Published in final edited form as:

Postgrad Med. 2013 January ; 125(1): 128–135. doi:10.3810/pgm.2013.01.2628.

Ruxolitinib: An Oral Janus Kinase 1 and Janus Kinase 2 Inhibitor in the Management of Myelofibrosis

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Abstract

Myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET) are referred to as the classic Philadelphia chromosome (*BCR-ABL1*)-negative myeloproliferative neoplasms. Although each has distinct pathologic features, all 3 display alterations in Janus kinase (JAK) signal transduction activator of transcription signaling. Myelofibrosis is the most serious of the 3, associated with shortened survival (median survival, 5–7 years); bone marrow failure with anemia; progressive splenomegaly; and chronic, burdensome symptoms, including fatigue, night sweats, itching, abdominal discomfort, loss of appetite/early satiety, unintentional weight loss, and bone, chest, and abdominal pain. Treatments for MF have been mainly palliative, with the exception of allogeneic stem cell transplantation, which, although potentially curative, is feasible only in a small subpopulation of patients. In November 2011, ruxolitinib, an inhibitor of JAK1 and JAK2, was approved by the US Food and Drug Administration for the treatment of intermediate- or high-risk MF, including primary MF, post-PV MF, and post-ET MF. In clinical trials, ruxolitinib was shown to reduce spleen volume and improve MF-related symptoms and quality-of-life measures. Evidence also suggests that ruxolitinib therapy has a survival advantage over placebo and best available therapy. Thrombocytopenia and anemia were the most common adverse events with treatment. Ongoing trials are assessing the efficacy and safety of ruxolitinib therapy in patients with PV and ET.

Keywords

Janus kinase; myeloproliferative neoplasms; ruxolitinib; splenomegaly; JAK2 mutation

Introduction

Myeloproliferative neoplasms (MPNs) are a group of bone marrow disorders characterized by molecular abnormalities that result in increased proliferation of myeloid cells.¹ In its 2008 revision of the classification of myeloid neoplasms and acute leukemia, the World Health Organization included the following 8 disorders in the category of MPNs: chronic myelogenous leukemia (CML; classic Philadelphia chromosome [*BCR-ABL1*]-positive);

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Conflict of Interest Statement

Srdan Verstovsek, MD, PhD, is a researcher on clinical studies supported by Incyte Corporation.

chronic neutrophilic leukemia; polycythemia vera (PV); primary myelofibrosis (PMF); essential thrombocythemia (ET); chronic eosinophilic leukemia, not otherwise specified; mastocytosis; and MPNs, unclassifiable.² This article focuses on the *BCR-ABL1*-negative MPNs, including PV, ET, and myelofibrosis (MF).^{1,3}

Polycythemia vera and ET have a minimal impact on survival, with most patients achieving a near-normal life expectancy.¹ Thromboses (either arterial or venous) are common and constitute the main cause of morbidity and mortality in both patients with PV and ET.⁴ In contrast, MF, which is considered the most serious of the 3 *BCR-ABL1*-negative MPNs, has a median survival of only 5 to 7 years because of multiple disease complications.⁵ Myelofibrosis is characterized by extramedullary hematopoiesis (thought to be responsible for progressive splenomegaly and hepatomegaly), poor quality of life (QoL), body wasting, and progressive cytopenias.⁶ Patients often develop a constellation of chronic, burdensome symptoms: fatigue, night sweats, itching, bone pain, abdominal discomfort, loss of appetite/early satiety, unintentional weight loss, and chest and abdominal pain.⁶ Myelofibrosis can occur as a primary disease (PMF) or develop secondary to PV (post-PV MF) and ET (post-ET MF). As reviewed in Table 1, risk stratification in MF (corresponding with life expectancy), according to the International Prognostic Scoring System, encompasses the categories of low, intermediate-1, intermediate-2, and high risk on the basis of the number of prognostic factors, including the following 5 factors: age > 65 years, presence of constitutional symptoms, hemoglobin level < 10 g/dL, leukocyte count > $25 \times 10^9/L$, and circulating blast cell count $\geq 1\%$.⁵

