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Original Study

Safety and Efficacy of Ruxolitinib in Patients with Myelofibrosis and Low Platelet Counts ($50 – 100 \times 10^9$/L): Final Analysis of an Open-Label Phase 2 Study

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Abstract

Treatment options for myelofibrosis and platelet counts 50 – 100×10^9/L are limited. Ruxolitinib was initiated at 5 mg twice daily with gradual up-titration based on response and hematologic parameters. Improvements in spleen volume and symptoms were greatest with ruxolitinib 10 mg twice daily. A lower starting dose of ruxolitinib with gradual up-titration and subsequent dose optimization was safe and efficacious.

Introduction: Treatment options in patients with myelofibrosis (MF) presenting with thrombocytopenia are limited. Final results of the phase 2 study (NCT01348490) of ruxolitinib in patients with MF and low baseline platelet counts ($50 – 100 \times 10^9$/L) are reported. **Patients and Methods:** Patients received ruxolitinib 5 mg twice daily (BID), with optional up-titration to a maximum of 15 mg BID, provided platelet count remained $\geq 40 \times 10^9$/L. Assessments included spleen volume and length, Total Symptom Score (TSS), quality of life, and safety. **Results:** Of 66 patients, 52 (78.8%) completed the first 24 weeks of treatment. Median (range) percentage change from baseline in spleen volume and TSS (coprimary endpoints) were −20.5% (−55.8% to 38.5%, n=51) and −39.8% (−98.6% to 226.4%, n=53), respectively; greatest median reductions were in the 10 mg BID final titrated dose group. Of patients achieving ≥35% or ≥10% reduction in spleen volume, 8/11 (72.7%) and 21/34 (61.8%), respectively, were in the 10 mg BID final titrated dose group. Thirty-seven of 65 patients (56.9%) had ≥20% improvement in TSS, and 35/66 patients (53.0%) were Patient Global Impression of Change responders. Treatment-emergent adverse events led to dose interruption in 17/66 patients (25.8%), most commonly thrombocytopenia (n=3). **Conclusion:** A starting dose of ruxolitinib 5 mg BID with gradual up-titration and dose optimization based on hematologic parameters and response was efficacious and generally well-tolerated in patients with MF and low platelet counts. Median improvement in spleen volume and symptoms was greatest for patients receiving ruxolitinib 10 mg BID.

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Keywords: Janus kinase inhibitor, Myeloproliferative neoplasm, Spleen volume, Thrombocytopenia, Total Symptom Score

Abbreviations: AE, adverse event; BID, twice daily; CALR, calreticulin; COMFORT, Controlled myelofibrosis study with oral Jak inhibitor treatment; CTCAE, Common Terminology Criteria for Adverse Events; DIPSS, Dynamic international prognostic scoring system; EORTC QLQ-C30, European organisation for research and treatment of cancer quality of life questionnaire-core 30; ET, essential thrombocythemia; FDA, United States Food and Drug Administration; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia virus oncogene; MRI, magnetic resonance imaging; PET, post-essential thrombocythemia; PGIC, Patient global impression of change; PK, pharmacokinetic; PMF, primary myelofibrosis; PPV, post-polycythemia vera; PV, polycythemia vera; QD, once daily; QoL, quality of life; TEAE, treatment-emergent adverse event; TSS, Total Symptom Score.

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Introduction

Myelofibrosis (MF) is a Philadelphia-chromosome negative myeloproliferative neoplasm, presenting either de novo as primary MF (PMF) or secondary to polycythemia vera (PV) or essential thrombocythemia (ET).[1] Identified driver mutations in MF involve the genes Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukemia virus oncogene (*MPL*), occurring in 45% –68%, 25% –35%, and approximately 5% of patients, respectively.[1-4]

MF is characterized by clonal proliferation of a pluripotent hematopoietic stem cell, bone marrow fibrosis, stromal changes, and extramedullary hematopoiesis.[1,5,6] Although approximately 30% of patients are asymptomatic at diagnosis, most patients present with splenomegaly (leading to abdominal discomfort and pain, early satiety, and dyspnea) and constitutional symptoms (fatigue, low-grade fever, night sweats, and weight loss).[4,5,7,8] Some patients present with headache, insomnia, pruritus, bone pain, or inactivity, which may lower their quality of life (QoL).[4,9]

Hematologic manifestations most commonly include progressive anemia (hemoglobin <10 g/dL; 31% –51%) and thrombocytopenia (platelets $\leq 100 \times 10^9$/L; 16% –26%).[7,10-13] Others include leukopenia (leukocyte count $<4 \times 10^9$/L; 16%) or leukocytosis (leukocyte count $>25 \times 10^9$/L; 9% –14%), and thrombocytosis (platelets $>400 \times 10^9$/L; 30.5%).[10-13] Studies have shown that anemia, leukocytosis, and thrombocytopenia at diagnosis are independent predictors of shortened survival in PMF.[3,10,12,13]

