SPOTLIGHT REVIEW ARTICLE

Momelotinib (JAK1/JAK2/ACVR1 inhibitor): mechanism of action, clinical trial reports, and therapeutic prospects beyond myelofibrosis

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Received: January 2, 2023.
Accepted: February 20, 2023.
Early view: March 2, 2023.

https://doi.org/10.3324/haematol.2022.282612

Abstract

Janus kinase (JAK) 2 inhibitors are now part of the therapeutic armamentarium for primary and secondary myelofibrosis (MF). Patients with MF endure shortened survival and poor quality of life. Allogeneic stem cell transplantation (ASCT) is currently the only treatment modality in MF with the potential to cure the disease or prolong survival. By contrast, current drug therapy in MF targets quality of life and does not modify the natural history of the disease. The discovery of *JAK2* and other JAK-STAT activating mutations (i.e., *CALR* and *MPL*) in myeloproliferative neoplasms, including MF, has facilitated the development of several JAK inhibitors that are not necessarily specific to the oncogenic mutations themselves but have proven effective in countering JAK-STAT signaling, resulting in suppression of inflammatory cytokines and myeloproliferation. This non-specific activity resulted in clinically favorable effects on constitutional symptoms and splenomegaly and, consequently, approval by the Food and Drug Administration (FDA) of three small molecule JAK inhibitors: ruxolitinib, fedratinib, and pacritinib. A fourth JAK inhibitor, momelotinib, is poised for FDA approval soon and has been shown to provide additional benefit in alleviating transfusion-dependent anemia in MF. The salutary effect of momelotinib on anemia has been attributed to inhibition of activin A receptor, type 1 (ACVR1) and recent information suggests a similar effect from pacritinib. ACRV1 mediates SMAD2/3 signaling which contributes to upregulation of hepcidin production and iron-restricted erythropoiesis. Targeting ACRV1 raises therapeutic prospects in other myeloid neoplasms associated with ineffective erythropoiesis, such as myelodysplastic syndromes with ring sideroblasts or *SF3B1* mutation, especially those with co-expression of a *JAK2* mutation and thrombocytosis.

Introduction

Myelofibrosis (MF) is an operational terminology that refers to a primary form, a post-polycythemia vera form and post-essential thrombocythemia MF.[1] These three variants of MF are morphologically and molecularly inter-related myeloproliferative neoplasms (MPN) whose pathogenesis is centered around JAK-STAT activating *JAK2*, *CALR* or *MPL* mutations, with specific phenotypic expressions.[2] Morphologically, all three MPN variants display variable degrees of trilineage myeloproliferation associated with a bone marrow stromal reaction that is most intense in MF, in which abnormal megakaryocyte proliferation is often accompanied by bone marrow fibrosis, ineffective erythropoiesis (clinically apparent as anemia), aberrant cytokine expression (clinically apparent as constitutional symptoms and cachexia), and extramedullary hematopoiesis (clinically apparent as hepatosplenomegaly).[3] The three MPN variants also differ in disease course, survival outcome, and risk of progression into blast-phase disease, with reported median survivals for primary MF, post-polycythemia vera MF and post-essential thrombocytopenia MF being 4.4, 15, and 18 years, respectively, with corresponding leukemic transformation rates of 9.3%, 3.9%, and 2.6%.[4]

Patients with MF are subject not only to premature death[4] but also to poor quality of life.[5] The latter is manifest as severe anemia (often requiring red blood cell transfusions), marked hepatosplenomegaly, constitutional symptoms (including fatigue, night sweats, and low-grade fever), progressive cachexia with loss of muscle mass, bone pain, splenic infarct, pruritus, non-hepatosplenic extramedullary hematopoiesis, thrombosis and bleeding.[6] Consequences

of hepatosplenic extramedullary hematopoiesis include portal hypertension, which might lead to variceal bleeding or ascites, while those of non-hepatosplenic extramedullary hematopoiesis include spinal cord compression, ascites, pleural effusion, pulmonary hypertension or extremity pain.[6] The mechanism of anemia in MF involves multiple factors including ineffective erythropoiesis, bleeding, hemolysis, splenic sequestration of red cells, nutritional deficiency and the side effects of drugs. Ineffective erythropoiesis in MF might also contribute to extramedullary hematopoiesis and its underlying mechanisms might be similar to those seen in myelodysplastic syndromes (MDS) with ring sideroblasts (RS).[7]

Anemia and risk stratification in primary myelofibrosis

Among 1,109 consecutive patients with primary MF, a hemoglobin level of below the lower limit of normal, adjusted for sex, was present in 950 (86%) patients and ranged in severity from mild (hemoglobin ≥10 g/dL but less than sex-adjusted lower limit of normal) in 35%, to moderate (hemoglobin ≥8 and <10 g/dL) in 14%, to severe (hemoglobin <8 g/dL or transfusion-dependent) in 37%.[8] In the particular study, *U2AF1* mutations clustered with severe anemia and multivariable analysis confirmed prognostic relevance for all severity grades of anemia.[8] Anemia is currently included in contemporary risk models for primary MF, including MIPSS70[9] and MIPSS70+ version 2.0 (MIPSS*v2*).[10] MIPSS70 (Mutation-enhanced International Prognostic Scoring System for transplant-age patients) utilizes mutations and clinical variables[9] while MIPSS*v2* utilizes mutations, karyotype and clinical variables.[10] MIPSS*v2* scores very high-risk karyotype (4 points), unfavorable karyotype (3 points), ≥2 high molecular risk mutations (3 points), presence of one high molecular risk mutation (2 points), absence of type 1/like *CALR* mutation (2 points), constitutional symptoms (2 points), severe anemia (2 points), moderate anemia (1 point) and circulating blasts ≥2% (1 point).[10] MIPSS*v2* includes five risk categories: very high risk (≥9 points); high risk (5-8 points); intermediate risk (3-4 points); low risk (1-2 points); and very low risk (0 points) in patients aged 70 years or younger. The corresponding median survivals (10-year survival rates) were 1.8 years (<5%), 4.1 years (13%), 7.7 years (37%), 16.4 years (56%) and "median not reached" (92%).