Treatment strategies for PV and ET focus largely on the control of blood cell counts and the prevention of thrombotic events, which are the most common complications. Treatments primarily include administration of hydroxyurea (hydroxycarbamide) for cytoreduction and aspirin for thromboprophylaxis; additional options include androgen therapy, low-dose melphalan, cladribine, thalidomide, interferon- α ,⁶ and anagrelide (for ET only).⁷ Most traditional treatment strategies for MF have been forms of palliative-intent management, such as hydroxyurea (hydroxycarbamide) for cytoreduction, and splenectomy or splenic irradiation to ameliorate splenomegaly, along with corticosteroids and immunomodulatory agents. None of these options have been approved by the US Food and Drug Administration (FDA) for the treatment of MF. Allogeneic stem cell transplantation has curative potential in a small subpopulation of patients with MF who are considered eligible candidates; however, for most patients, this procedure is not feasible.^{3,6} Patient characteristics that should be considered when determining eligibility for allogeneic stem cell transplantation include anticipated survival < 5 years,⁸ age < 55 to 57 years,^{9,10} and few comorbidities.¹¹ Given these limitations, many health care professionals consider “watchful waiting” as a management strategy for MF, particularly in the earlier phases of the disease. Thus, there has been an unmet need for effective and durable treatments for patients with MF.

In November 2011, the FDA approved ruxolitinib (formerly known as INCB018424) as a new MF treatment that targets the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway. Ruxolitinib is a potent and selective oral JAK1 and JAK2 inhibitor that is indicated for treating patients with intermediate- or high-risk MF, including PMF, post-PV MF, and post-ET MF.^{12,13} It is currently under investigation in

clinical trials for patients with PV and ET, as well as other select hematologic malignancies and solid tumors. This article reviews the characteristics of MF, PV, and ET; the efficacy and safety of ruxolitinib in the treatment of MF; and the design and preliminary results of clinical trials of ruxolitinib in patients with PV and ET.

Pathologic Profiles of *BCR-ABL* 1-Negative MPNs

A brief summary of the pathologic features of these MPNs highlights the primary differences between them and potential targets for their treatment and evaluation. Myelofibrosis is characterized by megakaryocyte proliferation and atypia, as well as collagen and reticulin bone marrow fibrosis. As a compensatory response for the resultant compromised bone marrow function, extramedullary hematopoiesis takes place in the spleen and liver, which leads to splenomegaly and hepatomegaly, respectively. These conditions are frequently symptomatic, with painful organomegaly. In addition, patients display an overproduction of cytokines, leukoerythroblastosis, and anemia.^{1,3} Patients with PV have increased red cell mass, such that the blood becomes more viscous and more likely to clot. Patients also have megakaryocyte pleomorphism and low (or inappropriately normal) levels of serum erythropoietin.^{1,3} Essential thrombocythemia is characterized by the overproduction of megakaryocytes and high platelet counts, which also lead to a high risk of thrombosis.^{1,3} Conversely, extremely high platelet counts can lead to a paradoxical hemorrhagic diathesis because of a relative deficiency of secondary von Willebrand factor.¹⁴ A common feature among these 3 MPNs is dysregulation of JAK–STAT signaling.

Role of the JAK Signaling Pathway in MPNs

The JAKs (JAK1, JAK2, JAK3, and tyrosine kinase 2) are intracellular tyrosine kinases that respond to receptor binding by activating STAT proteins to stimulate the production of molecules involved in cell growth, differentiation, survival, and immune function. The signaling of erythropoietin and thrombopoietin receptors is mediated by JAK2 and stimulates growth and proliferation. Both JAK1 and JAK2 stimulate the production of proinflammatory cytokines.³ In *BCR-ABL*-negative MPNs, the JAK–STAT pathway becomes dysregulated (or overactive), resulting in excessive proliferation of hematopoietic stem cells and excessive stimulation of inflammatory processes. A variety of mechanisms and mutations may contribute to this aberrant signaling.