The median survival in patients with MF is 5.2 years (95% confidence interval, 4.9 –5.9 years).[13] The risk of progression to acute myeloid leukemia is approximately 20% during the first 10 years after diagnosis of MF, with a median overall survival of 2.6 months after transformation.[3] Prognostic models support therapeutic decision-making for PMF.[10,11] The International Prognostic Scoring System includes 5 risk factors at the time of diagnosis (age >65 years, constitutional symptoms, hemoglobin level <10 g/dL, leukocyte count $>25 \times 10^9$/L, and peripheral blood blasts ≥1%) to identify 4 risk categories for survival: low, intermediate-1, intermediate-2, and high.[10] The Dynamic International Prognostic Scoring System Plus (DIPSS Plus) may be used at any time point in the disease course post-diagnosis and includes the same 5 risk factors, but with the addition of thrombocytopenia, red cell transfusion dependence, and unfavorable karyotype.[12]

Aberrant activation of Janus kinase (JAK)–signal transducer and activator of transcription signaling is common to all myeloproliferative neoplasms,[1,3] irrespective of driver mutation status.[14] Ruxolitinib is a potent and selective JAK1/2 inhibitor approved for the treatment of intermediate-/high-risk MF[15,16] based on the results of the COMFORT-I (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment-I) and COMFORT-II trials.[17,18] In both studies, ruxolitinib treatment resulted in reduced spleen volume and improved MF-related symptoms and QoL measures. Adverse events (AEs) of dose-dependent anemia and thrombocytopenia (which were anticipated because thrombopoietin and erythropoietin both signal through JAK2)[19,20] were manageable with dose modifications and/or red blood cell transfusions.[17,18]

The COMFORT studies enrolled patients with a baseline platelet count of $\geq 100 \times 10^9$/L; starting doses of ruxolitinib were 15 or 20 mg twice daily (BID), depending on baseline platelet count. However, approximately one-quarter of patients with PMF have a platelet count $<100 \times 10^9$/L[21] and treatment options for these patients are limited.[19,22]

An interim analysis of study INCB 18424-258, a phase 2 study assessing the efficacy and safety of ruxolitinib in patients with MF who had baseline platelet counts of 50 –100×10^9/L, has been reported.[23] Based on this study, the ruxolitinib label includes a recommended starting dose of ruxolitinib 5 mg BID for patients with MF with baseline platelet count of 50 to $<100 \times 10^9$/L, with recommendations for dose modifications for thrombocytopenia and upward dose titration for insufficient response.[15] Final results from this study are presented here.

Patients and Methods

Study Design and Study Population

The study was approved by institutional review boards of participating institutions and was conducted in accordance with the Declaration of Helsinki, as outlined in the International Conference on Harmonisation: Guideline for Good Clinical Practice, and applicable regulatory requirements. All patients provided written informed consent.

Details on the study design of the phase 2, multicenter, open-label study (INCB 18424-258; NCT01348490) evaluating ruxolitinib in patients with PMF, post-PV (PPV) MF, or post-ET (PET) MF and platelet counts of 50×10^9/L to 100×10^9/L have been published previously.[23] The study consisted of 4 phases: (1) screening (up to 21 days) plus baseline phase (7 days), (2) core treatment phase (24 weeks), (3) extended treatment phase (132 weeks; patients receiving benefit continued ruxolitinib treatment until week 156 [Protocol Amendment 2, dated August 9, 2013, per request from the United States Food and Drug Administration (FDA) to collect 3 years of safety data in patients with low platelet counts]), and (4) safety follow-up phase (30 –37 days after the last dose of study drug).

Briefly, patients ≥18 years with PMF, PPV-MF, or PET-MF for whom MF treatment was indicated, with platelet count of 50 – 100×10^9/L (at screening or baseline visit), hemoglobin ≥6.5 g/dL, peripheral blood blast count <5% (screening visit), DIPSS ≥1, active MF symptoms (at screening visit), and life expectancy >6 months, were eligible for inclusion. Patients received ruxolitinib at a starting dose of 5 mg BID. Dose escalation criteria allowed optional dose increases from week 4 to 16, in 5-mg once-daily (QD) increments every 4 weeks to a maximum 15 mg BID dose during the core treatment phase (Supplementary Material, Supplementary Methods).