Current treatment approaches

Survival-directed treatment

At present, allogeneic stem cell transplantation (ASCT) is the only treatment modality in MF with the potential to cure the disease or prolong survival.[11] In a multicenter, retrospective study of 4,142 patients with MF receiving ASCT and followed for a median of 48 months, 3-year survival, relapse, and non-relapse mortality rates were 58%, 22% and 29%, respectively.[12] The study showed a significant trend in terms of older age distribution (median 59.3 years) and utilization of matched unrelated donors (45.2%) in more recent times.[12] The study also showed decreasing rates of acute and chronic graft-*versus*-host disease, with recent rates of extensive chronic graft-*versus*-host disease at 23%. Observations from other studies were consistent regarding the value of ASCT in older patients[13] and the possibility of using family mismatched/haplo donors.[14] In a recent study of 556 transplanted patients with MF aged ≥65 years (median 67; range, 65-76), followed for a median of 3.4 years, 5-year survival, non-relapse mortality, and relapse rates were 40%, 37%, and 25%, respectively.[13] The possibility of transplant-related mortality and morbidity dictates careful risk-benefit analysis in the individual patient with MF and a number of risk models assist in this regard: MIPSS*v2*[10] and the Myelofibrosis Transplant Scoring System (MTSS).[15] Newer effective therapies for graft-*versus*-host disease (e.g. ruxolitinib) have contributed to recent improvements in post-transplant outcome in MF[16-18] while the use of JAK inhibitors before and after ASCT is currently under investigation.[19]

Symptom-directed treatment: conventional non-JAK inhibitor drugs

Unlike the case with ASCT, current drug therapy in MF is directed at improving quality of life through control of splenomegaly, constitutional symptoms, and anemia. Prior to the introduction of JAK inhibitors, the drugs used depended on specific treatment indications. Accordingly, drugs used for the treatment of anemia include androgen preparations, prednisone, immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), or danazol.[6] Lenalidomide works best in the presence of del(5q31)[20] while there is limited benefit from using erythropoiesis-stimulating agents[21,22] or luspatercept.[23,24] Anemia response rates to each one of the aforementioned drugs are less than 25% and responses are temporary, often lasting for less than 2 years. The aforementioned drugs used for combating anemia are often ineffective in controlling splenomegaly, which is typically treated with hydroxyurea.[24] Patients not responding to hydroxyurea or who manifest constitutional symptoms are best served by treatment with JAK inhibitors (discussed below). Treatment options for drug-resistant splenomegaly include splenectomy and involved-field radiotherapy. The latter is most effective for symptomatic non-hepatosplenic extramedullary hematopoiesis or localized bone pain.

Symptom-directed therapy: Food and Drug Administration-approved JAK2 inhibitors

The discovery of *JAK2*^{V617F} in 2005[25] opened Pandora's box for the development of several JAK inhibitors, with the objective of targeting constitutive JAK-STAT activation resulting from gain-of-function mutations involving *JAK2*, *CALR* and *MPL*. Currently available JAK inhibitors are not specific to mutation-induced JAK-STAT activation[26] but their non-specific inhibition of JAK2 produces broad suppression of inflammatory cytokines and myeloproliferation with resultant favorable effects on constitutional symptoms and splenomegaly.[6,27] The demonstration of benefit in quality of life, by way of effective control of splenomegaly and constitutional symptoms, has allowed Food and Drug Administration (FDA) approval of ruxolitinib (2011), fedratinib (2019), and pacritinib (2022).[6] None of these currently FDA-approved JAK inhibitors induces morphological or molecular remissions and their value is mostly palliative.[6,26] Furthermore, ruxolitinib and fedratinib have not been recognized for their impact on transfusion-dependent anemia in MF.[28,29]

The COMFORT clinical trials demonstrated the superiority of ruxolitinib over placebo (42% *vs*. <1%) or best available therapy (BAT; 28.5% *vs*. 13.9%) in reducing spleen size.[30,31] Ruxolitinib treatment was also associated with alleviation of symptoms in approximately half of affected patients. Ruxolitinib-associated side effects, compared to placebo, included anemia (31% *vs*. 13.9%) and thrombocytopenia (34.2% *vs*. 9.3%). Fedratinib has also been compared to placebo, with spleen response rates of 36% *versus* 1% (JAKARTA-1).[29] By contrast, spleen response rates for pacritinib were lower at 19% *versus* 5% (compared to BAT excluding JAK inhibitors; PERSIST-1)[32] and 18% *versus* 3% (compared to BAT including JAK inhibitors; PERSIST-2).[33] The latter study included patients with platelet counts <100x10^9/L. Fedratinib is currently approved for use in patients intolerant of or resistant to ruxolitinib, with a reported response rate of approximately 31% (JAKARTA-2),[34] although this has not been validated in a real-world setting, in which spleen response rates were 0% in patients who were on ruxolitinib ≥20 mg BID dosing prior to the switch to fedratinib.[35] Pacritinib is currently approved for patients with platelet count <50x10^9/L and recent observations suggest additional value in combating anemia through ACRV1 or IRAK1 inhibition.[36]

JAK inhibitors are immunosuppressive and can therefore be associated with serious opportunistic infections[37-39] and poor response to COVID-19 vaccination.[40] Long-term experience with ruxolitinib has also revealed high treatment discontinuation rates and the occurrence of "ruxolitinib withdrawal syndrome" with abrupt treatment discontinuation, characterized by a rapid relapse of symptoms, splenomegaly, worsening of cytopenias and occasional hemodynamic decompensation.[41,42] Treatment-emergent side effects for fedratinib included Wernicke encephalopathy, anemia, thrombocytopenia, gastrointestinal distress and elevations in serum liver function tests and pancreatic enzymes; and for pacritinib included cardiac events, severe diarrhea, nausea, thrombocytopenia, anemia and hemorrhage.

Momelotinib: mechanism(s) of action

Momelotinib is an ATP-competitive small molecule that inhibits JAK1 (half maximal inhibitory concentration [IC$_{50}$]=11 nM), JAK2 (IC$_{50}$=18 nM), JAK3 (IC$_{50}$=155 nM) and TYK2 (IC$_{50}$=17 nM), among other kinases.[43,44] The drug is orally administered in a tablet form and a 200 mg dose was shown to provide plasma exposure similar to that of a 300 mg capsule formulation, in healthy subjects; the effect of food or omeprazole was not considered clinically meaningful.[45] Additional pharmacokinetic and safety studies have suggested that dose adjustment for momelotinib might not be necessary in patients with renal or mild to moderate hepatic impairment but dose reduction was advised for patients with severe hepatic impairment.[46] *In vitro*, momelotinib has been shown to inhibit growth of Ba/F3-*JAK2*^{V617F} and human erythroleukemia (HEL) cells (IC$_{50}$=1,500 nM) and Ba/F3-*MPL*^{W515L} cells (IC$_{50}$=200 nM), but not *BCR-ABL1*-harboring K562 cells (IC$_{50}$=58,000 nM).[43] In addition, cell lines harboring mutated *JAK2* were inhibited more potently than those harboring mutated *JAK3* alleles, and STAT-5 phosphorylation was inhibited in HEL cells with an IC$_{50}$ of 400 nM. Momelotinib selectively suppressed the *in vitro* growth of erythroid colonies harboring *JAK2*^{V617F} from patients with polycythemia vera[43] and induced growth suppression and apoptosis in *JAK2*-dependent hematopoietic cell lines. In a murine model of MPN, momelotinib normalized blood counts and spleen size, and suppressed the levels of inflammatory cytokines.[44] Additional targets for momelotinib include CDK2/cyclin A, MAPK8 (JNK1), PRKCN (PKD3), PRKD1 (PKCμ), ROCK2, TBK1, FLT3-ITD, and ACVR1.[44,47,48]