Although several mutations have been identified in patients with MPNs,¹ the most common and well-known mutation is the JAK2V617F gain-of-function mutation, which induces JAK–STAT hyperactivation.¹ The incidence of this mutation varies among the MPNs (PMF, ~60%; PV > 95%; ET, ~60%).¹ However, dysregulated JAK–STAT activity is common among all MPNs regardless of JAK2 mutational status.² High levels of cytokines also contribute to increased signaling through this pathway. Aberrant JAK–STAT signaling results in excessive cytokine and growth factor production, thus leading to a feed-forward loop and further activation of the JAK–STAT cascade. The recognition of aberrant JAK–STAT signaling in MPNs has led to the development of JAK inhibitors, such as ruxolitinib, for these indications.

Ruxolitinib

Pharmacology

Ruxolitinib is an orally administered, selective JAK1 and JAK2 inhibitor. The drug is rapidly absorbed with an elimination half-life of approximately 3 hours; 74% is excreted in urine and 22% in feces.^{15,16} Dose- and time-dependent inhibition of STAT3 phosphorylation has been demonstrated in cytokine-stimulated blood cells from healthy subjects treated with ruxolitinib and in blood cells from ruxolitinib-treated patients with MF.^{15,17}

In MF, blockade of overactive JAK2 signaling with ruxolitinib decreases the proliferation of hematopoietic stem cells, and blockade of overactive JAK1 and JAK2 signaling decreases the production of proinflammatory cytokines. Because ruxolitinib does not target a mutation (as imatinib in CML), clinical activity would be expected in patients with MF with and without the V617F mutation. In addition, because ruxolitinib inhibition of overactive JAK2 interferes with erythropoietin stimulation of erythropoiesis and thrombopoietin stimulation of thrombopoiesis, anemia and thrombocytopenia are expected adverse effects of therapy.

Dosing

The starting dose of ruxolitinib is based on platelet count: 20 mg twice daily (bid) for patients with a platelet count $> 200 \times 10^9/L$ and 15 mg bid for patients with a platelet count between $100 \times 10^9/L$ and $200 \times 10^9/L$. In patients with moderate or severe renal impairment or any degree of hepatic impairment, ruxolitinib must be initiated at a reduced dose. In addition, because ruxolitinib is metabolized primarily by the cytochrome P450 (CYP) 3A4 isozyme, a reduced dose must be used in patients taking strong CYP3A4 inhibitors (provided that they have adequate platelet counts). Specific guidelines for dose adjustments in these clinical situations are listed in Table 2.¹² A phase 2 study is in progress that is evaluating a starting dose of 5 mg bid, with subsequent dose optimization, in patients with baseline platelet counts from $50 \times 10^9/L$ to $100 \times 10^9/L$. For most patients, ruxolitinib was titrated to doses of 10 mg bid, and preliminary findings suggest that this dosing strategy may be effective and well tolerated.¹⁸

Clinical Efficacy in PMF, Post-PV MF, and Post-ET MF

Ruxolitinib has been evaluated in a phase 1/2 clinical trial and 2 pivotal phase 3 clinical trials of patients with primary MF, post-PV MF, and post-ET MF.^{17,19,20} The findings in these studies indicate that ruxolitinib provides significant clinical benefits, such as reduction of splenomegaly, symptom improvements, improvements in QoL measures, decreases in elevated cytokine levels, and the potential for improved survival. In addition, ruxolitinib was generally well tolerated, with manageable adverse events (AEs).

Reduction of Splenomegaly—In a phase 1/2 open-label clinical trial in which spleen response was defined as a 50% reduction in palpable splenomegaly, patients with spleen enlargement at baseline had a response rate of 44% after 3 months of treatment.¹⁷ The Controlled Myelofibrosis Study With Oral JAK Inhibitor Therapy (COMFORT)-I and COMFORT-II were phase 3, randomized, controlled trials of ruxolitinib versus placebo (blinded trial) and versus best available therapy (open-label trial), respectively, in patients

with intermediate-2 and high-risk MF. In both studies, spleen response was defined as a 35% reduction in spleen volume from baseline as seen on magnetic resonance imaging or computed tomography scan (corresponding with a 50% reduction in palpable splenomegaly).^{19,20} Response rates were 41.9% with ruxolitinib treatment versus 0.7% with placebo at week 24 ($P < 0.001$) in COMFORT-I,¹⁹ and 28% with ruxolitinib treatment versus 0% with best available therapy at week 48 ($P < 0.001$) in COMFORT-II.²⁰