Endpoints and Assessments

The coprimary endpoints were correlation of percentage change from baseline to week 24 in spleen volume according to final titrated dose group, and correlation of percentage change from baseline to week 24 in Total Symptom Score (TSS) as measured by the modified Myelofibrosis Symptom Assessment Form v2.0 diary according to final titrated dose group; final titrated dose is defined as the average total daily dose during the last 28 days of available dosing data either

before week 24 or before the last dose for patients who discontinued treatment early. Secondary endpoints included the following at week 24 compared with baseline: percentage change in spleen volume, percentage change in TSS, proportion of patients with reduction in spleen volume (≥35%, ≥10%), and proportion of patients with ≥50% improvement in TSS. Other secondary endpoints included long-term efficacy of ruxolitinib as assessed by monitoring change and percentage change in spleen length and change in Patient Global Impression of Change (PGIC) score from baseline to each visit through week 156. Safety endpoints were safety and tolerability through week 156, including proportion of patients with new-onset grade 4 thrombocytopenia events, and new-onset grade 2 or higher hemorrhage, as assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Exploratory endpoints included proportion of patients with ≥20% improvement in TSS at week 24 compared with baseline; PGIC score at each visit where the variable was measured through week 156; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) scores from baseline to each visit where the variable was measured through week 156; and pharmacokinetics (PK) of ruxolitinib by population PK approach.

Spleen volume was measured by magnetic resonance imaging (MRI) or computed tomography (in patients who were not candidates for MRI or MRI not available) at baseline and at week 24. TSS was measured by the modified Myelofibrosis Symptom Assessment Form version 2.0 at baseline (average of days –7 to 1) and at week 24 (average of the 28 days preceding week 24). Patients provided daily ratings for the severity of the following 7 MF-related symptoms on a scale from 0 ("absent") to 10 ("worst imaginable"): night sweats, itching, abdominal discomfort, pain under the ribs on left side, early satiety, bone/muscle pain, and inactivity.[24] Severity scores for each symptom except inactivity were summed for the TSS (maximum TSS, 60). Spleen length below the left costal margin was assessed by manual palpation at baseline, every 4 weeks through week 24, then every 12 weeks through week 156. The PGIC was administered every 4 weeks through week 24, then every 12 weeks through week 156, and utilized a single question regarding MF symptoms, to which the patient responded on a scale from 1 ("very much improved") to 7 ("very much worse"). The EORTC QLQ-C30 was administered at baseline, week 4, 12, and 24, then every 12 weeks through week 156. It is a 30-item questionnaire including 5 functional domains (physical, cognitive, role, emotional, and social), 3 symptom scales (pain, fatigue, and nausea and vomiting), 6 additional single-symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status scale.[25]

An ad hoc analysis was performed to assess whether baseline hemoglobin, baseline DIPSS, and week 24 spleen response differed based on week 24 platelet response (ie, $\geq 20 \times 10^9$/L platelet count increase from baseline vs. other patients [$<20 \times 10^9$/L platelet count increase, no change in platelets, decrease in platelets, platelet change not evaluable]).

Safety was assessed by AEs (graded according to the CTCAE v4.03, with the exception of death [CTCAE severity grade 5], which was collected as an outcome), laboratory results (hematology, coagulation parameters, and serum chemistry), physical examination, vital signs, and electrocardiography.

Table 1 Patient Demographics and Disease Characteristics at Baseline

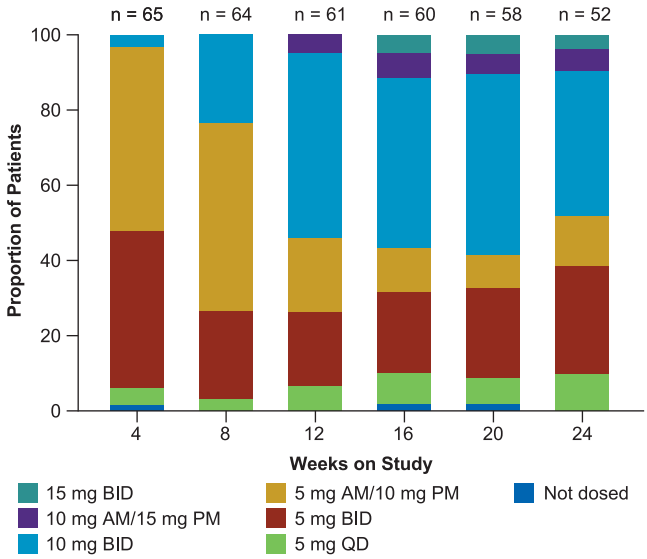
Parameter	Value ($n = 66$)
Mean age (range), ys	68.7 (44.0 –91.0)
Men, *n* (%)	39 (59.1)
Race, *n* (%)	
White	58 (87.9)
Black	4 (6.1)
Asian	2 (3.0)
Native Hawaiian or Pacific Islander	1 (1.5)
Other	1 (1.5)
Mean body mass index (SD), kg/m^2	24.9 (4.2)
Myelofibrosis subtype, *n* (%)	
PMF	42 (63.6)
PPV-MF	19 (28.8)
PET-MF	5 (7.6)
DIPSS risk category, *n* (%)	
High	10 (15.2)
Intermediate-2	42 (63.6)
Intermediate-1	13 (19.7)
Low	1 (1.5)
ECOG performance status, *n* (%)[a]	
0	11 (16.7)
1	47 (71.2)
2	7 (10.6)
History of blood component transfusion, *n* (%)	25 (37.9)
Previous HU use, *n* (%)	24 (36.4)
Platelet count, $\times 10^9$/L	
Mean (SD)	73.1 (21.1)
Median (range)	69.0 (39 –140)
Mean hemoglobin (SD), g/dL	98.6 (16.4)
Mean WBC (SD), $\times 10^9$/L	20.9 (26.5)
Mean TSS (SD)	17.9 (11.2)
Mean spleen length (SD), cm	12.8 (7.1)
Mean spleen volume (SD), cm^3	2263.3 (1451.9)