Momelotinib's inhibition of JAK2 is primarily responsible for its well-established palliative value in patients with MF, which includes reduction of spleen size and alleviation of constitutional symptoms. These effects are realized through inhibition of JAK-STAT-mediated activation of genes that are important for myeloid cell proliferation and survival, as well as suppression of cytokine-mediated inflammatory and constitutional symptoms (Figure 1). In addition, unlike the case with ruxolitinib and fedratinib, momelotinib and pacritinib also inhibit ACVR1, which is particularly appealing in the context of MF-associated anemia.[36,48]

ACVR1 (Activin A Receptor type 1 gene) is located on chromosome 2q24.1 and encodes ACVR1, which is a transmembrane serine/threonine kinase belonging to the

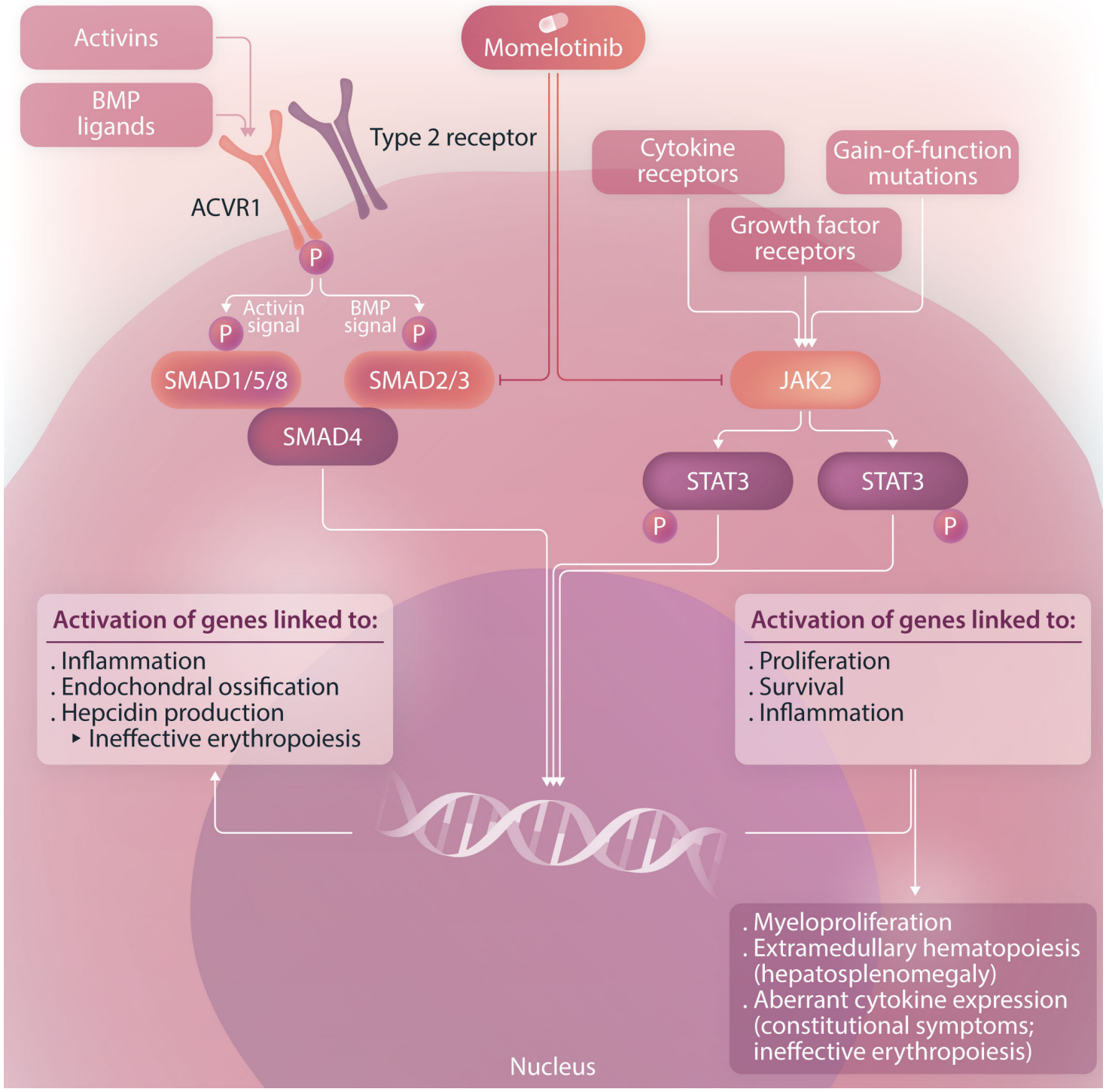

Figure 1. Mechanism of action of momelotinib.

transforming growth factor-beta (TGF-β) receptor superfamily and is also known as Activin Receptor-Like Kinase 2 (ALK2).[49] Signaling through ACVR1 is complex and involves other type 1 and type 2 receptors that engage various ligands, including activins and bone morphogenetic proteins (BMP) (Figure 1).[50,51] These ligands are involved in multiple physiological and disease processes through distinct Smad (similar to the gene products of Drosophila mothers against decapentaplegic' and the *C. elegans* gene Sma) pathways; activins signal via Smad2/3 and BMP Smad1/5/8. Germline mutation of *ACVR1* causes a rare heterotropic ossification disease, fibrodysplasia ossificans progressiva,[52] and *ACVR1* has also been implicated as a cancer-driver gene in childhood brainstem glioma (diffuse intrinsic pontine glioma). ACVR1 interacts with type II receptors to form heterotetrameric receptor complexes (two type I and two type II) that can bind various ligands, including activins and BMP (Figure 1). Ligand-receptor engagement leads to canonical SMAD and non-canonical non-SMAD signaling, resulting in nuclear translocation and regulation of transcription.[49] SMAD2/3 signaling has also been implicated in ineffective erythropoiesis and inhibition of terminal erythroid differentiation.[53] The latter has led to the development of luspatercept, a recombinant activin receptor type IIB fusion protein that was designed to trap TGF-β superfamily ligands (including activin), for the treatment of anemia associated with transfusion-requiring β-thalassemia and low/intermediate-risk MDS-RS without thrombocytosis or with thrombocytosis (MDS-RS-T).[23,54,55] Luspatercept is currently being investigated in a phase III study in transfusion-dependent patients with MF on JAK inhibitor therapy (ClinicalTrials.gov Identifier: NCT04717414). In a rat model of anemia of chronic disease, momelotinib treatment normalized hemoglobin concentration and red blood cell count, believed to have resulted from direct inhibition of ACVR1, and associated reduction of hepcidin

