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JAK inhibitor selection in challenging scenarios of myelofibrosis: a review

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Abstract

Myelofibrosis is a progressive myeloproliferative neoplasm characterized by dysregulated Janus kinase (JAK)/signal transducer and activator of transcription signaling. Common clinical manifestations include constitutional symptoms, splenomegaly, and anemia, which can significantly impact quality of life and survival. Although hematopoietic stem cell transplant is the only curative treatment modality in myelofibrosis, JAK inhibitors have transformed management by providing symptom relief and reducing spleen size in many patients; newer JAK inhibitors also offer anemia-related benefits. A total of four JAK inhibitors—ruxolitinib, fedratinib, pacritinib, and momelotinib—are now available for the treatment of myelofibrosis, each with distinct profiles and safety considerations that may inform selection. However, head-to-head trial comparisons are limited, and real-world experience with most of these JAK inhibitors is only just emerging; therefore, first-line selection and optimal sequencing in particular patients can be challenging. This review summarizes the current data surrounding available JAK inhibitors for the treatment of patients with myelofibrosis and examines how individual patient characteristics can help guide selection among them. To illustrate the diverse clinical factors and key considerations associated with JAK inhibitor selection in practice, we discuss these data in the context of four hypothetical patient cases representing possible real-world scenarios, offering treatment recommendations based on our collective expertise in the field. As the myelofibrosis therapeutic landscape continues to evolve, a thorough understanding of the strengths and limitations of each JAK inhibitor relative to a given patient's presentation will support individualized treatment decisions for optimal long-term outcomes.

Introduction

Myelofibrosis is a rare and progressive myeloproliferative neoplasm characterized by dysregulation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway due to activating mutations in driver genes such as *JAK2*, *CALR*, or *MPL*.[1, 2] Patients with myelofibrosis have reduced life expectancy, with a US study estimating a 5-year overall survival (OS) rate of 49%.[3] Common manifestations include bone marrow fibrosis, systemic symptoms, and splenomegaly [**Figure 1**].[1, 2] Anemia, which affects an estimated 38% of patients at myelofibrosis diagnosis and 58% within 1 year,[4] is driven by diverse mechanisms and can present a significant additional burden [**Figure 2**].[5-7] Addressing anemia in myelofibrosis is an increasing priority, given its negative impacts on work and productivity, and progression to red blood cell (RBC) transfusion dependency is associated with increased costs and healthcare resource utilization, poor quality of life, and shorter OS.[6-10]

Although hematopoietic stem cell transplant (HSCT) is the only curative myelofibrosis treatment, the introduction of JAK inhibitors changed the intermediate- to high-risk myelofibrosis landscape, beginning with the US Food and Drug Administration (FDA) approval of ruxolitinib in 2011.[1, 11-13] Three other JAK inhibitors were subsequently approved in the US: fedratinib in 2019, pacritinib in 2022 (for patients with platelet counts $<50\times10^9$/L), and momelotinib in 2023 (for patients with anemia) [**Table 1; Figure 3**].[14-18] All have demonstrated efficacy in improving symptom burden and splenomegaly, with momelotinib and pacritinib also providing cytopenia-related benefits; however, JAK inhibitors have limited disease-modifying effects and are not known to prevent leukemic transformation.[12, 14-16, 19] While the class-wide safety profile is well characterized, individual JAK inhibitors have distinct considerations [**Table 2**].[12, 14-16, 20] Given some recent JAK inhibitor approvals, there are limited real-world data to help guide treatment selection and sequencing in scenarios in which there may be multiple appropriate options. Here,

we present real-world clinical cases representing several such scenarios and provide recommendations based on our collective expertise in the field.

Case 1: Newly diagnosed primary MF with severe symptom burden and moderate anemia

Patient history

A 69-year-old man with a new diagnosis of primary myelofibrosis with *JAK2* V617F (60% variant allele frequency [VAF]) and *ASXL1* frameshift (35% VAF) mutations presents with a spleen size of 8 cm below the left costal margin (LCM). His symptoms include fatigue, night sweats, a 15% weight loss in 6 months, left upper abdominal discomfort, and early satiety, for a Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) of 45. His white blood cell (WBC) count is 32×10^9/L, hemoglobin level is 9.8 g/dL without RBC transfusions, and platelet count is 141×10^9/L; no peripheral blood blasts are observed, erythropoietin is 200 IU/L, creatinine is 1.9 mg/dL and creatinine clearance is 42 mL/min. He was classified as high risk by the Dynamic International Prognostic Scoring System (DIPSS) and Mutation-Enhanced International Prognostic Scoring System 70-plus version 2.0 (MIPSS70+ v2.0). History includes diabetic neuropathy and two successfully excised squamous cell cancers in the last 5 years.

Treatment selection: first-line JAK inhibitor

In the absence of contraindications, this patient would be an excellent candidate for HSCT, which should be given due consideration for all patients with myelofibrosis per the 2024 European Society for Blood and Marrow Transplantation and European LeukemiaNet recommendations.[21] These updated guidelines suggest that patients with primary myelofibrosis and an intermediate-2– or high-risk DIPSS score, a high-risk MIPSS70 or MIPSS70+ v.2.0

score, and a low- or intermediate-risk Myelofibrosis Transplant Scoring System score should be considered.[21]

Regardless of transplant decision, a JAK inhibitor-based treatment would be recommended here for spleen and symptom improvement, as further discussed in Case 3. In this case, ruxolitinib, fedratinib, and momelotinib would all be reasonable on-label options[**Table 3; Figure 3**]. Ruxolitinib is more commonly considered in first-line settings than fedratinib, given that it is the most established JAK inhibitor, initially approved in 2011 based on spleen and symptom benefits observed in the COMFORT-I and -II trials[12] and now supported by >12 years of real-world experience.[12, 22] However, momelotinib is worth considering, as it is indicated specifically for patients with anemia; the FDA label does not specify a particular hemoglobin threshold, while the EU indication is for moderate to severe anemia.[16, 18, 23]

In terms of the patient's history, peripheral neuropathy was a notable adverse event (AE) with momelotinib in phase 1/2 studies of a capsule formulation, as opposed to the approved tablet formulation; rates ranged from 27% (N=60) to 44% (N=100), and events were typically low grade and not progressive.[24, 25] However, a pooled long-term safety analysis of 725 patients across momelotinib phase 3 trials (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM) subsequently found that peripheral neuropathy was reported in only 14.8%, with 1.2% experiencing grade ≥3 events and decreasing incidence over time.[26] Different momelotinib doses or inclusion criteria such as preexisting neuropathy in earlier trials may have contributed to the higher rates in those studies that were not confirmed in the larger phase 3 trials.[27] Thus, while low-grade neuropathy should be included in this patient's workup, its presence is not a contraindication to momelotinib.

The patient's history of squamous cell cancers should be considered given the warnings and precautions associated with JAK inhibitors [**Table 2**], including a warning for nonmelanoma skin cancer (NMSC) with ruxolitinib.[12, 14-16] In long-term phase 3 trial analyses, exposure-adjusted NMSC rates were comparable between ruxolitinib and placebo in COMFORT-I, while

higher rates were observed with ruxolitinib vs best available therapy (BAT) in COMFORT-II (6.1 vs 3.0 per 100 patient-years).[22] One real-world study (N=700) showed that 11.4% of patients developed second primary malignancies with ruxolitinib, of which half were NMSCs.[28] While NMSC with momelotinib has not been as thoroughly characterized, in the pooled long-term analysis, NMSC incidence was 4.8% and did not increase over time.[26] Collective evidence suggests that active skin surveillance is prudent with all JAK inhibitors.