Abbreviations: DIPSS = Dynamic International Prognostic Scoring System; ECOG = Eastern Cooperative Oncology Group; HU = hydroxyurea; PET-MF = post-essential thrombocythemia myelofibrosis; PMF = primary myelofibrosis; PPV-MF = post-polycythemia vera myelofibrosis; SD = standard deviation; TSS = Total Symptom Score; WBC = white blood cell.
[a] An ECOG value was not available for 1 patient until week 8 (postbaseline).

Statistical Analysis

The efficacy analysis was assessed in the intent-to-treat population, which included all patients enrolled and treated in the study; for spleen and TSS analyses, patients without baseline assessments were not included in analyses; patients who discontinued treatment before week 24 were included in responder category analyses (ie, dichotomous classification above and below predetermined response thresholds) but considered nonresponders at week 24. The safety analysis was based on the safety population, which included all patients who received at least 1 dose of study drug. Patients who

Figure 1 Distribution of ruxolitinib daily dose over the 24-week study period. The number of patients with available dose information is specified on the top of each bar. Abbreviations: BID = twice daily; QD = once daily.



received at least 1 dose of study drug and provided at least 1 plasma sample were included in the PK analysis.

Summary statistics are used for demographics and outcomes. Median change and median percentage change from baseline to week 24 in spleen volume, palpable spleen length, and TSS for each final titrated dose group are reported. In addition, the proportion of patients achieving ≥35% or ≥10% reduction in spleen volume and ≥50% or ≥20% improvement in TSS were determined at week 24. For ad hoc analyses, *t* tests were used to compare continuous variables and Pearson Chi-square tests were used for categorical variables. Statistical analyses were performed with SAS® software (SAS Institute Inc, Cary, NC; v9.1.3). The PK analyses were done with NONMEM version 7.0 and the Intel Fortran Compiler 11.0.

Results

Patient Characteristics and Disposition

Data obtained from June 15, 2011 (first patient dosed) to December 19, 2018 (last patient completed) are reported. S66 patients were enrolled from 27 study sites in the United States. Patient demographics and disease characteristics at baseline are presented in Table 1. The median age (range) was 68.5 (44.0 – 91.0) years and 63.6% ($n = 42$) of patients had PMF. The median (range) time since initial diagnosis was 1.2 (0.1 –29.9) years and median (range) baseline spleen volume was 1921.9 (458.5 –7235.1) cm^3. Median (range) baseline platelet count was 69.0 (39.0 – 140.0) $\times 10^9$/L; patients with a qualifying screening platelet count (50 – 100 $\times 10^9$/L) and subsequent baseline count $<50 \times 10^9$/L ($n = 1$) or $>100 \times 10^9$/L ($n = 6$) were eligible for enrollment. Most patients (63.6%) were classified as intermediate-2 risk by DIPSS.

Exposure

Of the 66 patients enrolled, 52 (78.8%) completed the first 24 weeks of treatment. 14 patients (21.2%) discontinued treatment during the first 24 weeks of treatment, because of AEs ($n = 4$), consent withdrawal ($n = 2$), disease progression ($n = 2$), death ($n = 1$), and other reasons ($n = 5$). 23 patients (34.8%) entered the extension phase. The median (range) duration of exposure to ruxolitinib for all 66 patients was 24.4 (4.0 –173.4) weeks, and median (range) final titrated ruxolitinib daily dose was 15.6 (6.5 –26.9) mg.

4 groups were classified by the final titrated dose at week 24 ($n = 52$): 5 mg QD or 5 mg BID ($n = 20$); 5 mg AM/10 mg PM ($n = 7$); 10 mg BID ($n = 20$); 10 mg AM/15 mg PM or 15 mg BID ($n = 5$) (Figure 1).