production.[48] Such activity was not apparent for another JAK1/2 inhibitor, ruxolitinib, and did not appear to be mediated by inhibition of JAK2-mediated ferroportin degradation.[48] Momelotinib-induced inhibition of ACVR1 might therefore downregulate hepcidin expression and result in increased mobilization of cellular iron stores.[48] Consistent with this supposition, clinical documentation of an improvement in anemia in a phase II study of MF patients treated with momelotinib was associated with reduction in blood hepcidin levels and increased markers of iron availability and erythropoiesis.[56] The downregulation of hepcidin by momelotinib is particularly relevant in MF in which previous studies have shown increased circulating levels of hepcidin and inflammatory cytokines in patients with primary MF, compared to healthy controls;[57,58] increased hepcidin levels in the particular study correlated with anemia, red cell transfusion need, and serum ferritin of >500 μg/L.[57] In the same study, hepcidin and inflammatory cytokines were independently associated with inferior survival.[57,58] In another recently published report of MF patients receiving momelotinib therapy, anemia response correlated with lower serum ferritin level[59] whereas an earlier study had revealed increased plasma hepcidin levels in MF and their correlation with the degree of anemia and serum ferritin level.[57]

Taking these observations together, it is reasonable to consider that changes in hepcidin production, via ACVR1 inhibition, contribute to the salutary effect of momelotinib on anemia.[48,56,60] However, it should be noted that active erythropoiesis, *per se*, might result in downregulation of hepcidin via erythroferrone and clarification of the precise mechanism of momelotinib-induced improvement in MF-associated anemia requires additional studies.[61] Whether or not reported differences in transcriptional, proteomic, and phenotypic biomarker profiles, including disparately modulated inflammatory cytokine production and immune function, between momelotinib and other JAK inhibitors explain differences in their impact on response patterns and toxicity profile remains to be clarified.[62,63]

Momelotinib: published clinical reports

Table 1 presents summaries of published clinical reports on momelotinib therapy in MF and includes the original Mayo Clinic-centered early phase and subsequent phase II and phase III studies.

The original Mayo Clinic-centered phase I/II clinical trial

The findings of the first-in-human, phase I/II study of momelotinib in MF (n=166; NCT00935987) were serially published in 2013[64] and 2018.[65] Drug doses ranged between 100 and 400 mg once daily while the dose confirmation phase utilized 150 or 300 mg once daily (Table 1). The study population included 143 JAK inhibitor-naïve cases. In the particular study, momelotinib therapy produced responses in anemia (54%), resolution of red cell transfusion need (68%), and clinically assessed reduction in spleen size (40%). Although not uniformly assessed, improvement in constitutional symptoms was clinically documented in the majority of the study patients. Adverse events included grade 3/4 thrombocytopenia (34%) and neutropenia (8%), grade 1/2 diarrhea (48%), nausea (39%), vomiting (24%), dizziness (40%), peripheral neuropathy (30%), and first-dose effects of flushing, hypotension, dizziness and nausea (11%); in addition, increases in liver function tests and pancreatic enzymes were documented in 15-18% and 11-13% of cases, respectively. In 2015, we reported additional observations from the original phase I/II study including treatment-emergent peripheral neuropathy in 44% of the 100 consecutive patients treated at the Mayo Clinic.[66] Assessment of response in the first 60 patients on the original phase I/II study (NCT00935987), according to the 2013 revised International Working Group criteria included 0% complete remission, 2% partial remission, 57% clinical improvement, 45% anemia response (median response duration 13 months), 53% resolution of transfusion need (median response duration 12 months), and 42% spleen response (median response duration 10 months). In 2015, we published the initial analysis of genetic predictors of response and showed a correlation between spleen response and presence of *CALR* and absence of *ASXL1* mutation; a smaller spleen size and absence of constitutional symptoms were also predictive of spleen response in univariate but not multivariable analysis.[67]

Subsequent publications of the above-described phase I/II momelotinib clinical trial (NCT00935987) provided more mature data in terms of overall and leukemia-free survival and predictors of treatment response.[59,68,69] In 2018, we published the 7-year follow-up of the NCT00935987 study regarding the 100 Mayo Clinic participants, comprising 79 JAK inhibitor-naïve patients and 21 patients previously exposed to ruxolitinib.[69] At the time, protocol therapy was discontinued in 91% of the patients, after a median treatment duration of 1.4 years. In multivariable analysis, absence of *CALR* type 1/like and presence of *ASXL1* or *SRSF2* mutations adversely affected survival while *SRSF2* mutations, very high-risk karyotype, and circulating blasts ≥2% predicted leukemic transformation. Post-momelotinib treatment survival (median 3.2 years) was not significantly different from that of a risk-matched MF cohort not receiving momelotinib.[69]

More recently, we reported the 12-year survival data on the 79 JAK inhibitor-naïve patients from the aforementioned NCT00935987 phase I/II study and compared the results with 50 patients treated with ruxolitinib in a separate clinical trial (NCT00509899).[68] The median follow-up for living patients was 11.7 years for momelotinib and 14.2 years for ruxolitinib. Median survival periods from the initiation of

treatment with the study drug were 3.5 years (10-year survival 20%) for momelotinib and 4.0 years (10-year survival 23%) for ruxolitinib (*P*=0.32). 'Drug survival' (i.e., treatment discontinuation-free survival) was superior for momelotinib, compared to ruxolitinib, with 3-year drug discontinuation rates of 68% *versus* 88% (*P*<0.01). ASCT after failure of JAK inhibitor treatment had a favorable survival impact with a 10-year survival estimate of 68% *versus* 15% for non-transplanted patients (*P*<0.01).[68] A separate publication regarding 183 Mayo Clinic patients with high/intermediate-risk MF en-

Table 1. Clinical trials with momelotinib for the treatment of myelofibrosis.