Baseline factors such as renal function and platelet counts, as well as on-treatment cytopenias, may necessitate reduced ruxolitinib dosing [**Tables 2** and **4**].[12, 29] One option is to initiate ruxolitinib 10 mg twice daily (BID)—lower than the recommended starting dose—and uptitrate based on efficacy and platelet counts; addition of an erythropoiesis-stimulating agent (ESA) could be considered if hemoglobin levels decrease.[12, 29] Several studies have reported that this strategy provides spleen and symptom benefits in patients with low platelet counts (50-100×10^9/L).[29-31] Given this patient's symptom burden, it is worth noting that time to symptom improvement with ruxolitinib is typically rapid (≤4 weeks).[32] However, symptom benefit and, more substantially, spleen benefit with ruxolitinib are dose dependent; doses of ≥20 mg daily were post hoc identified as optimal.[33, 34] These results are bolstered by real-world evidence of higher spleen response rates with a 20-mg BID starting dose (vs 10 or 15 mg); reduced doses (leading to less robust spleen responses) are associated with lower OS.[35, 36] In contrast with these ruxolitinib dosing considerations, momelotinib is initiated at the full daily dose regardless of baseline platelet counts; however, dose reduction in the event of on-treatment thrombocytopenia and other AEs may be warranted [**Table 4**].[16]

As RBC transfusion reliance negatively impacts OS, it is worth considering therapies that can prevent progression to transfusion dependence.[8] Moreover, in the RR6 validated prognostic model used to evaluate patients after 6 months of ruxolitinib, both transfusion need and ruxolitinib doses <20 mg twice daily at baseline, 3 months, and 6 months predicted poor OS.[37]

In a post hoc analysis of SIMPLIFY-1, OS was longer among momelotinib-treated patients with either moderate or severe anemia who achieved a hemoglobin >10 g/dL by week 24; patients with moderate anemia were more likely to achieve this threshold and did so faster, further supporting early anemia intervention when possible.[38] This evidence, coupled with collective spleen, symptom, and anemia-related benefits including maintenance of transfusion independence, observed with momelotinib in SIMPLIFY-1 regardless of anemia severity (defined by baseline hemoglobin levels [severe, <8 g/dL; moderate to severe, <10 g/dL; mild, ≥10 to <12 g/dL]), supports momelotinib as an option for this moderately anemic patient.[39, 40] Among patients with moderate to severe anemia in that analysis, 72% maintained transfusion independence from baseline to week 24 with momelotinib vs 34% with ruxolitinib, and spleen and symptom benefits were consistent with those observed in the overall trial population.[40] In particular, response rates favored momelotinib vs ruxolitinib within the subset of patients with moderate to severe anemia and baseline platelets <200×10^9/L, the threshold at which the starting ruxolitinib dose is reduced per prescribing information.[12, 41] Numerically higher spleen (39% vs 27%) and transfusion independence (51% vs 21%) rates were observed with momelotinib vs ruxolitinib, along with a higher likelihood of achieving both of these responses (33% vs 2%).[41] Note, however, that the addition of anemia supportive therapy to ruxolitinib, which is common in routine practice, was not permitted in SIMPLIFY-1.[39, 42]

As a final consideration, this patient's mutational profile may also inform treatment, although the data are mixed and continuing to evolve. Studies have shown that *ASXL1* mutations, particularly when co-occurring with other high-risk mutations, are associated with decreased OS.[43, 44] Furthermore, the *ASXL1* mutation is included in the MIPSS70, MIPSS70+ v2.0, and Genetically Inspired Prognostic Scoring System (GIPSS) risk stratification tools, along with mutations in *SRSF2*, *EZH2*, *IDH1*, *IDH2,* and *U2AF1* Q157.[11] The prognostic value of *JAK2* VAF is less clear, with one study reporting no OS impact; instead, the presence of cytopenias

affected survival.[45] Another study reported suboptimal responses to ruxolitinib in patients with *JAK2* VAF of <50%.[46] Thus, VAF could be considered alongside the patient's clinical profile, symptoms, and risk factors when determining treatment.

Patient update 1

This patient was initially treated with ruxolitinib (10 mg BID, considering moderate renal impairment and hemoglobin level [**Table 4**]). After 6 months, his WBC count was 26×10^9/L; hemoglobin levels decreased to 7.0 g/dL (with transfusion requirement) and platelet counts to 100×10^9/L. Symptom improvement was noted, with night sweats subsiding and spleen size decreasing to 3 cm below the LCM.

Treatment selection: second-line JAK inhibitor/add-on therapy

While this patient's symptoms appear well controlled on ruxolitinib, worsening cytopenias and progression to transfusion requirement may warrant regimen adjustments. Options include switching to a less myelosuppressive JAK inhibitor [**Table 2**], such as momelotinib or pacritinib (see discussion in Case 2), or adding anemia supportive therapy to ruxolitinib, particularly as the spleen and symptom burdens are well controlled; of note, guidelines equally recommend switching and add-on therapy in this scenario.[47] Off-label anemia-directed therapies include ESAs, danazol, or luspatercept [**Figure 4**].[48] Across two small studies, 40%-60% of patients showed ESA responses, particularly those with low serum erythropoietin (<125 IU/L) and higher hemoglobin levels.[49, 50] Danazol is associated with response rates of ≈30%, with transfusion-independent patients more likely to benefit.[48] Week 24 transfusion independence rates with luspatercept ranged from 10%-26% in a phase 2 study in patients with myelofibrosis with and without ruxolitinib; the phase 3 INDEPENDENCE trial is ongoing.[51]

Patient update 2

Darbepoetin (500 mg subcutaneously every 3 weeks) was added to the patient's regimen, resulting in improvement of hemoglobin levels to 9.5-11 g/dL and reduced transfusion burden. Over the next 12 months, the patient had a 10% weight gain, and new squamous cell cancer growth was detected on his arm. The patient's symptom burden remained controlled with ruxolitinib despite these increasing AEs. Given his high-risk disease features, he agreed to consider HSCT, an option discussed in Case 3.

Case 1 discussion summary:

- HSCT should be considered for all patients with primary myelofibrosis and an intermediate-2– or high-risk DIPSS score, a high-risk MIPSS70 or MIPSS70+ v.2.0 score, and a low- or intermediate-risk Myelofibrosis Transplant Scoring System score
- Ruxolitinib is commonly considered in first-line settings for myelofibrosis, as it is the most established JAK inhibitor, supported by a large body of data supporting its use for improving symptoms and splenomegaly
- Transfusion dependence is associated with poor survival and quality of life in patients with MF, thus it is worth considering therapies such as momelotinib that can prevent progression to transfusion dependence in patients with mild to moderate anemia
- Monitoring for NMSC is prudent in all patients who are undergoing JAK inhibitor therapy
- The presence of *ASXL1* mutations, particularly when co-occurring with other high-risk mutations, may be associated with decreased survival

Case 2: JAK inhibitor-experienced, secondary MF with transfusion burden

Patient history

A 75-year-old woman with *CALR*-mutated post–essential thrombocythemia (ET) myelofibrosis presented with a WBC count of 17×10^9/L, hemoglobin level of 11.5 g/dL, platelet count of 467×10^9/L, and no peripheral blood blasts at diagnosis. She was classified as

intermediate-1 risk by the Myelofibrosis Secondary to PV and ET-Prognostic Model. She had been on ruxolitinib 20 mg BID to manage her symptoms and has had splenomegaly (13 cm below the LCM at baseline) for the past 3 years, with spleen size improving during treatment at best to 5 cm below the LCM. According to the RR6,[37] she was intermediate risk. Over the last year, hemoglobin levels decreased from 10.3 to 7.5 g/dL (one transfusion 2 weeks prior for a hemoglobin level of 7.3 g/dL) and platelet counts from 224×10^9/L (at 6 months post ruxolitinib) to 86×10^9/L. The presence of cytopenias necessitated a ruxolitinib dose decrease to 10 mg BID.

On further evaluation, her laboratory studies showed 2% circulating blasts and a WBC count of 15×10^9/L; a peripheral blood next-generation sequencing (NGS) test showed *CALR* type 2 (45% VAF), *EZH2*, and *SRSF2* mutations. Over the next 3 months, her spleen size increased to 10 cm below the LCM, and she reported worsening fatigue and the emergence of night sweats.

Treatment selection: second-line JAK inhibitor

For a patient experiencing disease progression on a first-line JAK inhibitor, treatment will depend on how the progression manifests. With worsening cytopenias, symptoms, and splenomegaly, and considering that ruxolitinib was already dose-reduced (reducing its efficacy), a treatment switch is warranted. Of note, patients with cytopenias during ruxolitinib treatment achieve lower spleen and symptom response rates and may be at increased risk of leukemic transformation.[52, 53] Discontinuation of ruxolitinib is sometimes necessary; one real-world study reported a 41% discontinuation rate at 3 years, and rates in long-term follow-up from COMFORT-I were 21% at year 1, 35% at year 2, and 51% at year 3.[54, 55] Common reasons for ruxolitinib discontinuation are disease progression, loss of response, and AEs such as cytopenias.[54-56] Overall, 50%-72% experience loss of response or intolerance within 3-5 years of starting ruxolitinib.[57] However, definitions of ruxolitinib failure vary [**Table 5**], and guidance on JAK inhibitor transition is lacking. A consensus panel was convened to address these

challenges and align on definitions of primary refractory status, loss of response, disease progression, and intolerance [**Figure S1**].[57] Guidance is also available through the online RR6 calculator.[37]