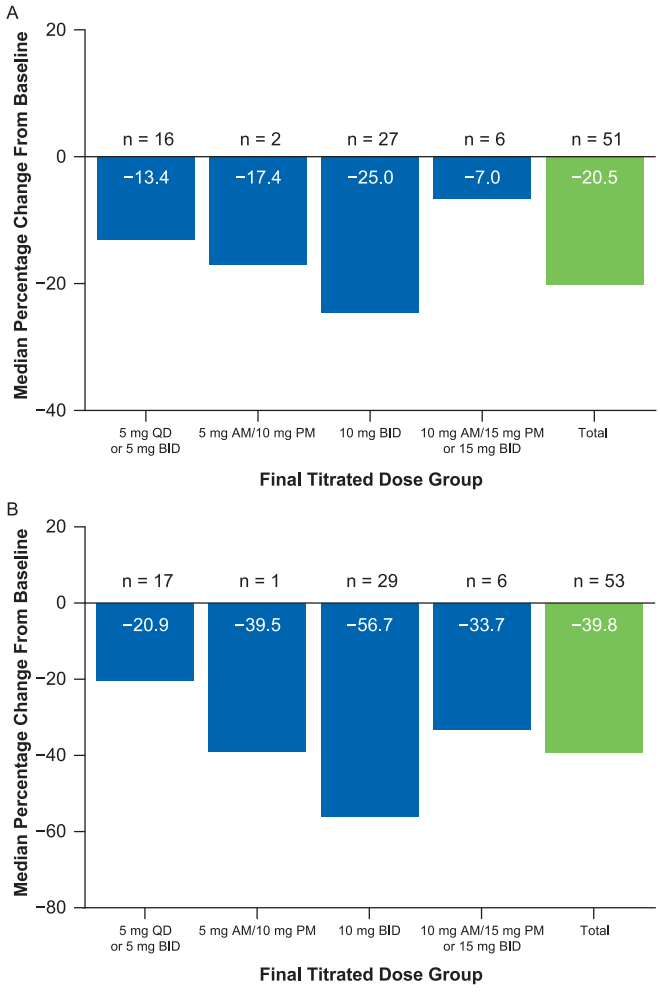
Efficacy

Coprimary Endpoints (Spleen Volume and Symptom Burden by Final Titrated Dose Group). Of the 66 patients enrolled, 64 were evaluable for spleen response (2 patients had no baseline spleen data available) and 65 were evaluable for TSS (1 patient had no baseline TSS data available).

At week 24, spleen volume data were available for an evaluable population of 51 patients (3 out of 64 spleen-evaluable patients missed the week 24 visit, and 10 patients discontinued before week 24; Figure 2A). The median (range) percentage change from baseline to week 24 in spleen volume in these 51 patients was −20.5% (−55.8% – 38.5%); the greatest reduction occurred in the 10 mg BID final titrated dose group ($n = 27$; −25.0% [−55.8% – 38.5%]).

At week 24, TSS data were available for an evaluable population of 53 patients (2 out of 65 TSS-evaluable patients had a missing value at the week 24 visit, and 10 patients discontinued before week

Figure 2 Efficacy by final titrated dose. (A) Median percentage change in spleen volume from baseline to week 24, by final titrated dose group ($n = 51$ of 64 patients with baseline spleen assessment: 3 patients missed the week 24 visit and 10 patients had discontinued before week 24; of note, 1 included patient had a magnetic resonance imaging on day 196, which was taken as their week 24 assessment). (B) Median percentage change in Total Symptom Score (TSS) as measured by the modified Myelofibrosis Symptom Assessment Form v2.0 diary from baseline to week 24, by final titrated dose ($n = 53$ of 65 patients with baseline TSS assessment: 2 patients had a missing value at week 24 and 10 patients discontinued before week 24). The number of patients with available dose information is specified on the top of each bar; the median value is specified inside the bar. Final titrated dose is defined as the average total daily dose during the last 28 days of available dosing data either before week 24 or before the last dose for patients who discontinued treatment early. Abbreviations: BID = twice daily; QD = once daily.



24; Figure 2B). The median (range) percentage change in TSS from baseline to week 24 in these 53 patients was −39.8% (−98.6% – 226.4%); the greatest change occurred in the 10-mg BID final titrated dose group ($n = 29$; −56.7% [−98.6% – 123.2%]).