Trial	Treatment arms dose & schedule	Spleen response	Anemia response (IWG-MRT)	Symptom response	Adverse effects
Phase I/II NCT00935987 Pardanani *et al.* Leukemia (2013)	Dose escalation 100-400 mg/day N=60 (JAKi-naïve and JAKi-exposed) N=49, JAKi-naïve	48% by palpation	Resolution of transfusion need 70%	3-month resolution Pruritus 75% Night sweats 79% Bone pain 63% Fever 100% Anorexia 40%	Grade 3/4 Thrombocytopenia (32%) ↑ AST (3%) ↑ ALT (3%) ↑ Lipase (5%) Headache (3%)
Phase I/II NCT00935987 Pardanani *et al.* Leukemia (2018)	Dose escalation 100-400 mg/day Dose confirmation 150 mg QD, 300 mg QD 150 mg bid N=166 (JAKi-naïve and JAKi-exposed)	40% by palpation	Week 12 Resolution of transfusion need 68%	Not uniformly assessed	Grade 3/4 Thrombocytopenia (33.7%) Anemia (40.4%) Neutropenia (7.8%) Grade 1/2 Peripheral neuropathy (30.1%)
Phase I/II NCT01423058 Gupta *et al.* Haematologica (2017)	Momelotinib 200 mg bid (N=54) Momelotinib 250 mg bid (N=7) (JAKi-naïve and JAKi-exposed) N=53, JAKi-naïve	Week 24 Spleen volume reduction ≥35% 45.8% 72% by palpation	Resolution of transfusion need 51.7%	Total symptom score reduction ≥ 50% 30.8%	All grades Diarrhea (45.9%) Peripheral neuropathy (44.3%) Thrombocytopenia (39.3%) Dizziness (36.1%) Hypotension (24.6%)
Phase II NCT02515630 Oh *et al.* Blood Adv (2020)	Momelotinib 200 mg QD N=41 Transfusion-dependent (JAKi-naïve and JAKi-exposed) N=36, JAKi-naïve	Week 24 Spleen volume reduction ≥35% 19%	Week 24/anytime Resolution of transfusion need 34%/41%	Total symptom score reduction ≥ 50% 29%	Grade 3/4 Anemia (12%) Neutropenia (12%)
Phase III NCT01969838 SIMPLIFY-1 Mesa *et al.* JCO (2017)	Momelotinib 200 mg QD *vs.* Ruxolitinib 20 mg bid N=432 (JAKi-naïve)	Week 24 Spleen volume reduction ≥35% 26.5% *vs.* 29% (*P*=0.01)	Week 24 Resolution of transfusion need 66.5% *vs.* 49.3% (*P*<0.001)	Total symptom score reduction ≥ 50% 28.4% *vs.* 42.2% (*P*=0.98)a	Grade 3/4 (Momelotinib arm) Thrombocytopenia (7%) Anemia (5.6%) Diarrhea (2.8%) Hypertension (2.8%) Neutropenia (2.8%)
Phase III NCT02101268 SIMPLIFY-2 Harrison *et al.* Lancet Haematol (2017)	Momelotinib 200 mg QD *vs.* Best available therapy including ruxolitinib N=156 (JAKi-exposed)	Week 24 Spleen volume reduction ≥35% 7% *vs.* 6% (*P*=0.90)	Week 24 Resolution of transfusion need 43% *vs.* 21% (*P*=0.0012)	Total symptom score reduction ≥ 50% 26% *vs.* 6% (*P*=0.0006)	Grade 3/4 (Momelotinib arm) Anemia (14%) Thrombocytopenia (7%)
Phase III NCT04173494 MOMENTUM Mesa *et al.* JCO (2022)	Momelotinib 200 mg QD N=130 *vs.* Danazol 600 mg QD N=65 (JAKi-exposed)	Week 24 Spleen volume reduction ≥35% 23.1% *vs.* 3.1% (*P*=0.0006)	Week 24 Resolution of transfusion need 30.8% *vs.* 20% (*P*=0.0064)	Week 24 Total symptom score reduction ≥ 50% 24.6% *vs.* 9.2% (*P*=0.0095)	Grade 3/4 (Momelotinib arm) Thrombocytopenia (22%) Infections (15%) Anemia (8%)

JAKi: JAK inhibitor.

rolled in consecutive phase I/II JAK inhibitor clinical trials included the aforementioned group of 79 momelotinib- and 50-ruxolitinib treated patients, as well as 23 cases treated with fedratinib and 31 treated with BMS-911543.[70] The 10-year survival rate for all 183 JAK inhibitor-treated patients was 16% and was not significantly different across the four drug cohorts (P=0.33). Multivariable analysis of pre-treatment variables identified age >65 years, absence of type 1/like *CALR* mutation, baseline transfusion need, and presence of *ASXL1/SRSF2* mutation as risk factors for survival. In addition, spleen and anemia responses were independently associated with improved short-term survival while long-term survival was secured only by ASCT (10-year survival rate 45% *vs*. 19% in non-transplanted patients; P<0.01).[70]

In our most recent updated analysis of 72 Mayo Clinic patients who were JAK inhibitor-naïve and anemic (i.e., hemoglobin level below sex-adjusted normal range) prior to treatment with momelotinib,[59] 44% experienced an anemia response at any time during treatment (median response duration ~20 months; range, 3-81). In the particular study, spleen and symptom responses were documented in 45% and 44% of evaluable patients, respectively. In multivariable analysis, predictors of anemia response included post-essential thrombocytopenia MF (83% *vs*. 37%), serum ferritin level <55 μg/L (89% *vs*. 38%), and time from diagnosis to initiation of momelotinib therapy of <23 months (65% *vs*. 26%). Among 28 patients who were transfusion-dependent at baseline, resolution of transfusion need was documented in 13 (46%) patients and the response lasted for a median of 20.3 months (range, 4-61.3); independent predictors of response in this group of patients included intermediate- *versus* high-risk disease (100% *vs*. 0%), serum ferritin level <833 μg/L (80% *vs*. 28%), and post-essential thrombocytopenia *versus* primary/post-polycythemia vera MF (80% *vs*. 39%).[59] Among all 72 study patients, treatment was discontinued in 93% after a median treatment duration of 20 months. The median post-momelotinib survival was 3.2 years with 5- and 10-year survival rates of 31% and 19%, respectively. In multivariable analysis, survival was positively affected by anemia response (median 3.8 *vs*. 2.8 years), presence of type 1/like *CALR* mutation (median 11 *vs*. 3 years), and absence of *ASXL1* or *SRSF2* mutation (median 3.7 *vs*. 2.9 years). The favorable impact of anemia response on survival was also confirmed in transfusion-dependent patients (median 3.7 *vs*. 1.9 years: 10-year survival 8% *vs*. 0%).

Taken together, the above-elaborated series of analyses from the original NCT00935987 phase I/II study of patients treated with momelotinib suggested therapeutic value in terms of all three quality of life offenders in MF: anemia, splenomegaly, and constitutional symptoms. In addition to thrombocytopenia and peripheral neuropathy, adverse events included gastrointestinal disturbances and liver and pancreas function test abnormalities. Analyses of mature data suggested short-term survival benefit associated with favorable genetic profile and anemia response, but long-term survival remained dismal without intervention with ASCT.