Spleen responses in both phase 3 trials were durable, with the majority of responding patients maintaining their response for 48 weeks.^{19,20} Importantly, most patients who received ruxolitinib experienced some benefit in spleen volume reduction, whereas the majority of those who received placebo or best available therapy experienced spleen growth (Figure 1). Post hoc analyses of both trials showed that response rates and mean decreases in spleen volume with ruxolitinib therapy were similar regardless of the presence of the JAK2V617F mutation, type of MF (ie, primary, post-PV, or post-ET), sex, age, risk category, or baseline spleen size.^{21,22}

Improvements in Disease-Specific Symptom Burden and QoL Measures—In the phase 1/2 trial, patients reported improvements in MF-related symptoms, including night sweats, itching, bone/muscle pain, and abdominal pain/discomfort as measured by the Myelofibrosis Symptom Assessment Form (MFSAF).^{17,23} In the phase 3 COMFORT-I trial, which used the modified MFSAF v2.0 diary, the total symptom score (comprising scores for abdominal discomfort, pain under ribs on the left side, early satiety, itching, night sweats, and bone/muscle pain) improved by 50% in 45.9% in the ruxolitinib group and 5.3% in the placebo group ($P < 0.001$).¹⁹ In addition, individual symptom scores improved with ruxolitinib therapy and worsened with placebo treatment (Figure 2). Improvements in symptoms correlated with reductions in spleen volume, although patients with even small changes in spleen volume experienced improvement in symptoms.²⁴

Quality-of-life measures also improved significantly with ruxolitinib treatment in both phase 3 trials compared with the corresponding controls (placebo and best available therapy, respectively). In COMFORT-I, the improvements in MF-related symptoms with ruxolitinib therapy were mirrored by improvements in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30, Patient-Reported Outcomes Measurement System Fatigue Scale, and Patient Global Impression of Change.^{19,24} In COMFORT-II, which incorporated the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 and Functional Assessment of Cancer Therapy–Lymphoma, patients treated with ruxolitinib showed greater improvements in global health status and QoL, role functioning, physical condition and functioning, and symptoms (eg, appetite loss, dyspnea, fatigue, insomnia, and pain) compared with best available therapy.²⁰

Reductions in Cytokine Levels—In the phase 1/2 study, treatment with ruxolitinib reduced the levels of circulating proinflammatory cytokines. Changes in the levels of cytokines (interleukin [IL]-1ra, macrophage inflammatory protein 1 β , matrix metalloproteinase 2, tumor necrosis factor- α , and IL-6), along with the acute-phase reactant C-reactive protein, correlated with improvements in symptoms.¹⁷ In the COMFORT-I and

COMFORT-II trials, ruxolitinib reduced the levels of tumor necrosis factor- α , IL-6, and C-reactive protein.^{19,20}

Survival—Ruxolitinib survival data from the phase 1/2 trial were compared with those of historical controls in 2 separate analyses from different study sites. An analysis of 107 patients at 1 site (MD Anderson Cancer Center, Houston, TX) showed that they had a significantly better survival rate than 310 patients in a historical control group ($P = 0.022$).²⁵ Fifty-one patients at another site (Mayo Clinic, Rochester, MN) showed no improvement compared with a historical control group of 410 patients, although discontinuation rates were higher and doses lower at the Mayo Clinic, Rochester site.²⁶ In COMFORT-I, an analysis conducted at the time of a planned follow-up (median, 51 weeks) showed a significant survival benefit ($P = 0.04$) with ruxolitinib treatment compared with placebo (hazard ratio, 0.5); there were 13 (8.4%) deaths in the ruxolitinib group compared with 24 (15.6%) in the placebo group.¹⁹ In COMFORT-II, results reported at a median follow-up of 61 weeks did not show a survival benefit for ruxolitinib over best available therapy.²⁰ The results of longer-term follow-up (median, 2 years) in both of the COMFORT studies indicated that ruxolitinib treatment confers a survival advantage over placebo and best available therapy.^{27,28}