Survival following ruxolitinib discontinuation tends to be poor, with one study reporting a median of 4.9 months with observation alone.[55, 56, 58] However, these retrospective studies were performed at a time when no other JAK inhibitors were approved. Clinicians should also be cognizant that ruxolitinib discontinuation syndrome occurs in 11%-15% of patients.[59-61] Symptoms typically occur within 3 weeks and may include life-threatening AEs such as respiratory distress, septic-like shock, symptom relapse, and rapid spleen enlargement.[59, 60] Thus, patients should be carefully monitored and be made aware of possible withdrawal symptoms; steroids should be initiated at the first sign.[57, 60]

For this patient, treatment possibilities following ruxolitinib include fedratinib, momelotinib, and pacritinib [**Table 1**].[5, 62, 63] When transitioning to a second-line JAK inhibitor, the consensus panel suggested tapering ruxolitinib based on the current dose, disease status, and comorbidities; overlapping tapering with second-line treatment; or discontinuation followed by immediate initiation of second-line therapy.[57] Regulatory labels for both pacritinib and fedratinib, which have long half-lives and low to no clinically relevant JAK1 inhibition, note that prior treatments such as ruxolitinib should be tapered and discontinued per prescribing information.[14, 15] There is no reference to tapering of prior therapy for momelotinib; a post hoc analysis of patients transitioning directly from ruxolitinib to full-dose momelotinib in SIMPLIFY-1 found no evidence of ruxolitinib discontinuation syndrome and reported rapid hemoglobin improvement without compromising splenic control.[64] No prospective study has systematically addressed JAK inhibitor use post fedratinib, pacritinib, or momelotinib, but we would suggest employing similar principles as previously described post ruxolitinib. Taper and overlap, although not mandatory, could be considered when switching from momelotinib to pacritinib or fedratinib, but not ruxolitinib. However, tapering fedratinib or pacritinib may not be required

when switching to another JAK inhibitor. Real-world evidence is just starting to accumulate and will guide more informed decisions in the future. Transition between JAK inhibitors should also be reviewed with the patient to ensure adherence, with close monitoring throughout the subsequent weeks for withdrawal symptoms and continued spleen and symptom control.

Given this patient's advancing cytopenias, fedratinib is not the optimal choice, as it can be associated with new or worsening cytopenias [**Table 2**].[14, 17] Although pacritinib approval is limited to patients with platelet counts <50×10^9/L, guidelines endorse its use in the second line for patients with platelet counts ≥50×10^9/L.[47] When considering momelotinib, SIMPLIFY-2 and MOMENTUM showed anemia, symptom, and spleen benefits in JAK inhibitor–experienced patients, including those with thrombocytopenia.[65-67] In a post hoc analysis of SIMPLIFY-2 in patients with hemoglobin levels <10 g/dL or transfusion burden at baseline, switching to momelotinib was associated with higher spleen, symptom, and transfusion independence response rates at week 24 vs continuing ruxolitinib and adding transfusions or anemia supportive therapies.[68] Thus, momelotinib is an option for addressing this patient's anemia, as well as improving her worsening splenomegaly and symptoms. A retrospective analysis showed that patients with post-ET myelofibrosis, lower serum ferritin levels, and shorter time from diagnosis were more likely to show an anemia response with momelotinib.[69] The achievement of transfusion independence can carry significant benefits for patients, as it was linked to improved OS in a post hoc analysis of the SIMPLIFY studies, providing additional rationale for prioritizing anemia-related benefit.[70]

In terms of the patient's NGS profile, *CALR* mutation is associated with lower risk of developing cytopenias or thrombosis and longer survival compared with other driver mutations.[71] Two types of *CALR* mutations have been described: type 1 is associated with a more favorable prognostic impact with longer survival, while type 2 is linked to shorter survival.[72, 73] Treatment response may also differ, with post hoc analyses of the COMFORT-II trial showing that the efficacy of ruxolitinib is retained in patients with *CALR* mutations or high

molecular risk status.[74, 75] A subanalysis of the RUX-MF study, however, suggested that patients with *CALR* mutations have inferior spleen and symptom responses to ruxolitinib and are more commonly affected by anemia vs those with *JAK2* mutations.[76] Notably, the *CALR* mutation is a predictor of good survival outcomes with momelotinib, although this is unlikely to be a drug-specific effect.[77]

Patient update

After discussing the available options, this patient chose to switch to momelotinib; treatment was initiated (200-mg dose) 1 day after the last dose of ruxolitinib. No discontinuation syndrome signs were noted, and, after 2 months, hemoglobin levels improved to 8.9 g/dL without need for transfusions, and platelet counts were 70×10^9/L. Additionally, the patient reported reduced fatigue and night sweats, while spleen length decreased to 6 cm below the LCM.

Case 2 discussion summary:

- Outcomes tend to be poor for patients discontinuing ruxolitinib due to progression or lack of response, and momelotinib and pacritinib represent reasonable second-line options in the presence of worsening cytopenias
- Recommendations for JAK inhibitor tapering and switching vary and are primarily based on ruxolitinib; patients should be monitored early on for response and signs of withdrawal syndrome
- In patients with available NGS profiles, *CALR* mutations are notably associated with lower risk of developing cytopenias or thrombosis and longer survival vs other driver mutations

Case 3: Newly diagnosed primary MF with severe anemia and thrombocytopenia

Patient history

A 63-year-old woman with hypertension presents with a new diagnosis of primary myelofibrosis; spleen size was 3 cm below the LCM. She reports night sweats, easy fatigability, and dyspnea on exertion. An NGS panel shows *JAK2* V617F (35% VAF), *ASXL1* frameshift (43 % VAF), and *U2AF1* S34 (26% VAF) mutations with no karyotypic abnormalities. At diagnosis, her WBC count was 8×10^9/L, hemoglobin level was 7.4 g/dL (four transfusions over 2 months), platelet count was 45×10^9/L, and peripheral blood blasts were 4%. Her MPN-SAF TSS was 11, while risk stratification showed high-risk disease by MIPSS70 and very high–risk disease by MIPSS70+ v2.0.

Treatment selection: peritransplant considerations

As discussed in Case 1, this patient would be an excellent candidate for HSCT. A further consideration is whether peritransplant JAK inhibitor use may be warranted, given that posttransplant outcomes are generally better in patients whose disease, notably splenomegaly, is well controlled.[78] Several observational studies have found that peritransplant ruxolitinib is safe and well tolerated, with no impairment of engraftment and reduced relapse risk.[78, 79] The majority of these studies involved tapering ruxolitinib before conditioning, but the necessity of tapering remains unclear; some studies have shown that continuing low-dose ruxolitinib during transplant does not negatively impact engraftment, and, in fact, may be beneficial, which is consistent with its approval for graft-vs-host disease.[78, 80] Ultimately, peritransplant JAK inhibition appears safe and advantageous, although further data are required.

The presence of multiple cytopenias in this patient may be explained in part by the *U2AF1* mutation, which is associated with anemia and may identify patients who would benefit from therapies targeting this disease feature.[81, 82] Notably, however, only the *U2AF1* Q157

variant is included as negatively prognostic in the MIPSS70+ v2.0/GIPSS risk calculations.[11] Based on these cytopenias, pacritinib or momelotinib are suitable options, which are both guideline recommended in patients with high-risk myelofibrosis and platelet counts <50×10^9/L.[47] Pacritinib is indicated in the US for this subpopulation, based on spleen volume reduction in this 31-patient subgroup of PERSIST-2;[12] the confirmatory phase 3 PACIFICA trial is ongoing. Momelotinib has also demonstrated efficacy in this subpopulation; minimum platelet counts for eligibility were ≥25×10^9/L in MOMENTUM and ≥50×10^9/L in SIMPLIFY-1, with no minimum platelet count requirement in SIMPLIFY-2.[67] In a post hoc analysis of patients with thrombocytopenia across these trials, including 27 with baseline platelet counts <50×10^9/L randomized to receive momelotinib in MOMENTUM and SIMPLIFY-2, spleen, symptom, and transfusion independence response rates were comparable to or better than those observed in the overall trial populations.[67]

Both pacritinib and momelotinib also have data supporting their use in patients with anemia, based at least in part on their inhibition of activin A receptor type 1 [**Figure 4**].[39, 65, 66, 83] While anemia supportive therapies such as ESAs may stabilize hemoglobin levels, they provide little relief for splenomegaly and symptoms.[48] Transfusions often become necessary, but carry associated time and cost burdens, as well as risks of complications such as iron overload.[10, 48] Transfusions may also factor into the decision whether and how to treat with JAK inhibition before transplant, as delaying transplant could lead to the requirement for more transfusions if anemia is not well controlled; notably, there are little data on pacritinib or momelotinib in the peritransplant setting, despite their established anemia-related benefits.