Subsequent phase I/II clinical trials

Several other phase I/II studies of momelotinib in both MF[56,71] and essential thrombocytopenia and polycythemia vera[72] were subsequently published. The most notable in this regard (NCT02515630) included 41 transfusion-dependent patients with MF among whom momelotinib-induced resolution of transfusion need was documented in 17 patients (41%).[56] In the particular study, 21 (50%) patients experienced grade 3 or higher adverse events, similar in spectrum to those seen in the above-discussed phase I/II study. Laboratory correlative studies demonstrated a momelotinib treatment-associated decrease in circulating hepcidin levels and increased markers of iron availability and effective erythropoiesis. Predictors of anemia response included lower hepcidin level.[56] Another phase I/II study included 61 patients with MF who received momelotinib at a dose of 200 mg twice daily;[71] based on conventional response criteria, anemia response was documented in 45%, spleen response in 72% by palpation and 46% by imaging, and symptom response in the majority of patients. Adverse events in the particular study included diarrhea (45.9%), peripheral neuropathy (44.3%), thrombocytopenia (39.3%), and first-dose associated dizziness (36.1%). Laboratory correlative studies showed drug-induced suppression of inflammatory cytokines.[71] Momelotinib was also evaluated at daily doses of 100 mg and 200 mg in 28 patients with polycythemia vera and 11 with essential thrombocytopenia; only two patients among all 39 cases showed a response, as per study response criteria; adverse events included peripheral neuropathy in seven (18%) patients.[72] Taken together, the phase I/II studies after NCT00935987 confirmed the observations from the initial NCT00935987 study and, in addition, provided a mechanistic explanation for the erythropoietic effect of momelotinib in MF.[56]

Phase III studies

The aforementioned observations from phase I/II studies were subsequently confirmed in three phase III studies, which ultimately led to acceptance of a New Drug Application (NDA) for momelotinib. In SIMPLIFY-1 (NCT01969838), 432 JAK inhibitor-naïve patients with high/intermediate-risk MF were assigned to receive either momelotinib (200 mg once daily; n=215) or ruxolitinib (20 mg twice daily; n=217).[73] At week 24, spleen volume reduction of ≥35% was achieved at a similar rate (26.5% and 29%, respectively) while symptom reduction score was higher in the ruxolitinib arm (42.2% *vs*. 28.4%). Transfusion independence at week 24 was documented in 66.5% and

49.3% of patients treated with momelotinib and ruxolitinib, respectively. Furthermore, achievement of transfusion-independence in patients receiving momelotinib was associated with a higher 3-year survival rate of 77.2% *vs*. 51.6%. Treatment-emergent myelosuppression was similar in the two treatment arms, with the exception of more anemia in the ruxolitinib arm and first-dose effects in the momelotinib arm. Peripheral neuropathy was reported in 10% and 5% of patients receiving momelotinib or ruxolitinib, respectively.

In SIMPLIFY-2 (NCT02101268), 156 MF patients with either suboptimal response to or intolerance of ruxolitinib were randomly assigned to receive momelotinib 200 mg once daily (n=104) or BAT (which included ruxolitinib in 89% of the cases; n=52). Spleen volume response of ≥35% was reported in 7% of the momelotinib group and 6% of the BAT group. As was the case in SIMPLIFY-1, the rate of transfusion-independence at week 24 was higher in the momelotinib group than in the BAT group (49.3% *vs*. 21%).[74] Peripheral neuropathy occurred in 11% of momelotinib-treated patients. In a recent updated analysis of the SIMPLIFY trials, 2-year overall and leukemia-free survival data for JAK inhibitor-naïve patients enrolled in SIMPLIFY-1 were similar in patients initially treated with momelotinib (81.6% and 80.7%, respectively) and those initially treated with ruxolitinib (80.6% and 79.3%, respectively). Results were similar in the context of previously ruxolitinib-exposed patients in SIMPLIFY-2 assigned to momelotinib or BAT. Baseline transfusion need in both SIMPLIFY trials was associated with inferior survival while momelotinib-induced transfusion-independence in SIMPLIFY-1 was associated with superior survival.[75]

The most recent phase III study included 195 JAK inhibitor-exposed patients with high/intermediate-risk MF with a hemoglobin <10 g/dL, a symptom score of ≥10, and a platelet count ≥25x10^9/L, assigned to either momelotinib (200 mg daily; n=130) or danazol (600 mg daily; n=65), both in conjunction with placebo pills, for 24 weeks, after which patients could receive open-label momelotinib.[76] Transfusion-independence rates at baseline and at week 24 were 13% *versus* 31% for momelotinib and 15% *versus* 20% for danazol (P<0.05; met criteria for non-inferiority); rates of no transfusions to week 24 were 35% for momelotinib and 17% for danazol (met criteria for superiority). At week 24, spleen volume reduction of ≥35% occurred in 23% of patients treated with momelotinib *versus* 3% treated with danazol (met criterion for superiority); the corresponding symptom score response rates were 24.6% and 9.2% (met criteria for superiority). Grade ≥3 hematologic and non-hematologic side effects were similar in the momelotinib and danazol treatment groups.[76] The follow-up period for the MOMENTUM study remains relatively short (approximately 9 months) and the crossover design of the study confounds estimation of comparative survival; regardless, it is unlikely that momelotinib-treated patients in the MOMENTUM trial would behave differently from their counterparts in earlier phase II/III trials, in terms of survival or duration of treatment response.

Momelotinib: therapeutic prospects beyond myelofibrosis

The somewhat unexpected discovery of ACVR1-SMAD pathway inhibition by momelotinib opens up new therapeutic avenues for the drug in other myeloid neoplasms and non-hematologic conditions associated with ineffective or iron-restricted erythropoiesis.[61] The BMP-ACVR1-SMAD pathway is central to regulation of hepcidin transcription and also contributes to ineffective erythropoiesis driven by other pathogenic mechanisms.[61,77] Inflammatory cytokines, such as interleukin-6, are markedly increased in MF and likely contribute to increased circulating levels of hepcidin.[58,61] Similar mechanisms of hepcidin upregulation are considered in other myeloid neoplasms and non-hematologic conditions associated with iron-restricted erythropoiesis, including anemia of inflammation.[61]

In addition to MF, myeloid neoplasms associated with anemia include MDS with (MDS-RS) or without ring sideroblasts and with (MDS-*SF3B1*) or without *SF3B1* mutation.[78,79] The underlying mechanisms for anemia associated with MDS are complex but likely include ineffective erythropoiesis and aberrant SMAD signaling, which is now considered a legitimate target for the development of drugs, such as luspatercept (TGF-β ligand trap).[54,55,80] Luspatercept is a recombinant activin receptor type IIB fusion protein that was designed to trap TGF-β superfamily ligands (including activin) and thus inhibit SMAD2/3 signaling, which is believed to inhibit terminal erythroid differentiation.[53] Luspatercept is currently approved for use in adult patients with transfusion-requiring β-thalassemia and low/intermediate-risk MDS-RS and MDS/MPN-RS-T, based on controlled evidence of efficacy in alleviating anemia.[23,54,55] Galunisertib (an ALK5 inhibitor) is another drug that targets SMAD signaling and has shown modest activity in ameliorating transfusion-dependent anemia in patients with low/intermediate-risk MDS.[81] These observations suggest a similar activity as that of momelotinib in these myeloid neoplasms, especially in MDS-RS/MDS-*SF3B1* in which a subset of patients display *JAK2* mutations and thrombocytosis (MDS-RS-T). However, it is unlikely that the drug will be able to overcome other underlying contributors to disease-associated anemia, including intrinsic clonal defects, which explains the incomplete and non-durable anemia responses seen so far with momelotinib and luspatercept. We are also aware of emerging information on the drug's potential as a FLT3-ITD inhibitor[47] and ongoing clinical trials in solid tumors (clinicaltrials.gov).