Safety and Tolerability in Patients With MF

In COMFORT-I, common nonhematologic AEs that occurred more frequently with ruxolitinib therapy than with placebo were ecchymosis, dizziness, and headache (Table 3).¹⁹ The most common grade 3 AEs with ruxolitinib therapy in the pivotal trials were thrombocytopenia and anemia, which mainly occurred in the first 2 to 3 months of treatment; these were generally managed with dose reductions, dose interruptions, or, in the case of anemia, transfusions.^{19,20} After the initial decreases in platelet counts and with appropriate management, the mean platelet counts remained consistent over time, and the mean hemoglobin levels returned to near-baseline levels. Recommended dose reductions for thrombocytopenia are shown in Table 4. Neutropenia, although less common than anemia and thrombocytopenia, was also a dose-related hematologic AE of ruxolitinib treatment. The US prescribing information states that platelet counts and signs of infection should be monitored at baseline and during treatment.¹² Myelofibrosis symptoms typically return during a 1-week period after discontinuation of ruxolitinib. Although no withdrawal or rebound effects were seen with ruxolitinib in phase 3 clinical trials, gradual tapering of the dose can be considered when not discontinuing for thrombocytopenia.¹²

Molecular Targets of Ruxolitinib in Patients With MF

In the COMFORT-I and COMFORT-II trials, patients without the JAK2V617F mutation responded to ruxolitinib treatment, showing improvements in spleen volume and symptoms.²⁹ Ruxolitinib binds in the adenosine triphosphate-binding pocket of JAK2, which is distinct from the region of JAK2 that contains the V617F mutation; therefore, it inhibits both mutant and wild-type JAK2. Ruxolitinib also inhibits JAK1.

Unlike CML, the pathogenesis of MF is not caused by a single mutation. The overactivation of JAK1 and JAK2 in MF can result from various mutations or mechanisms that are not

linked to a common ancestral clone.³⁰ Although the pathogenesis of MF is not fully understood, data from the COMFORT trials indicate that the presence of the JAK2V617F mutation is not a prerequisite for therapy. In addition, any clinical benefit of ruxolitinib on JAK2V617F allele burden should be interpreted with caution, although this question is being investigated in an ongoing study.³¹

Ongoing Research of Ruxolitinib Therapy in MPNs

Ruxolitinib is approved by the FDA for the treatment of MF that occurs secondary to PV and ET (ie, post-PV MF and post-ET MF).^{12,13} However, it is currently not approved for PV or ET. In the MF clinical trials, ruxolitinib treatment had similar efficacy in patients with post-PV MF and post-ET MF, and its efficacy in those conditions did not differ from its efficacy in patients with PMF.^{21,22} Clinical trials of ruxolitinib treatment for PV and ET are in progress.

Phase 2 Study in PV and ET—A phase 2, randomized, open-label trial (currently closed to enrollment) with long-term follow-up of patients is being conducted. Enrolled patients had PV or ET and were refractory to, intolerant of, or otherwise unsuitable for hydroxyurea (hydroxycarbamide) treatment. Patients were given ruxolitinib 10 mg bid, 25 mg bid, or 50 mg once daily during a 56-day dose-ranging phase, after which the dose and regimen were adjusted on an individual basis to achieve an optimal balance of safety and efficacy.³²

Interim findings from the trial have been presented for 34 patients with PV and 39 patients with ET.³³ After the run-in phase, the starting doses for the expansion cohorts were ruxolitinib 10 and 25 mg bid. In both populations, at a median follow-up of 15 months, rapid and durable clinical benefits were observed. In the PV population, 97% achieved hematocrit control (< 45%) and were phlebotomy independent; 59% of those with splenomegaly at baseline achieved a 50% reduction in palpable splenomegaly; and leukocytosis and thrombocytosis improved or normalized in the majority of patients (among those with abnormal values at baseline). The most common grade 3 AE was thrombocytopenia (n = 2). In the ET population, 49% of patients achieved normalization of white blood cell counts and platelet counts with nonpalpable splenomegaly. The most common grade 3 AE was leukopenia (n = 2). No grade 4 AEs occurred in either population. Both groups had reductions in symptom scores for pruritus, night sweats, and bone pain.³³