In a retrospective analysis of PERSIST-2 that included patients who were not transfusion independent at baseline, 37% achieved transfusion independence (no transfusions for ≥12 weeks through week 24) with pacritinib vs 7% with BAT.[83] For momelotinib, transfusion independence was assessed as a prespecified endpoint in phase 3 trials (no transfusions or

hemoglobin levels <8 g/dL for the 12 weeks immediately preceding week 24), with higher rates observed with momelotinib vs comparators across SIMPLIFY-1 (67% vs 49% for ruxolitinib), SIMPLIFY-2 (43% vs 21% for BAT), and MOMENTUM (30% vs 20% for danazol).[39, 65, 66] The retrospective pacritinib and prospective momelotinib datasets highlight the lack of consistency in how anemia-related endpoints are defined in myelofibrosis trials, with varying definitions based on transfusion status, with or without a minimum hemoglobin stipulation.[84] The issue is further compounded by lack of head-to-head data between JAK inhibitors with anemia-related benefits. The recently updated International Working Group-European LeukemiaNet criteria for anemia response (no transfusions and an average hemoglobin level increase of ≥1.5 g/dL over any rolling 12-week period) may bring much-needed consensus.[85]

This patient's multiple cytopenias suggest cytopenic (or myelodepletive) myelofibrosis, which is distinct from the so-called myeloproliferative phenotype.[86, 87] In general, cytopenic myelofibrosis tends to present with more severe anemia and thrombocytopenia with normal or low WBC counts and is typically associated with primary myelofibrosis, lower *JAK2* V617F VAF, less prominent splenomegaly, and poorer prognosis.[86, 87] When considering treatment, note that ruxolitinib has demonstrated efficacy in patients with the myeloproliferative phenotype, but has a lower probability of spleen and symptom response and higher discontinuation rates in cytopenic myelofibrosis.[52, 86]

This patient's peripheral blast percentage may also inform treatment. Ruxolitinib is associated with prolonged OS in patients with <10% peripheral or bone marrow blasts, with one study demonstrating incrementally better survival and spleen response rates among those with baseline peripheral blast percentages of 0% vs 1%-4% vs 5%-9%.[88, 89] Pacritinib has been shown to benefit patients with elevated peripheral blasts, lowering median blast percentage on treatment while platelet counts and hemoglobin levels remained steady.[90] In general, results

from retrospective studies suggest that ≥5% bone marrow blasts and ≥4% peripheral blasts are associated with reduced survival.[88, 89]

Patient update

While awaiting transplant, this patient opted to initiate a JAK inhibitor to ameliorate symptoms and address cytopenias.[78] She was US based and therefore started on pacritinib (200 mg BID), planning to receive treatment for 3-4 months and stop 1 day before conditioning; mild gastrointestinal toxicities consistent with pacritinib's established safety profile necessitated use of antiemetics and antidiarrheals in the first month.[15] The patient's blood counts stabilized, and she notably required only one transfusion in 3 months. Four months following pacritinib initiation, she successfully underwent HSCT with a full match donor.

Case 3 discussion summary:

- In patients with multiple cytopenias, suggestive of cytopenic (or myelodepletive) myelofibrosis, pacritinib or momelotinib represent suitable options due to their established anemia-related benefits
- Genomic features may help to inform treatment selection, but evidence in this area is still evolving
- In patients who are awaiting HCST, peritransplant JAK inhibition appears to be safe and advantageous; most studies in this setting focus on ruxolitinib and further evidence is needed for other JAK inhibitors

Case 4: JAK inhibitor-experienced, higher-risk secondary MF with splenomegaly

Patient history

A 78-year-old man with polycythemia vera (PV) was treated with hydroxyurea for 15 years, followed by ruxolitinib 20 mg BID for post–PV myelofibrosis. His symptom burden was largely restricted to mild fatigue, and splenomegaly improved from 8 cm below the LCM to

nonpalpable. Four years later, his splenomegaly worsened to 15 cm below the LCM, with a 20-lb weight loss (12% of body weight) over 6 months. Additionally, his fatigue worsened, and previously controlled symptoms of pruritus, bone pain, and night sweats reemerged; the MPN-SAF TSS score was 35. His blood work showed a WBC count of 41×10^9/L, hemoglobin level of 11.5 g/dL, platelet count of 257×10^9/L, and 1% blasts. Peripheral blood NGS showed *JAK2* V617F (85% VAF), *TP53* (35% VAF), and *SRSF2* (55% VAF) mutations. The patient was designated as intermediate-2 risk by DIPSS and high risk by MIPSS70+ v2.0.

Treatment selection: second-line JAK inhibitor

For this case, fedratinib, momelotinib, and pacritinib are all appropriate based on the patient's profile and previous ruxolitinib experience, as discussed previously.[14-16] Given the myeloproliferative features, fedratinib warrants consideration, supported by data from phase 2 and 3 trials—JAKARTA-2, FREEDOM, and FREEDOM-2—in patients previously treated with ruxolitinib.[62, 91-93] However, some of these trials had limited enrollment due to an FDA clinical hold (JAKARTA-2; N=97) or the COVID-19 pandemic (FREEDOM; N=38).[91, 92] In the larger FREEDOM-2 trial (N=201), fedratinib showed higher spleen (36% vs 6%) and symptom (34% vs 17%) response rates vs BAT.[93] These trial findings are bolstered by consistent real-world outcomes observed with fedratinib post ruxolitinib.[94] Gastrointestinal AEs and prophylactic strategies as well as thiamine supplementation should be considered in fedratinib-treated patients [**Table 2**].[14]

As the evolution of this patient's disease illustrates, myelofibrosis progression is accompanied by a host of complications.[1, 11] Aside from key features present at diagnosis,[11] lesser-known complications may arise, including comorbidities that can be attributed to the older average age of patients with myelofibrosis [**Figure 1**].[1] Hepatomegaly, particularly when combined with splenomegaly, can result in portal hypertension and ascites.[1] As bone marrow fibrosis progresses, extramedullary hematopoiesis outside the spleen and liver may lead to

complications such as intracranial hypertension, pulmonary hypertension, and worsening abdominal symptoms.[1] Physicians should be aware of cardiovascular, thromboembolic, and hemorrhagic complications in myelofibrosis as well as the increased risk of leukemic transformation over time.[1] The latter finding is notable given that this patient's NGS findings indicate the *TP53* mutation, which has been suggested as a high-risk molecular feature associated with poorer OS and increased risk of leukemic transformation.[95, 96] Challenges in diverse patient presentations and prognoses are reflected in a recent survey that identified considerable heterogeneity in the approach to managing myelofibrosis-related comorbidities.[97] These findings underscore the need for increased awareness of possible complications and individualized treatment decisions considering the potential impacts of different JAK inhibitors [**Table 3**].

Patient update

This patient initiated fedratinib (400 mg daily) with prophylactic thiamine supplementation (100 mg daily) and antiemetic and antidiarrheal medications as needed. Although he reported improvement in pruritus and bone pain, the severity of night sweats remained largely unchanged. His weight stabilized, and spleen length improved to 10 cm below the LCM.

Six months later, his WBC count was 22×10^9/L, hemoglobin level was 8.5 g/dL (one transfusion in the previous 3 months), and platelet count was 151×10^9/L. After another 6 months, worsening splenomegaly, dyspnea, and ascites were noted, and portal hypertension and cirrhosis were detected on ultrasound. Momelotinib was initiated (150 mg daily per prescribing information for Child Pugh C hepatic impairment [**Table 4**]), and the patient did well, requiring just one transfusion in 15 months.

Case 4 discussion summary:

- Fedratinib can be considered as a second-line JAK inhibitor in ruxolitinib-treated patients with preserved blood counts; physicians should be aware of prophylactic gastrointestinal AE mitigation strategies and thiamine supplementation
- Myelofibrosis progression can be accompanied by lesser-known complications including hepatomegaly, portal hypertension, ascites, intracranial hypertension, pulmonary hypertension, as well as leukemic transformation and complications associated with cardiovascular, thromboembolic, or hemorrhagic conditions

Discussion

The FDA approval of ruxolitinib in November 2011 marked an epochal moment in myelofibrosis management,[12] upending the existing treatment landscape and leading various suboptimal palliative approaches to give way to JAK/STAT-targeted therapies. Ruxolitinib approval was based on two novel endpoints in the COMFORT studies, improvement in spleen volume and disease-related symptoms, which validated the benefits of inhibiting hyperactive JAK/STAT signaling.[12] The ruxolitinib trial designs and regulatory journey became a template for its successors and is still largely followed in myelofibrosis drug development.