Secondary and Exploratory Endpoints. Individual patient changes in spleen volume at week 24 ($n = 51$) are presented in Figure 3A. Spleen response at week 24 was based on all 64 patients who had baseline spleen data (see Statistical Methods). Week 24 spleen response (≥35% reduction in spleen volume from baseline to week 24) was achieved by 17.2% (11/64) of patients, with most responders (72.7%, 8/11) belonging to the 10-mg BID final titrated dose group (Figure 3B). A ≥10% reduction in spleen volume from baseline to week 24 was achieved by 53.1% (34/64) of patients, with most responders (61.8%, 21/34) belonging to the 10-mg BID final titrated dose group (Figure 3C).

At week 24, spleen length data were available for an evaluable population of 47 patients (1 out of 64 spleen-evaluable patients had baseline spleen volume but no baseline spleen length recorded owing to abdominal distension that prevented measurement of spleen length at baseline visit, 6 patients missed the week 24 visit, and 10 patients discontinued before week 24). The median (range)

Figure 3 Efficacy results at 24 weeks. (A) Percentage change in spleen volume for individual patients from baseline to week 24 ($n = 51$ of 64 patients with baseline spleen assessment: 3 patients missed week 24 and 10 patients discontinued before week 24). Proportion of patients with (B) ≥35% reduction and (C) ≥10% reduction in spleen volume from baseline to week 24 ($n = 64$ of 64 patients with baseline spleen assessment; of note, 1 patient had a magnetic resonance imaging on day 196, which was taken as their week 24 assessment). (D) Median percentage change in spleen length from baseline to week 24 ($n = 47$ of the 64 patients with baseline spleen assessment: 1 patient had baseline spleen volume but no baseline spleen length recorded, 6 patients missed the week 24 visit, and 10 patients discontinued before week 24). (E) Percentage change in Total Symptom Score (TSS) for individual patients from baseline to week 24 ($n = 53$ of 65 patients with baseline TSS assessment: 2 patients had a missing value at week 24 and 10 patients discontinued before week 24). (F) Proportion of patients with ≥50% improvement in TSS as measured by the modified Myelofibrosis Symptom Assessment Form v2.0 diary from baseline to week 24 ($n = 65$ of 65 patients with baseline TSS assessment). For panels B, C, and F, the number of patients with available data is specified on the top of each bar; the percentage of patients is specified inside the bar. For panel D, the number of patients with available dose information is specified on the top of each bar; the median value is specified inside the bar. Final titrated dose is defined as the average total daily dose during the last 28 days of available dosing data either before week 24 or before the last dose for patients who discontinued treatment early. Abbreviations: BID = twice daily; QD = once daily.