Phase 3 Trials in PV—An active phase 3 trial of patients with PV refractory to or unsuitable for hydroxyurea (hydroxycarbamide) treatment is being conducted. Patients must also have a phlebotomy requirement (because of inadequate hematocrit control) and palpable splenomegaly. The trial is comparing ruxolitinib 10 mg bid with best available therapy. The primary endpoint is response, defined as the achievement of the absence of protocol-defined phlebotomy eligibility and a 35% reduction from baseline in spleen volume, as determined by imaging, at week 32. Other endpoints include duration of response and hematologic remission.³⁴ An additional study is under way evaluating symptoms in patients with PV who are treated with ruxolitinib compared with those who are treated with hydroxyurea.³⁵

Summary

The *BCR-ABL1*-negative MPNs are progressive hematologic disorders. Until recently, the unmet medical need in MPNs, specifically in MF (ie, PMF, post-PV MF, post-ET MF), as well as in select subpopulations of PV and ET (eg, chronically symptomatic patients with these neoplasms, despite the use of recommended treatment medications) has been high. Indeed, the medications and nonpharmacologic modalities (eg, splenectomy) that have traditionally been used for MPNs have been largely palliative and have demonstrated little or no benefit in these patient subgroups.

Myeloproliferative neoplasms share a common underlying pathology of aberrant JAK–STAT signaling. The discovery of this dysregulated pathway provided the rationale for the development of JAK inhibitors. Ruxolitinib is the first JAK1 and JAK2 inhibitor approved in the United States for the treatment of MF, and it is currently undergoing clinical trial investigation as treatment for patients with PV and ET. Ruxolitinib significantly reduces spleen volume, improves debilitating symptoms, improves scores on QoL measures, and reduces elevations in proinflammatory cytokines in patients with PMF, post-PV MF, and post-ET MF. Evidence also suggests that ruxolitinib therapy may have a survival advantage over placebo and best available therapy. Two ongoing trials^{34,35} are evaluating the benefits of ruxolitinib in patients with PV, and 1 trial³² is also continuing to investigate ruxolitinib for the treatment of ET or PV. In PV and ET, which are characterized by overproduction of blood cells and subsequent thrombosis, interference with JAK–STAT signaling by ruxolitinib with control of blood cell counts has the potential to reduce the incidence of thrombosis. Future investigations may suggest a role for JAK inhibitors in carefully selected combination therapies in MPNs.

Acknowledgments

The author would like to thank Stephanie Leinbach, PhD, for providing medical writing assistance funded by Incyte Corporation, as well as Dr. Nicholas J. Sarlis, Incyte Corporation, for helpful discussions.

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Figure 1.

Reduction in spleen volume with ruxolitinib in COMFORT-I and COMFORT-II. **A)** For COMFORT-I, individual patient changes from baseline to week 24 or last evaluation are shown. **B)** For COMFORT-II, best individual patient changes at any time within the first 48 weeks are shown.^{19,20}

Abbreviations: BAT, best available therapy; BL, baseline; COMFORT, Controlled Myelofibrosis Study With Oral JAK Inhibitor Therapy; JAK, Janus kinase.

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Figure 2.

Improvement in individual symptoms on the MFSAF v2.0 in COMFORT-I. Mean percent change in score for each symptom on the MFSAF v2.0 is shown. Ruxolitinib-treated patients showed improvement in all 7 individual symptoms evaluated on the MFSAF v2.0; in contrast, patients who received placebo did not show improvement in any of these symptoms ($P < 0.01$ for each symptom, ruxolitinib vs placebo).¹⁹

Abbreviations: COMFORT, Controlled Myelofibrosis Study With Oral JAK Inhibitor Therapy; JAK, Janus kinase; MFSAF, Myelofibrosis Symptom Assessment Form.

