[74–77] CPI-0610 is an oral BET inhibitor that is currently being studied in the ongoing phase 2 MANIFEST study (NCT02158858).[78] In this 3-arm study, CPI-0610 is being assessed as monotherapy (arm 1) in patients previously treated with a JAK inhibitor, as an "add-on" to ruxolitinib in patients with suboptimal response to ruxolitinib (arm 2), and up-front in combination with ruxolitinib (arm 3). Primary endpoints differ based on study arm and baseline transfusion dependency.

Updated results of this study were presented at the ASH 2020 Annual Meeting. In arm 1, conversion to transfusion independence occurred in 21.4% (3 of 14) transfusion-dependent patients, with 0% (0 of 10) and 8.3% (1 of 12) achieving a spleen response or symptom response, respectively, at 24 weeks. In non–transfusion-dependent patients, 23.8% (5 of 21) achieved a spleen response and 47.4% (9 of 19) achieved a symptom response at week 24. Eleven (57.9%) non–transfusion-dependent patients with anemia achieved a $\geq$ 1.5 g/dL increase in hemoglobin levels over 12 weeks.[79]

In arm 2, CPI-0610 was added to ruxolitinib in patients with suboptimal response to ruxolitinib. Patients were further stratified by transfusion dependence. In the transfusion-dependent cohort, 34.4% (11 of 32) achieved conversion to transfusion independence, with 20.8% (5 of 24) and 46.2% (12 of 26) achieving a spleen or symptom response at week 24, respectively. In the non–transfusion-dependent cohort, 22.2% (4 of 18) of patients achieved a spleen response and 36.8% (7 of 19) achieved a symptom response at week 24.[80]

In arm 3, frontline treatment with CPI-0610 and ruxolitinib resulted in a spleen response rate of 63.3% (19 of 30) at week 24 and a symptom response rate of 58.6% (17 of 29). The most common treatment-emergent AEs were diarrhea (26.6%), anemia (23.4%), thrombocytopenia (20.3%), respiratory tract infections (18.8%), nausea (18.8%), and abdominal pain (15.6%).[81]

Although this study is still ongoing, CPI-0610 has clearly demonstrated encouraging activity in multiple different settings, demonstrating an ability, in combination with ruxolitinib, to induce frequent spleen responses while having a favorable impact on anemia in both the transfusion-dependent and non–transfusion-dependent settings. A randomized phase 3 study (NCT04603495), deemed MANIFEST-2, will compare CPI-0610 and ruxolitinib to ruxolitinib and placebo in the frontline setting.[82]

Ruxolitinib + Navitoclax

Bcl-xL is an antiapoptotic regulator that is overexpressed in cells from patients with essential thrombocythemia (ET), polycythemia vera (PV), and MF.[83] Navitoclax, a Bcl-xL inhibitor, has shown synergism with ruxolitinib in primary cell lines with activated JAK/STAT signaling, and Bcl-xL inhibition has been shown to overcome acquired resistance to JAK2 inhibitors.[84,85] The addition of navitoclax to patients on a stable dose of ruxolitinib with continued splenomegaly is being studied in the ongoing REFINE study (NCT03222609). Updated results presented at the ASH 2020 Annual Meeting showed that the addition of navitoclax to ruxolitinib led to spleen responses in 27% (9 of 34) of patients at week 24, with symptom response seen in 30% (6 of 20) of patients. Most patients (58%) were noted to have high-risk mutations and 42% (8 of 19) had $\geq$ 2 high-risk mutations. The combination of ruxolitinib and navitoclax was well-tolerated, although on-target thrombocytopenia was common and manageable with dose modification.[86,87]

These encouraging outcomes have led to the development of two phase 3 studies (NCT04472598 and NCT04468984) that will assess the combination in the treatment-naïve (TRANSFORM-1) and relapsed/refractory (TRANSFORM-2) setting.[88,89]