Today, four JAK inhibitors approved for myelofibrosis.[12, 14-16] While all inhibit JAK2, differing individual kinomes contribute to unique efficacy and AE profiles. All have line agnostic approvals, providing more options to patients and providers, albeit without a definitive “winner” for individual patient scenarios.[12, 14-16] At the heart of this issue is the lack of head-to-head studies, aside from momelotinib vs ruxolitinib in SIMPLIFY-1.[39] Meanwhile, the approved labels and guideline recommendations have significant, but incomplete, overlap.[12, 14-16, 47] This has created areas of uncertainty in our field, accentuated by the considerable clinical heterogeneity of myelofibrosis, and evidence-based algorithms for JAK inhibitor selection remain challenging

to develop. Unlike some malignancies such as chronic myeloid leukemia, myelofibrosis lacks specific treatment milestones that a patient must hit to achieve “optimal” long-term benefits, and no resistance, intolerance, or definitively predictive biomarkers have been identified. However, with four JAK inhibitors now approved in the US and three in Europe, switching among them when the drug and patient profiles align may be optimal, with physician experiences and emerging data guiding management.

How, then, should one select a JAK inhibitor? First, we should remember the fundamental objectives of myelofibrosis therapy: Provide spleen and symptom relief, and improve cytopenias and survival. All JAK inhibitors have generally demonstrated benefits for splenomegaly and symptoms, some in specific subpopulations.[12, 14-16] Only momelotinib and pacritinib have demonstrated anemia benefits, although anemia supportive therapy could be added to any JAK inhibitor.[15, 16, 48] Finally, although the data for OS improvement is strongest with ruxolitinib, it is likely a class effect.[98] Unfortunately, study designs and regulatory hurdles (eg, study holds or terminations) preclude us from reaching firm conclusions. In the event of no significant splenomegaly or low symptom burden, one could even delay JAK inhibitor treatment.[11, 47] Personalizing treatment includes consideration of patient-specific factors (severity of symptoms and splenomegaly, anemia and/or thrombocytopenia, and comorbidities), treatment-specific factors (AE profile in the individual patient, potential drug-drug interactions, cost/insurance approvals, and previous treatment responses), and the totality of clinical trial and real-world evidence based on a patient’s profile. It is this collective framework that we tried to capture in our cases.

Beyond current JAK inhibitors, the myelofibrosis field is in dire need of disease-modifying treatments,[11] and various treatments targeting alternative pathways are being investigated.[99] These notably include type II JAK inhibitors, which may circumvent JAK2 inhibitor persistence, and *JAK2* V617F–selective inhibitors, possibly avoiding myelosuppressive effects

of nonselective inhibitors.[100] Combination regimens with JAK inhibitor backbones are also under investigation, and immunotherapeutic approaches targeting mutant *CALR* are in development.[99] Ultimately, we hope these novel approaches will further improve patient outcomes, allow for additional personalization, and perhaps eliminate some of the uncertainties in our current JAK inhibitor selection paradigm. For all these reasons, we couldn't be more *jak*static about the future.

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Tables

Table 1: Overview of approved JAK inhibitors in myelofibrosis

JAK inhibitor	Ruxolitinib[12, 13]	Fedratinib[14, 17]	Pacritinib[15]	Momelotinib[16, 18]
Target/MOA	JAK1, JAK2	JAK2, FLT3	JAK2, FLT3, IRAK1, ACVR1	JAK1, JAK2, ACVR1
Clinical trials	COMFORT-I and -II	JAKARTA and JAKARTA-2	PERSIST-1 and -2, PAC-203	SIMPLIFY-1 and -2, MOMENTUM
Approval date (US and Europe)	US: Nov 2011 EU: Aug 2012	US: Aug 2019 EU: Feb 2021	US: Feb 2022	US: Sep 2023 EU: Jan 2024
Approved indication	US: intermediate- or high-risk MF, including primary or secondary MF in adults EU: disease-related splenomegaly or symptoms in adults with primary or secondary MF	US: adults with intermediate-2– or high-risk primary or secondary MF EU: disease-related splenomegaly or symptoms in adults with primary or secondary MF who are JAK inhibitor naive or have been treated with ruxolitinib	US: adults with intermediate- or high-risk primary or secondary MF with Plt count <50×10^9/L EU: not approved	US: intermediate- or high-risk MF, including primary or secondary MF in adults with anemia EU: disease-related splenomegaly or symptoms in adult patients with moderate to severe anemia who have primary or secondary MF and who are JAK inhibitor naive or have been treated with ruxolitinib
Approved dose	US: • 20 mg twice daily (Plt count >200×10^9/L) • 15 mg twice daily (Plt count 100-200×10^9/L) • 5 mg twice daily (Plt count 50 to <100×10^9/L) EU: • 20 mg twice daily (Plt count >200×10^9/L) • 15 mg twice daily (Plt count 100-200×10^9/L) • 10 mg twice daily (Plt count 75 to <100×10^9/L) • 5 mg twice daily (Plt count 50 to <75×10^9/L)	US: • 400 mg once daily for those with Plt count ≥50×10^9/L EU: • 400 mg once daily for those with Plt count >50×10^9/L and ANC >1.0×10^9/L	US: • 200 mg orally twice daily	US/EU: • 200 mg once daily

ACVR1, activin A receptor type 1; ANC, absolute neutrophil count; FLT3, fms related receptor tyrosine kinase 3; IRAK1, interleukin 1 receptor associated kinase 1; JAK, Janus kinase; JAK1,

Janus kinase 1; JAK2, Janus kinase 2; MF, myelofibrosis; MOA, mechanism of action; Plt, platelet.

Table 2: Common and notable adverse events with JAK inhibitors in myelofibrosis[a]

JAK inhibitor	Ruxolitinib[12,13]	Fedratinib[14, 17,20]	Pacritinib[15]	Momelotinib[16,18]
Common hematologic AEs	• Anemia • Thrombocytopenia • Neutropenia	• Anemia • Thrombocytopenia • Neutropenia	• Worsening thrombocytopenia	• Thrombocytopenia • Neutropenia
Common nonhematologic AEs	• Infections • NMSC • Secondary malignancies • Lipid level elevations • MACE • Thrombosis	• Gastrointestinal toxicity • Hepatic toxicity • Elevated amylase and lipase levels • Increased creatinine level • MACE • Thrombosis • Secondary malignancies	• Hemorrhage • Diarrhea • Prolonged QT interval • MACE • Thrombosis • Secondary malignancies • Infections	• Infections • Hepatotoxicity • SCARs • MACE • Thrombosis • Secondary malignancies
Other notable AEs	NA	• Black box warning: serious and fatal encephalopathy, including Wernicke encephalopathy, from thiamine deficiency	NA	NA

AE, adverse event; JAK, Janus kinase; MACE, major adverse cardiac events; NA, not applicable; NMSC, nonmelanoma skin cancer; SCAR, severe cutaneous adverse reaction.

[a] Listed AEs are based on the warnings and precautions noted in regulatory labeling.

Table 3: Prevention and management of adverse events with JAK inhibitors in myelofibrosis based on collective clinical experience[a]

JAK inhibitor	Ruxolitinib **(anemia, thrombocytopenia, weight gain, cholesterolemia, and infections)**	Fedratinib **(anemia, thrombocytopenia, nausea, vomiting, diarrhea, and Wernicke encephalopathy)**	Pacritinib **(nausea, vomiting, diarrhea, and cardiac events)**	Momelotinib **(nausea, vomiting, diarrhea, neuropathy, and dizziness)**
Prevention	• Cytopenia: - For moderate anemia, start at 10 mg BID and consider ESAs (if serum EPO level <500 mU/mL) or danazol • Infections: - Test for hepatitis B and hepatitis C virus; follow up viral load every 3 months - Test for latent tuberculosis • Herpes zoster vaccine • Pneumococcal vaccine	• Thiamine supplementation (or monitoring if feasible) • Cytopenia: - ESAs may be considered - Adjust doses if cytopenia worsens	No specific recommendations	• Awareness about potential first dose effects (eg, hypotension, dizziness, nausea, headache, flushing) • Bedtime dosing to minimize potential dizziness/hypotension • Address other potential causes of neuropathy (eg, diabetes, vitamin deficiencies)
Management	• For thrombocytopenia, danazol, steroids, or off-label low-dose immunomodulatory drugs could be used • Yearly dermatologic evaluations for NMSC should be performed • For severe infections, consider decreasing doses or discontinuing ruxolitinib	• Primary prevention of nausea and diarrhea may be used during the first 2 cycles, then only as needed	• Primary prevention of nausea and diarrhea may be used during the first 2 cycles, then only as needed	No specific recommendations

AE, adverse event; BID, twice daily; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; JAK, Janus kinase; NMSC, nonmelanoma skin cancer.