Table 2. Comparison of Food and Drug Administration-approved JAK2 inhibitors with momelotinib for treatment of myelofibrosis.

	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Mechanism of action	JAK1/JAK2 inhibition	JAK2/FLT3/RET inhibition	JAK2/FLT3/ACVR1 IRAK1/CSF1R inhibition	JAK1/JAK2/ACVR1 inhibition
FDA-approved indication	IPSS High/intermediate risk	IPSS High/intermediate-2 risk First-line and second-line	DIPSS High/intermediate risk First-line and second-line for platelet count <50x10^9/L	Approval pending *MOMENTUM trial* *DIPSS High/Intermediate risk* *Anemia* *Palpable spleen ≥5 cm* *Symptoms*
FDA-approved dose & schedule	20 mg twice daily (platelet count >200 x10^9/L) 15 mg twice daily (platelet count 150-200 x10^9/L)	400 mg twice daily (platelet count ≥50 x10^9/L)	200 mg twice daily (Platelet count <50x10^9/L)	Approval pending *MOMENTUM trial* *200 mg daily*
Spleen response*	COMFORT-1 (41.9%) COMFORT-2 (28%)	JAKARTA-1 (36%) JAKARTA-2 (55%)	PERSIST-1 (19%) PERSIST-2 (18%)	SIMPLIFY-1 (26.5%) SIMPLIFY-2 (7%) MOMENTUM (23.1%)
Anemia response#	Not well defined	Not well defined	Resolution of transfusion need PERSIST-1 (25%) PERSIST-2 (37%/24%)$^{\mu}$	Resolution of transfusion need SIMPLIFY-1 (66.5%) SIMPLIFY-2 (43%) MOMENTUM (30.8%)
Symptom response†	COMFORT-1 (45.9%)	JAKARTA-1 (36%) JAKARTA-2 (26%)	PERSIST-1 (19%) PERSIST-2 (25%)	SIMPLIFY-1 (28.4%) SIMPLIFY-2 (26%) MOMENTUM (24.6%)
Adverse effects	Thrombocytopenia Anemia Bruising Dizziness Headache Withdrawal syndrome Opportunistic infections Poor response to COVID-19 vaccines	Anemia Thrombocytopenia GI symptoms ↑ Liver function tests ↑ Amylase/lipase Wernicke encephalopathy (boxed warning)	Diarrhea Thrombocytopenia GI symptoms Anemia Peripheral edema Pneumonia Cardiac failure Pyrexia Squamous cell skin cancer	Thrombocytopenia Neutropenia Anemia Infections ↑ Liver function tests ↑ Amylase/lipase Peripheral neuropathy First-dose effect$^{€}$
Monthly average wholesale price	$19,440	$27,520	$25,715	Approval pending

COMFORT-1: ruxolitinib *vs*. placebo; COMFORT-2: ruxolitinib *vs*. best available therapy; JAKARTA-1: fedratinib *vs*. placebo; JAKARTA-2: fedratinib in patients previously treated with ruxolitinib; PERSIST-1: pacritinib *vs*. best available therapy excluding JAK inhibitors; PERSIST-2: pacritinib *vs*. best available therapy including ruxolitinib in patients with platelet count <100x10^9/L; SIMPLIFY-1: momelotinib *vs*. ruxolitinib; SIMPLIFY-2: momelotinib *vs*. best available therapy including ruxolitinib; MOMENTUM: momelotinib *vs*. danazol. *Spleen response: spleen volume reduction ≥35% at week 24. #Anemia response: Gale criteria: absence of red blood cell transfusions for 12 weeks in the PERSIST-1 trial; IWG-MRT criteria: absence of red blood cell transfusions and hemoglobin ≥8 g/dL in the prior 12 weeks at week 24 in SIMPLIFY-1/2 and MOMENTUM trials; Gale criteria/IWG criteria in the PERSIST-2 trial. †Symptom response: total symptom score reduction ≥50% at week 24. €Hypotension, flushing, dizziness, nausea. FDA: Food and Drug Administration; IPSS: International Prognostic Scoring System; DIPSS: Dynamic International Prognostic Scoring System; COVID-19: coronavirus disease 2019; GI: gastrointestinal; IWG-MRT: International Working Group for Myelofibrosis Research and Treatment.

Momelotinib-inclusive treatment algorithm and concluding remarks

ASCT currently remains the only treatment option in MF that can secure long-term survival. The number of allogeneic transplants in MF has increased in recent years and it is encouraging to witness, over time, a higher number of patients who are older and less fit but are transplanted, increased utilization of matched unrelated donors, improvements in overall and relapse-free survival, decreased incidence of graft-*versus*-host disease and stable incidence of non-relapse mortality.[12] In transplant-ineligible patients, optimal palliative care requires attention to all three quality-of-life offenders: anemia, splenomegaly, and constitutional symptoms.[6] In this regard, because of its salutary effect on anemia, as well as splenomegaly and constitutional symptoms, momelotinib might have an edge over currently FDA-approved JAK inhibitors. However, scientifically sound comparisons between different JAK inhibitors can only be accomplished through prospective controlled studies and should also consider other factors, including side effects (Table 2). Emerging information suggests similar erythropoietic benefit from pacritinib but it is not certain whether its activity against splenomegaly and constitutional symptoms would be as potent as that of momelotinib.[36]

Currently available JAK inhibitors, including momelotinib, are inherently immunosuppressive and carry multiple side