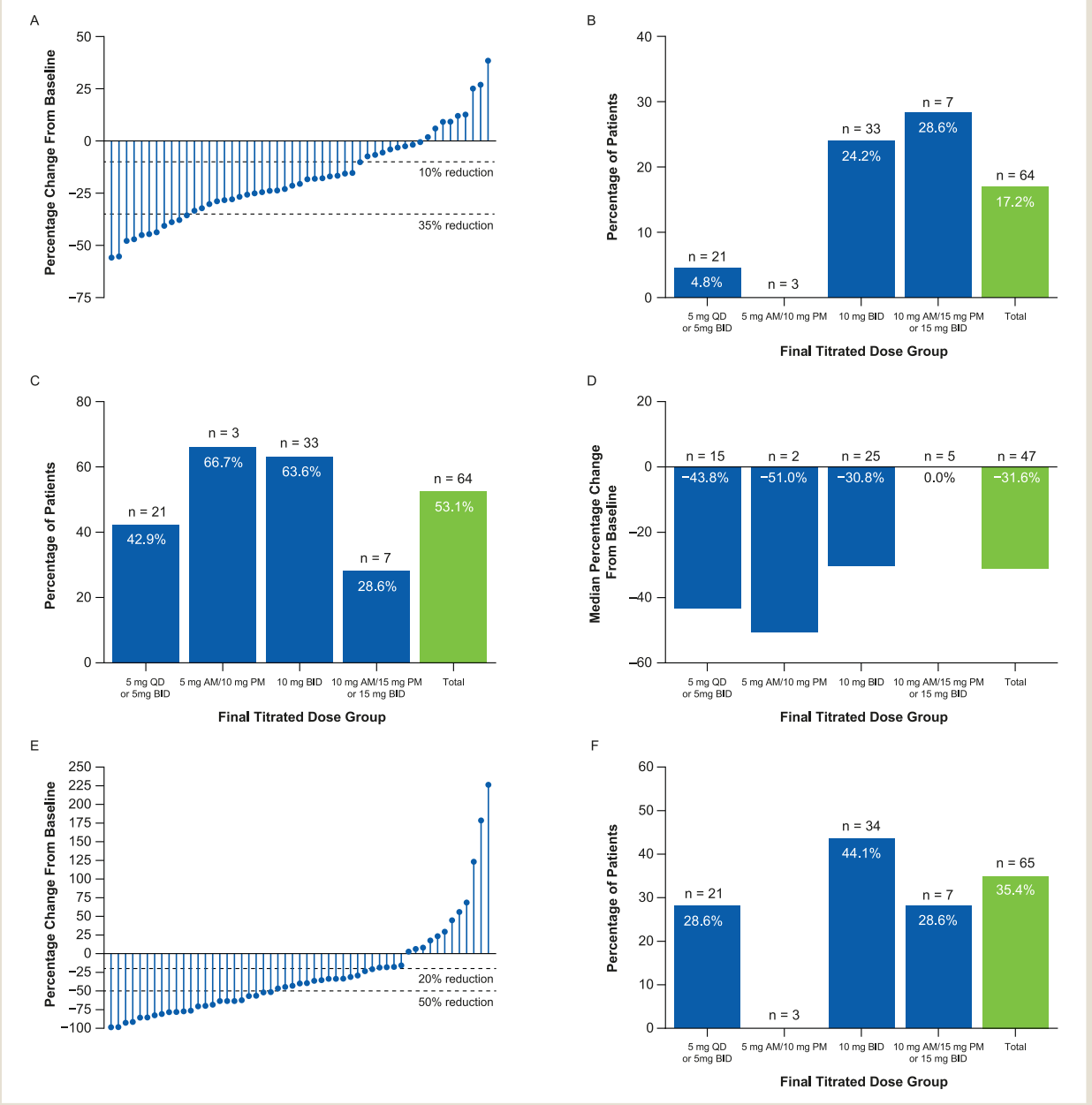
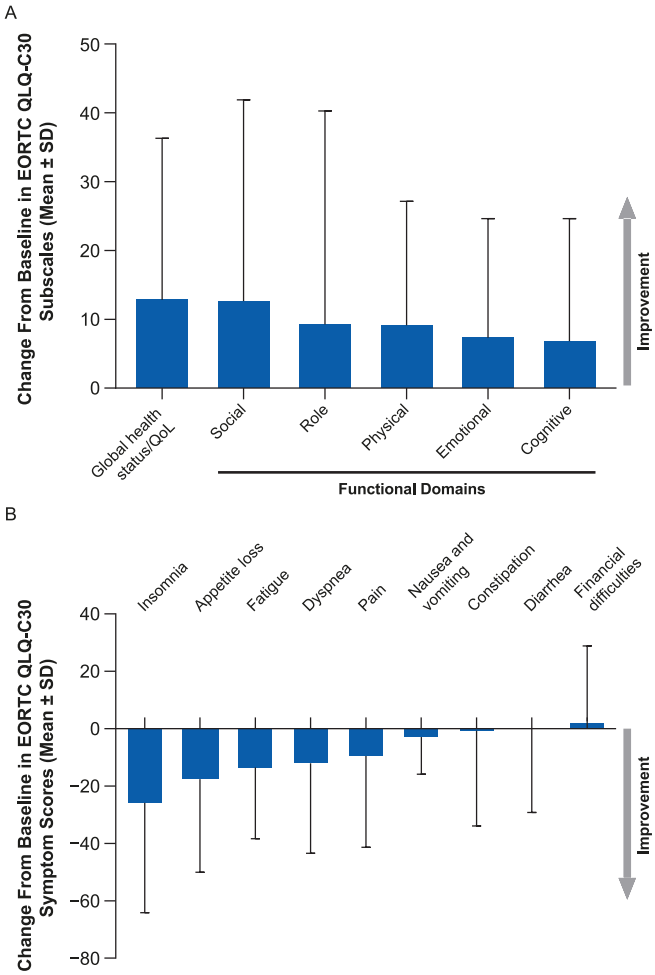


Figure 4 Mean change from baseline to week 24 in (A) global health status/QoL and functional domains, and (B) symptom scores assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Abbreviations: QoL = quality of life; SD = standard deviation.



percentage change from baseline to week 24 in palpable spleen length in these 47 patients was −31.6% (−100.0% – 58.3%); the largest reductions in spleen length were reported in the 5 mg AM/10 mg PM ($n = 2$; −51.0 [−68.8 to −33.3]) and 5 mg QD or 5 mg BID ($n = 15$; −43.8 [−100.0 to 58.3]) dose groups (Figure 3D).