Ruxolitinib + Parsaclisib

JAK2 mediates downstream signaling through the PI3K/AKT/mTOR as well as other pathways. Preclinically, combining ruxolitinib with inhibitors of this pathway has led to enhanced activity against MPN cell lines and mouse models, even demonstrating the ability to overcome JAK2 inhibitor persistence.[90–92] Prior attempts to combine the PI3K inhibitors, umbralisib and buparlisib with ruxolitinib demonstrated clinical efficacy in terms of spleen volume reduction in a small cohort of patients; however, gastrointestinal and infectious complications were common.[93,94] Recently, the highly selective PI3K-delta inhibitor, parsaclisib, has been studied in combination with ruxolitinib in patients with MF with a suboptimal response to ruxolitinib (NCT02718300).[95] Early results of this study have identified an optimal dosing schedule with daily dosing, leading to a median 13% reduction in spleen volume at week 12 ($n = 11$) and median 27.1% reduction at week 24 ($n = 6$), with median 51.4% reduction in total symptom score at week 12 ($n = 6$). Although treatment-related AEs led to parsaclisib interruption in 8 of 18 patients treated with the daily dosing schedule, no colitis or dose-limiting diarrhea or rash was observed.[94] Based on these data, two phase 3 randomized studies have been designed looking at the combination of ruxolitinib and parsaclisib in the frontline and the addition of parsaclisib to ruxolitinib in patients with suboptimal response (NCT04551066, NCT04551053).[96,97]

Ruxolitinib + Luspatercept

Luspatercept is a first-in-class erythroid maturation agent that binds to TGF-β superfamily ligands resulting in enhanced late-stage erythropoiesis. TGF-β is known to

Table 2. Summary of ongoing phase 3 clinical trials in myelofibrosis

Identifier	Name	Agent	Patient Population	Estimated Enrollment	Comparator	Primary Endpoint (wk)	Estimated Study Start—Completion
NCT03165734[65]	PACIFICA	Pacritinib	Severely thrombocytopenic (< 50 × 10^9/L) with minimal exposure to JAK2 inhibitor, splenomegaly, active symptoms	348	Physician's choice	Spleen response (24)	2017–2022
NCT03755518[101]	FREEDOM	Fedratinib ± Luspatercept	Intolerant/Resistant to ruxolitinib with splenomegaly	110	N/A	Spleen response (24)	2019–2023
NCT03952039[105]	FREEDOM2	Fedratinib	Intolerant/Resistant to ruxolitinib with splenomegaly	192	Best available therapy	Spleen response (24)	2019–2022
NCT04173494[69]	MOMENTUM	Momelotinib	Anemic, prior treatment with JAK2 inhibitor with splenomegaly and active symptoms	180	Danazol	Symptom response (24)	2019–2021
NCT04576156[103]	IMpactMF	Imetelstat	Refractory to JAK inhibitor therapy with splenomegaly and active symptoms	320	Best available therapy	Overall survival	2021–2024
NCT04603495[82]	MANIFEST-2	Pelabresib (CPI-0610)	JAK2 inhibitor naïve with splenomegaly and active symptoms	310	Ruxolitinib + Placebo	Spleen response (24)	2020–2023
NCT04472598[88]	TRANSFORM-1	Navitoclax	JAK2 inhibitor naïve with splenomegaly and active symptoms	230	Ruxolitinib + Placebo	Spleen response (24)	2020–2022
NCT04468984[89]	TRANSFORM-2	Navitoclax	Current or prior JAK2 inhibitor use with suboptimal response or intolerance	330	Best available therapy	Spleen response (24)	2020–2022
NCT03662126[106]	BOREAS	KRT-232	Relapsed/Refractory to JAK inhibitor therapy with splenomegaly	385	Best available therapy	Spleen response (24)	2019–2023
NCT04551066[96]	LIMBER-313	Parsaclisib	JAK2 inhibitor naïve with splenomegaly and active symptoms	440	Ruxolitinib + Placebo	Spleen response (24)	2021–2023
NCT04551053[97]	LIMBER-304	Parsaclisib	On stable dose of ruxolitinib with continued splenomegaly and active symptoms	212	Ruxolitinib + Placebo	Spleen response (24)	2021–2023
NCT04717414[102]	INDEPENDENCE	Luspatercept	Transfusion-dependent patients on approved JAK2 inhibitor	309	Placebo	Red blood cell transfusion independence (24)	2021–2025