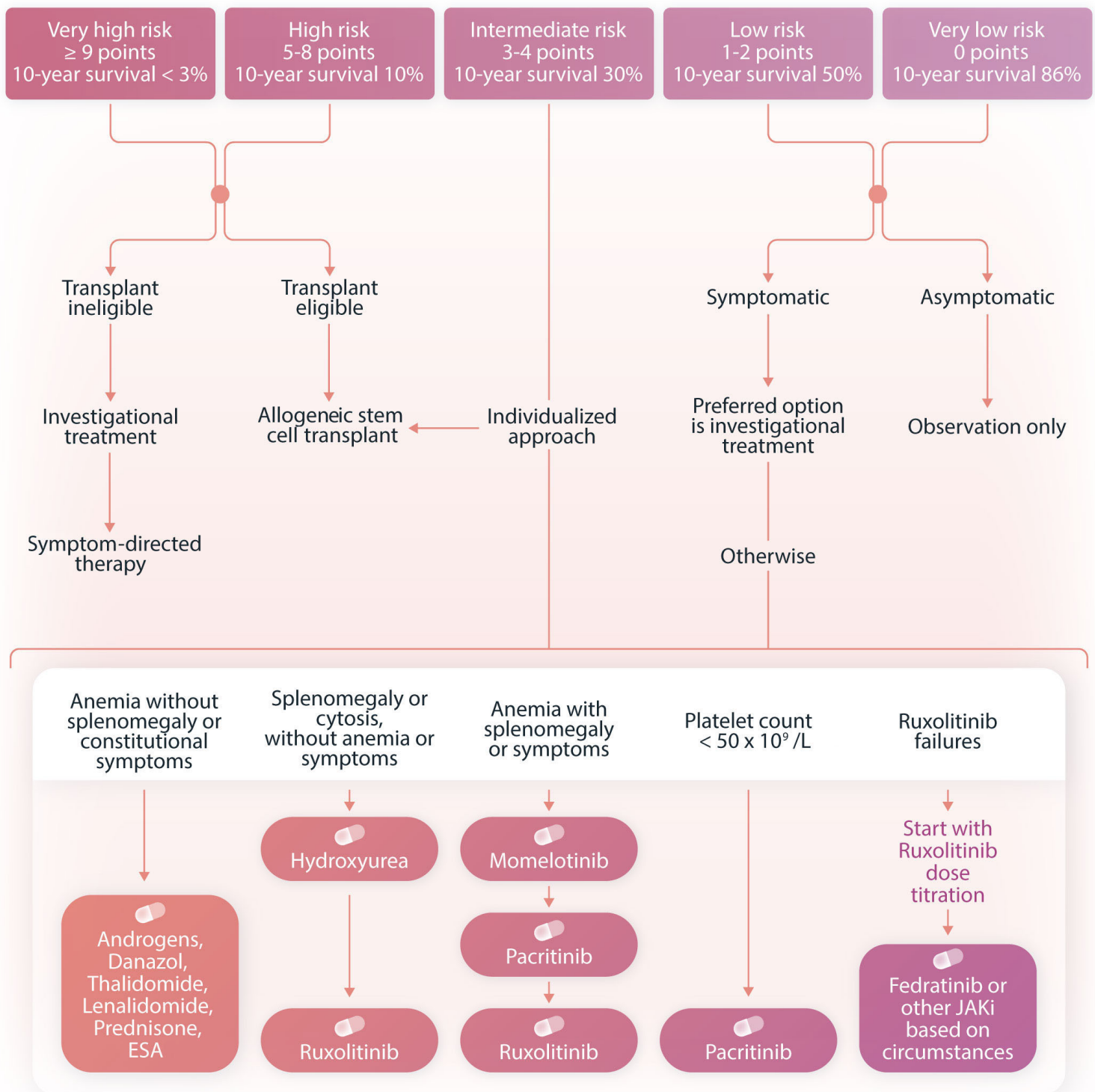

Figure 2. Our current risk-adapted treatment approach in primary myelofibrosis based on impending approval of momelotinib. Risk stratification is based on the Mutation-enhanced International Prognostic Scoring System, version 2.0. (MIPSS*v2*): very high risk karyotype = 4 points; unfavorable karyotype = 3 points; ≥2 high molecular risk mutations = 3 points; one high molecular risk mutation = 2 points; absence of a type 1 *CALR* mutation = 2 points; constitutional symptoms = 2 points; severe anemia = 2 points; moderate anemia = 1 point; ≥2% circulating blasts = 1 point. ESA: erythropoiesis-stimulating agents; JAKi: JAK inhibitors.

effects that necessitate due diligence in their use (Table 2). Current indications for JAK inhibitor therapy in MF include hydroxyurea-refractory splenomegaly and severe constitutional symptoms. The availability of momelotinib in the near future might expand the list of indications to include anemia. However, in the absence of symptomatic splenomegaly or constitutional symptoms, we prefer initial therapy with non-JAK inhibitor drugs (Figure 2). Similarly, we prefer initial treatment with hydroxyurea, for the treatment of splenomegaly, leukocytosis, or extreme thrombocytosis, in the absence of associated anemia or severe constitutional symptoms (Figure 2); such an approach considers the superior activity of hydroxyurea, compared to JAK inhibitors, in terms of controlling leukocytosis and thrombocytosis as well as the fact that the spleen effect of ruxolitinib or other JAK inhibitors is often not durable and the value of these inhibitors might be best reserved for those patients in whom treatment with hydroxyurea fails. Our second-line drug of choice in the latter instance is ruxolitinib, considering its comparatively better toxicity profile, compared to that of other JAK inhibitors (Table 2).

The projected approval of momelotinib might result in modification of the current treatment algorithm in MF, including the possibility of its use as the first-line JAK inhibitor of choice in the presence of anemia (Figure 2). We prefer pacritinib as the first-line JAK inhibitor of choice in the presence of a platelet count <$50x10^9$/L. The more favorable toxicity profile of ruxolitinib, compared to that of all other JAK inhibitors, argues for its use as the first-line JAK inhibitor of choice, in the absence of anemia. In cases in which ruxolitinib fails, we prefer ruxolitinib dose modification first before switching treatment to other JAK inhibitors (Figure 2). Real-world experience suggests limited value of switching from ruxolitinib to fedratinib in MF patients already receiving adequate doses of ruxolitinib (≥20 mg twice daily).[35,82]

There is currently no evidence to support the value of JAK inhibitors in asymptomatic patients with MIPSS*v2* low or very low risk disease, whose expected 10-year survival rates were reported to be 50% and 86%, respectively.[10] Furthermore, the risk-benefit balance for ASCT in such patients favors deferring the procedure until there is evidence of progressive disease.[83] On the other hand, ASCT is the preferred treatment of choice for patients with MIPSS*v2* high or very high risk disease, in whom 10-year expected survival rates, without transplantation, might be as low as 10% and <3%, respectively (Figure 2).[10] ASCT might also be considered for carefully selected MIPSS*v2* intermediate-risk patients in whom 10-year projected survival without a transplant is estimated to be 30%.[10] In general, investigational therapy is preferred for transplant-ineligible patients with high/very high-risk or symptomatic lower-risk disease (Figure 2).

The possibility of further enhancing benefit from momelotinib by changing the dose schedule (i.e., 100 mg twice daily), without increasing the total daily dose (i.e., 200 mg), warrants exploration, based on recently published data on jaktinib, a deuterated form of momelotinib,[84] where a phase II multicenter study (NCT03886415) revealed higher rates of spleen and anemia response using the drug at a dose of 100 mg twice daily rather than 200 mg once daily.[85] However, it should be noted that the twice-daily dosing schedule in the latter study (NCT03886415) was associated with a higher frequency of serious adverse events.[85] Finally, we underscore that our proposed treatment algorithm outlined in Figure 2 assumes approval of momelotinib in the current calendar year and reflects our current preferences and practice, which are subject to change based on emerging new information.

Disclosures

The authors participated in the original phase I/II study of momelotinib, ruxolitinib, and fedratinib for myelofibrosis. They have no other conflicts of interest to disclose.

Contributions

AT wrote the paper. All authors participated in the concept and design of the study and approved the final manuscript.

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