[a] Listed AEs and strategies are based on the collective clinical experience of the authors and may not be comprehensive or align with the warnings and precautions from regulatory labeling.

Table 4: Dose selection, dose adjustments, and drug-drug interactions of JAK inhibitors in myelofibrosis

JAK inhibitor	Ruxolitinib[12, 13]	Fedratinib[14, 17]	Pacritinib[15]	Momelotinib[16, 18]
Starting dose	US: • Plt count >200×10^9/L: 20 mg twice daily • Plt count 100-200×10^9/L: 15 mg twice daily • Plt count 50 to <100×10^9/L: 5 mg twice daily EU: • Plt count >200×10^9/L: 20 mg twice daily • Plt count 100-200×10^9/L: 15 mg twice daily • Plt count 75 to <100×10^9/L: 10 mg twice daily • Plt count 50 to <75×10^9/L: 5 mg twice daily	US: • Plt count ≥50×10^9/L: 400 mg once daily EU: • Plt count >50×10^9/L and ANC >1.0×10^9/L: 400 mg once daily	US: • Plt count <50×10^9/L: 200 mg twice daily	US/EU: • Patients with anemia: 200 mg once daily

Renal adjustment of dose	US:
	• Moderate or severe renal impairment (creatinine clearance 30 to 59 or 15 to 29 mL/min):
	  • Plt count >150×10^9/L: no dose adjustment
	  • Plt count 100-150×10^9/L: 10 mg twice daily
	  • Plt count 50 to <100×10^9/L: 5 mg daily
	  • Plt count <50×10^9/L: avoid use
	• ESRD on dialysis (avoid use in patients with ESRD not requiring dialysis):
	  • Plt count 100-200×10^9/L: 15 mg once after dialysis session
	  • Plt count >200×10^9/L: 20 mg once after dialysis session
	
	EU:
	• Severe renal impairment (creatinine clearance <30 mL/min): reduce dose by ≈50%, administered twice daily
	• ESRD on hemodialysis: single dose of 15-20 mg or two doses of 10 mg given 12 hours apart to be administered post dialysis and on the day of hemodialysis
	  • Plt count 100-200×10^9/L: single 15-mg dose
	  • Plt count >200×10^9/L: single 20-mg dose or two 10-mg doses given 12 hours apart
	  • Subsequent doses administered only on hemodialysis days following each dialysis session
		US/EU:
		• Severe renal impairment (creatinine clearance 15 to 29 mL/min): dose reduce to 200 mg once daily
			US:
			• Avoid use in patients with creatinine clearance <30 mL/min
				US/EU
				• No modification required

Hepatic adjustment of dose	US:
	• Mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, C)
	  • Plt count >150×10^9/L: no dose adjustment
	  • Plt count 100-150×10^9/L: 10 mg twice daily
	  • Plt count 50 to <100×10^9/L: 5 mg daily
	  • Plt count <50×10^9/L: avoid use
	
	EU:
	• For any hepatic impairment: reduce starting dose based on Plt count by ≈50%, administered twice daily; subsequent doses adjusted based on safety and efficacy monitoring
		US/EU:
		• No modification required based on Child-Pugh class; dose interruption/reduction may be warranted if certain enzyme elevations occur on treatment
			US:
			• Avoid use in moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C)
				US/EU:
				• Severe hepatic impairment (Child-Pugh class C): 150 mg once daily
				• Dose interruption/ reduction may be warranted if certain enzyme elevations occur on treatment

Other on-treatment dose reduction criteria	US/EU: • Hematologic toxicity (eg, Plt count, neutrophil count) • Concomitant strong CYP3A4 inhibitors or dual CYP2C9/3A4 inhibitors (eg, fluconazole)	US: • Hematologic toxicity (eg, Plt count, neutrophil count, anemia with transfusions) • Nonhematologic toxicity (eg, GI AEs, ALT/AST/bilirubin increase, other grade ≥3 AEs) • Concomitant strong CYP3A4 inhibitors EU: • Hematologic toxicity (eg, Plt count, neutrophil count, anemia with transfusions) • Nonhematologic toxicity (eg, GI AEs, ALT/AST/bilirubin increase, amylase/lipase increase, other grade ≥3 AEs) • Thiamine levels/signs or symptoms of Wernicke encephalopathy • Concomitant strong CYP3A4 inhibitors	US: • Diarrhea • Thrombocyto-penia • Hemorrhage • Prolonged QT interval	US/EU: • Hematologic toxicity (eg, Plt count, neutrophil count) • Hepatotoxicity (eg, AST/ALT/bilirubin increase) • Other nonhematologic toxicity (eg, grade ≥3 AEs)
Notable DDI	US: • CYP3A4 inhibitors, CYP3A4 inducers, fluconazole EU: • CYP3A4 inhibitors, CYP3A4 inducers, dual CYP2C9/3A4 inhibitors (eg, fluconazole)	US/EU: • CYP3A4 inhibitors, CYP3A4 inducers, dual CYP2C9/3A4 inhibitors (eg, fluconazole) • CYP3A4/2C19/2D6, OCT2, or MATE1/2-K substrates	US • Concomitant use contraindicated: CYP3A4 inhibitors, CYP3A4	US: • OATP1B1/B3 inhibitors • BCRP transporter substrates EU:

• P-glycoprotein or BCRP transporter substrates	inducers • CYP1A2/2C19/3A4, P-glycoprotein, or BCRP transporter substrates	• CYP3A4 inducers, OATP1B1/B3 inhibitors • BCRP transporter substrates • CYP450, P-glycoprotein, OCT-1, or MATE1/2-K substrates	

AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCRP, breast cancer resistance protein; CYP, cytochrome P450; DDI, drug-drug interaction; ESRD, end-stage renal disease; GI, gastrointestinal; JAK, Janus kinase; MF, myelofibrosis; NA, not applicable; Plt, platelet.

Table 5: Definitions of ruxolitinib failure based on collective clinical experience

Features of ruxolitinib failure

Feature	Definition	Action
Spleen	≥5 cm increase beyond baseline and more symptomatic	• Optimize dose • Switch JAK inhibitors • Consider splenectomy or radiotherapy
Symptoms	Worsening or new constitutional or spleen-related symptoms	• Review the cause • Optimize ruxolitinib dose • Consider alternative treatments • Switch JAK inhibitors
Cytopenias	Hb level <10 g/dL	• Exclude other causes (eg, drug-drug interactions) • Determine if treatment is needed • Consider switching JAK inhibitors, especially if the patient is transfusion dependent or severely thrombocytopenic or if symptoms and splenomegaly are not well controlled • Add EPO, danazol, or thalidomide if symptoms and splenomegaly are well controlled
Leukocytosis	To be considered on a case-by-case basis, particularly if leukocytosis corresponds with disease symptoms	• Exclude other causes (eg, infections, other hematologic cancers such as CML) • Determine threshold for treatment • Add hydroxycarbamide
Blasts	Threshold dependent on rate of rise	• Consider adding HMA or rarely AML induction therapy if transformation is expected

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; EPO, erythropoietin; Hb, hemoglobin; HMA, hypomethylating agent; JAK, Janus kinase.

Figure Legends

Figure 1. **Key features and complications of MF**

BMF, bone marrow fibrosis; MF, myelofibrosis; RBC, red blood cell; WBC, white blood cell.

Figure 2. **Etiologies of anemia in MF**

ACVR1, activin A receptor type 1; MF, myelofibrosis; RBC, red blood cell.