JAK: Janus kinase; N/A: Not applicable due to single-arm design.

play a critical role in the pathogenesis of bone marrow fibrosis in PMF through activation of the ALK5/Smad3 pathway, inhibition of which abrogates sustained collagen overproduction in MPN mouse models.[98] Approved for the treatment of thalassemia and MDS with ring sideroblasts, luspatercept holds potential for the treatment of anemia in patients with MF. In a phase 2 study (NCT03194542) using luspatercept in patients with MPN-associated anemia, luspatercept treatment led to transfusion independence in 27% (6 of 22) of transfusion-dependent patients who were concurrently taking ruxolitinib. Ten (46%) patients exhibited a $\geq$ 50% reduction in transfusion burden.[99,100] Responses in other cohorts (transfusion-independent patients receiving ruxolitinib and patients not receiving ruxolitinib) were less robust; however, strict response criteria may underestimate the clinical benefit of this agent. This trial continues to accrue, with expansion of the transfusion-dependent, ruxolitinib-treated cohort. In addition, luspatercept is being assessed in combination with fedratinib as part of the FREEDOM study (NCT03755518)[101] and in transfusion-dependent patients with MPN on an approved JAK2 inhibitor in the placebo-controlled phase 3 INDEPENDENCE study (NCT04717414).[102]

CONCLUSIONS

Despite the successes of JAK inhibitors in MF, there remains considerable unmet need for novel therapeutic strategies in these patients. Thrombocytopenia and anemia are common and frequently complicate treatment, resulting in early discontinuation and suboptimal responses. In addition, patients with high-risk mutations and suboptimal responses to JAK inhibitor therapy have complex disease that is difficult to control with current treatment options. The continued development of momelotinib and pacritinib hopes to address the former challenge, as these agents control spleen size and improve disease-related symptoms without adversely impacting hematologic parameters. Moreover, in the case of momelotinib, there appears to be the potential to induce a three-pronged benefit by improving splenomegaly, symptoms, and anemia simultaneously.

Combination therapies aim to enhance, broaden, or recapture responses to JAK inhibitor therapy. To date, navitoclax and parsaclisib have shown the potential to induce spleen responses in patients with suboptimal responses to ruxolitinib while favorably impacting disease-related symptoms. CPI-0610 has also demonstrated this ability while showing impressive frontline activity in combination with ruxolitinib and a favorable impact on erythropoiesis. All three agents are moving forward with registrational phase 3 clinical trials that have the potential to reshape the MF treatment landscape and provide additional therapeutic options to patients. For a summary of ongoing phase 3 studies in patients with MF see Table 2.

In an effort to focus on emerging JAK inhibitors and JAK inhibitor combinations, this review does not address non-JAK inhibitor therapies, such as imetelstat, a telomerase inhibitor with a planned phase 3 clinical trial (NCT04576156),[103] or bomedemstat (IMG-7289), which is being developed in MF, as well as essential thrombocythemia and polycythemia vera. These agents have demonstrated exciting activity in patients with MF and their continued development necessitates close monitoring.

As our armamentarium of JAK inhibitors and JAK inhibitor combinations becomes increasingly nimble, patients will emerge from what threatened to become a one-size-fits-all situation. In a notoriously heterogeneous disease, treatments should be individualized. Nevertheless, until disease-modifying or disease-eradicating treatment is identified, there will continue to be a critical unmet need for this patient population.

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