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Table 1Myelofibrosis Risk Groups (by IPSS) and Associated Survival⁵

Risk Group	Number of Risk Factors*	Median Survival, y
Low	0	11.3
Intermediate-1	1	7.9
Intermediate-2	2	4.0
High	3	2.6

* Risk factors include age > 65 years, constitutional symptoms, hemoglobin < 10 g/dL, white blood cell count > 25×10^9 /L, and blood blasts > 1%.

Abbreviation: IPSS, International Prognostic Scoring System.

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Table 2Recommended Ruxolitinib Starting Dose Adjustments¹²

Clinical Parameter	Platelet Count	Starting Dose
Renal impairment		
Moderate/severe ^a	$100 \times 10^9/\text{L}$ – $150 \times 10^9/\text{L}$	10 mg bid
Moderate/severe ^a	$< 100 \times 10^9/\text{L}$	Avoid use
ESRD undergoing dialysis	$100 \times 10^9/\text{L}$ – $200 \times 10^9/\text{L}$	15-mg single dose ^b
ESRD undergoing dialysis	$> 200 \times 10^9/\text{L}$	20-mg single dose ^b
ESRD not requiring dialysis		Avoid use
Hepatic impairment		
	$100 \times 10^9/\text{L}$ – $150 \times 10^9/\text{L}$	10 mg bid
	$< 100 \times 10^9/\text{L}$	Avoid use
Coadministration of strong CYP3A4 inhibitor ^c	$100 \times 10^9/\text{L}$	10 mg bid
	$< 100 \times 10^9/\text{L}$	Avoid use

^aModerate, creatinine clearance of 30 to 59 mL/min; severe, creatinine clearance of 15 to 29 mL/min.

^bSingle dose to be administered on dialysis days, following dialysis session.

^cIncluding but not limited to boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole.

Abbreviations: bid, twice daily; CYP, cytochrome P450; ESRD, end-stage renal disease.

Table 3

Adverse Events Occurring in 10% of Ruxolitinib-Treated Patients: Ruxolitinib Versus Placebo (COMFORT-I)¹⁹

Adverse Event, %	Ruxolitinib (n = 155)		Placebo (n = 151)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Nonhematologic				
Fatigue	25.2	5.2	33.8	6.6
Diarrhea	23.2	1.9	21.2	0
Peripheral edema	18.7	0	22.5	1.3
Ecchymosis	18.7	0	9.3	0
Dyspnea	17.4	1.3	17.2	4.0
Dizziness	14.8	0.6	6.6	0
Nausea	14.8	0	19.2	0.7
Headache	14.8	0	5.3	0
Constipation	12.9	0	11.9	0
Vomiting	12.3	0.6	9.9	0.7
Pain in extremity	12.3	1.3	9.9	0
Insomnia	11.6	0	9.9	0
Arthralgia	11.0	1.9	8.6	0.7
Pyrexia	11.0	0.6	7.3	0.7
Abdominal pain	10.3	2.6	41.1	11.3
Hematologic abnormalities *				
Anemia	96.1	45.2	86.8	19.2
Thrombocytopenia	69.7	12.9	30.5	1.3
Neutropenia	18.7	7.1	4.0	2.0

* Based on laboratory values. Worst grade is shown, regardless of whether it was a change from baseline.

Abbreviations: COMFORT, Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment; JAK, Janus kinase.

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Ruxolitinib Dosing Recommendations for Thrombocytopenia¹²

Table 4

Platelet Count ^a	Dose at Time of Platelet Decline					
	25 mg bid	New Dose, mg bid	20 mg bid	New Dose, mg bid	15 mg bid	New Dose, mg bid
100 to < 125 × 10 ⁹ /L	20		15	No change	No change	No change
75 to < 100 × 10 ⁹ /L	10		10	10	No change	No change
50 to < 75 × 10 ⁹ /L	5		5	5	5	No change
< 50 × 10 ⁹ /L	Hold		Hold	Hold	Hold	Hold

^a A phase 2 study is in progress evaluating ruxolitinib in patients with baseline platelet counts from 50 × 10⁹/L to 100 × 10⁹/L.³⁶
Abbreviation: bid, twice daily.