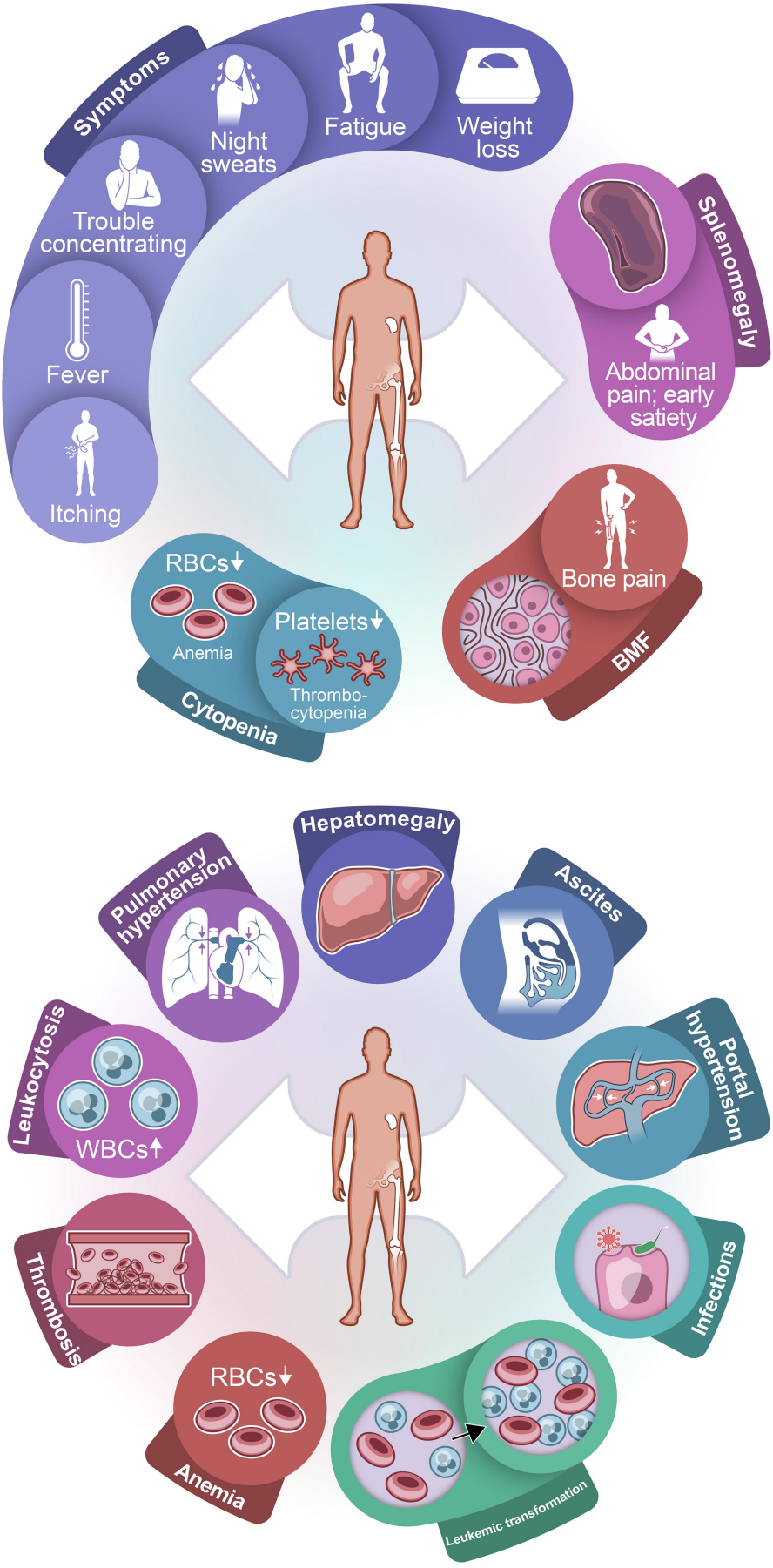
Figure 3. **Overview of JAK inhibitors in MF**

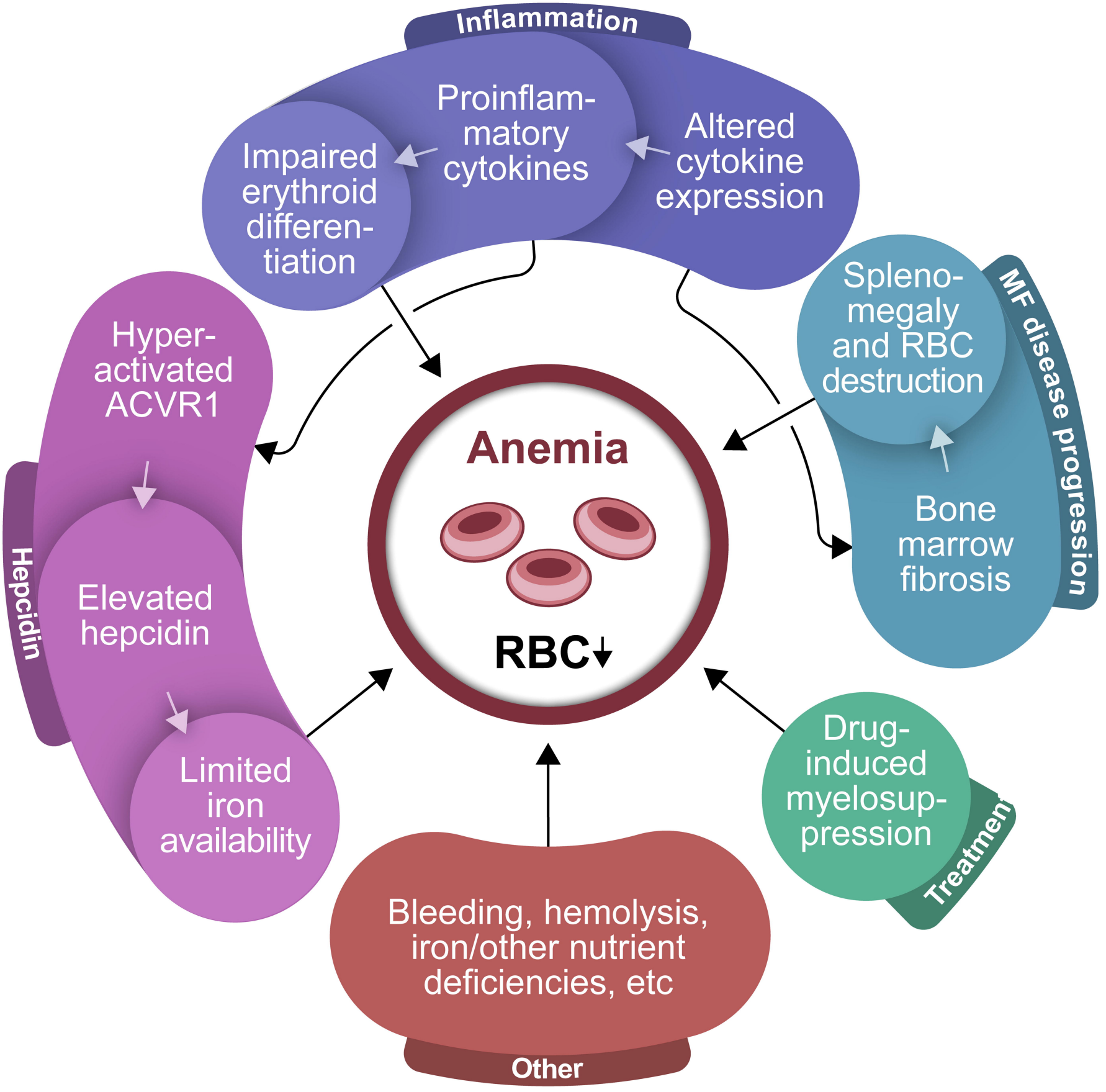
Refer to Table 1 and Table 4 for more details on dose modifications and adjustments. Refer to Table 3 and Table 4 for more detail on AEs; AEs shown here are based on the collective clinical experience of the authors and may not be comprehensive or align with the warnings and precautions from regulatory labeling.

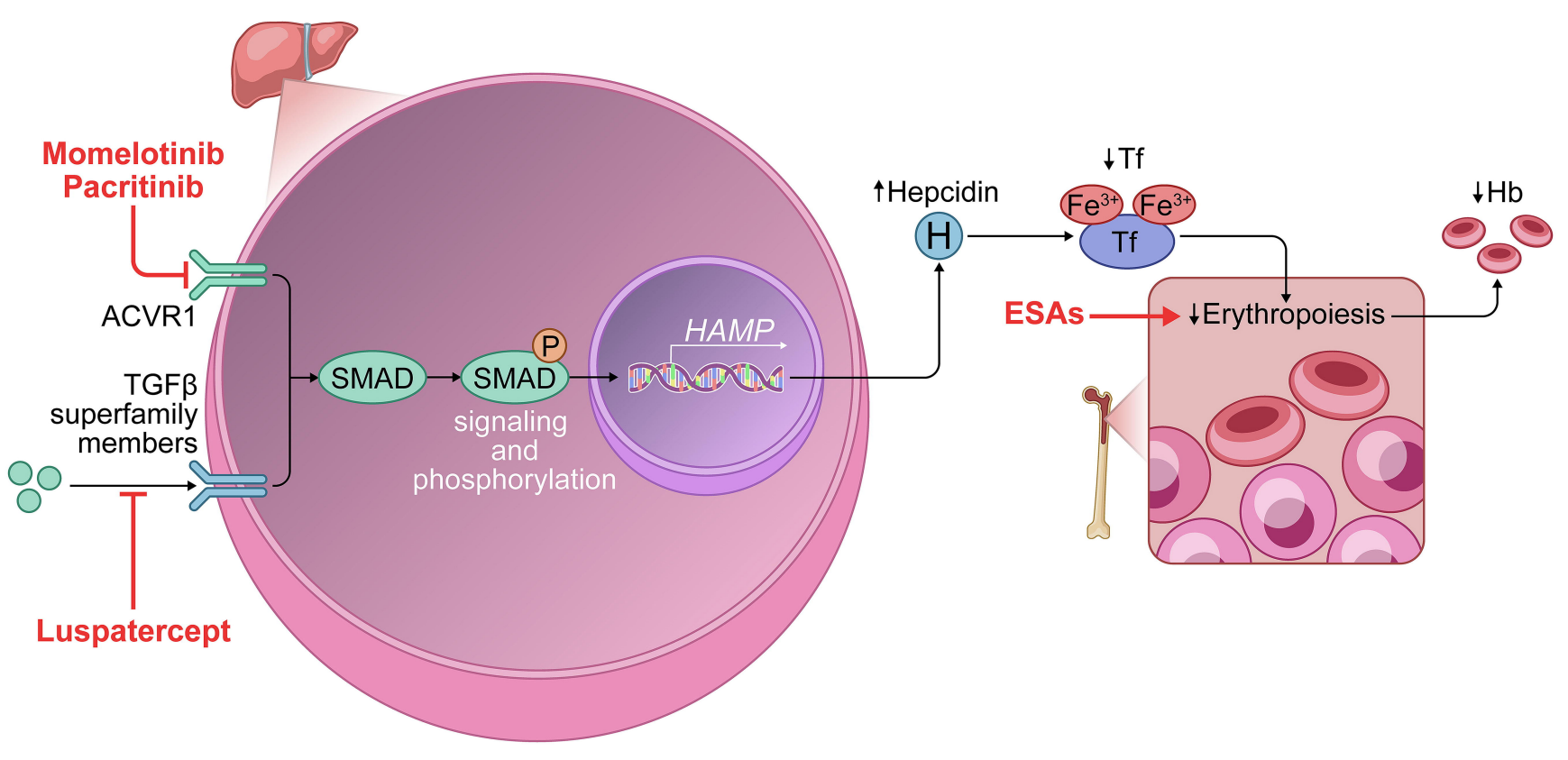
AE, adverse event; BID, twice daily; JAK, Janus kinase; MF, myelofibrosis; NMSC, nonmelanoma skin cancer; QD, once daily.

Figure 4. **Pathways targeted for anemia mitigation in MF**

ACVR1, activin A receptor type 1; ESA, erythropoiesis-stimulating agent; HAMP, hepcidin antimicrobial peptide; Hb, hemoglobin; MF, myelofibrosis; SMAD, mothers against decapentaplegic; Tf, transferrin; TGFβ, transforming growth factor beta.


Symptoms
Night sweats
Fatigue
Weight loss
Trouble concentrating
Fever
Itching
Splenomegaly
Abdominal pain; early satiety
RBCs↓
Anemia
Platelets↓
Thrombo-cytopenia
Cytopenia
Bone pain
BMF
Hepatomegaly
Pulmonary hypertension
Ascites
Leukocytosis
WBCs↑
Portal hypertension
Thrombosis
Infections
RBCs↓
Anemia
Leukemic transformation


Inflammation
Proinflam-matory cytokines
Impaired erythroid differen-tiation
Altered cytokine expression
Hyper-activated ACVR1
Hepcidin
Elevated hepcidin
Limited iron availability
Splenomegaly and RBC destruction
MF disease progression
Bone marrow fibrosis
Anemia
RBC↓
Drug-induced myelosup-pression
Treatment
Bleeding, hemolysis, iron/other nutrient deficiencies, etc
Other


Momelotinib
Pacritinib
ACVR1
TGFβ
superfamily
members
Luspatercept
SMAD
SMAD
P
signaling
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phosphorylation
HAMP
↑Hepcidin
H
↓Tf
Fe3+
Fe3+
Tf
ESAs
↓Erythropoiesis
↓Hb

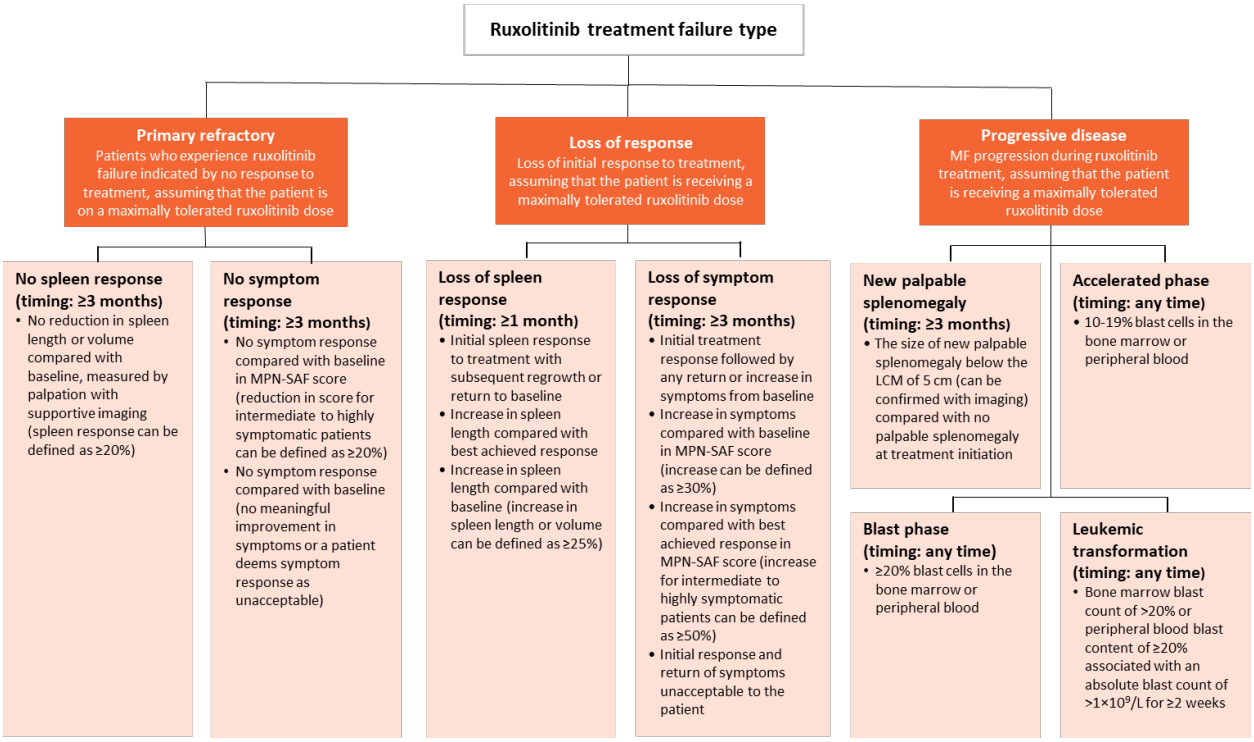
JAK inhibitors

	FDA Indication	EU Indication	Key AEs	Full Starting Dose
Ruxolitinib	**2011:** Intermediate- or high-risk primary or secondary MF	**2012:** Disease-related splenomegaly or symptoms in patients with primary or secondary MF	Anemia, thrombocytopenia, weight gain, cholesterolemia, infections, NMSC	**20 mg BID** (adjustments based on platelet count)
Fedratinib	**2019:** Intermediate- or high-risk primary or secondary MF	**2021:** Disease-related splenomegaly or symptoms in patients with primary or secondary MF who are JAK inhibitor naive or have been treated with ruxolitinib	Gastrointestinal toxicity, anemia, thrombocytopenia, Wernicke encephalopathy	**400 mg QD**
Pacritinib	**2022:** Intermediate- or high-risk primary or secondary MF with platelet count <50×10^9/L	Not approved	Diarrhea, cardiac events, bleeding	**200 mg BID**
Momelotinib	**2023:** Intermediate- or high-risk primary or secondary MF in patients with anemia	**2024:** Disease-related splenomegaly or symptoms in patients with moderate to severe anemia who have primary or secondary MF and are JAK inhibitor naive or have been treated with ruxolitinib	Diarrhea, neuropathy, thrombocytopenia, dizziness	**200 mg QD**

Supplemental information

Supplemental Figure 1

Definitions of ruxolitinib failure from the modified Delphi panel consensus study[1]



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