Individual patient changes in TSS at week 24 ($n = 53$) are presented in Figure 3E. Symptom response at week 24 was assessed for all 65 patients who had baseline TSS data, regardless of whether week 24 data were available (see Statistical Methods). Week 24 symptom response (≥50% improvement in TSS from baseline to week 24) was achieved by 35.4% (23/65) of patients (Figure 3F), and 56.9% (37/65) had a ≥20% improvement in TSS from baseline to week 24. At week 24, there was clinically meaningful improvement in all 6 individual symptoms that comprise the TSS as well as inactivity (median percentage change from baseline: itching, −81.6% [$n = 41$]; night sweats, −69.2% [$n = 43$]; pain under ribs on left, −56.1% [$n = 46$]; abdominal discomfort, −42.9% [$n = 52$]; early satiety, −39.4% [$n = 50$]; bone/muscle pain, −32.1% [$n = 49$]; inactivity, −25.2% [$n = 52$]; number of patients for individual symptoms or inactivity scores varied because of missing diary responses).

PGIC data were available for 55 patients at week 24; 48 patients (87.3%) noted at least minimal improvement (score of 1 –3), 4 patients (7.3%) noted no change (score of 4), and 3 patients (5.5%) rated themselves as "minimally worse" (score of 5). At week 24, 35 of 66 patients (53.0%) were responders (PGIC score of 1 –2); of the remaining 31 patients who were not responders, 20 (30.3%) did not have sufficient improvement, 10 (15.2%) discontinued before week 24, and 1 (1.5%) had a missing value.

Patients showed clinically meaningful improvement from baseline to week 24 in the EORTC QLQ-C30 global health status/QoL and all the functional domains (Figure 4A), as well as in many of the individual subscales (Figure 4B). There was no improvement in the

Table 2 Treatment-Emergent Adverse Events Regardless of Causality (Safety Population, $n = 66$)

	All Grades, *n* (%)	Grade 3 or 4, *n* (%)[a]
Nonhematologic AEs occurring in ≥10% of patients		
Peripheral edema	20 (30.3)	1 (1.5)
Diarrhea	17 (25.8)	2 (3.0)
Fatigue	17 (25.8)	2 (3.0)
Nausea	14 (21.2)	2 (3.0)
Upper respiratory tract infection	13 (19.7)	0
Abdominal pain	12 (18.2)	2 (3.0)
Headache	9 (13.6)	0
Vomiting	9 (13.6)	2 (3.0)
Dizziness	8 (12.1)	0
Night sweats	8 (12.1)	0
Pyrexia	8 (12.1)	0
Hyperuricemia	7 (10.6)	2 (3.0)
New-onset hematologic AEs		
Bruising (ecchymosis, contusion)	14 (21.2)	0
Laboratory values		
Anemia[b]	15 (22.7)	13 (19.7)
Thrombocytopenia	16 (24.2)	13 (19.7)[c]

Abbreviation: AE = adverse event.
[a] Among the nonhematologic grade 3 or 4 AEs, all were grade 3 except for the 2 patients who reported grade 4 hyperuricemia.
[b] Of 25 patients (37.9%) who were transfusion dependent at baseline, 1 patient (4.0%) was transfusion independent by end of study; of 41 patients (62.1%) who were transfusion independent at baseline, 5 patients (12.2%) were transfusion dependent by end of study.
[c] Grade 3/4 events of thrombocytopenia led to dose reduction in 4 patients (6.1%), dose interruption in 3 (4.5%), and dose discontinuation in 1 (1.5%).

subscale of constipation, diarrhea, or financial difficulties at week 24. Sample sizes were too small to make meaningful conclusions beyond week 24 for the endpoints of palpable spleen length, PGIC, and EORTC QLQ-C30 (results not shown).

A population PK analysis compared ruxolitinib plasma concentration data collected during this study (250 samples from 41 patients) to data from the final PK model (2-compartment disposition model with first-order absorption, absorption lag time, and linear elimination) from the COMFORT-I and -II studies.[18,26] No significant differences in ruxolitinib PK were observed in patients with MF and baseline platelet count of 50 –100 × 10^9/L, compared with baseline platelet count ≥100 × 10^9/L.

Safety and Tolerability

Treatment-emergent adverse events (TEAEs), regardless of causality, in the safety population ($n = 66$) are presented in Table 2. Overall, 93.9% ($n = 62$) of patients had a TEAE. TEAEs led to dose interruption in 17 patients (25.8%; most commonly thrombocytopenia [$n = 3$], abdominal pain [$n = 2$], nausea [$n = 2$], decreased neutrophil count [$n = 2$]), dose reduction in 7 patients (10.6%; thrombocytopenia [$n = 4$], abdominal pain [$n = 1$], diarrhea [$n = 1$], pneumonia [$n = 1$]), and dose discontinuation in 4 patients (6.1%; retroperitoneal hemorrhage [$n = 1$], metastatic lung adenocarcinoma [$n = 1$], chronic myelomonocytic leukemia [$n = 1$], thrombocytopenia [$n = 1$]). No TEAE led to patients withdrawing from the study.

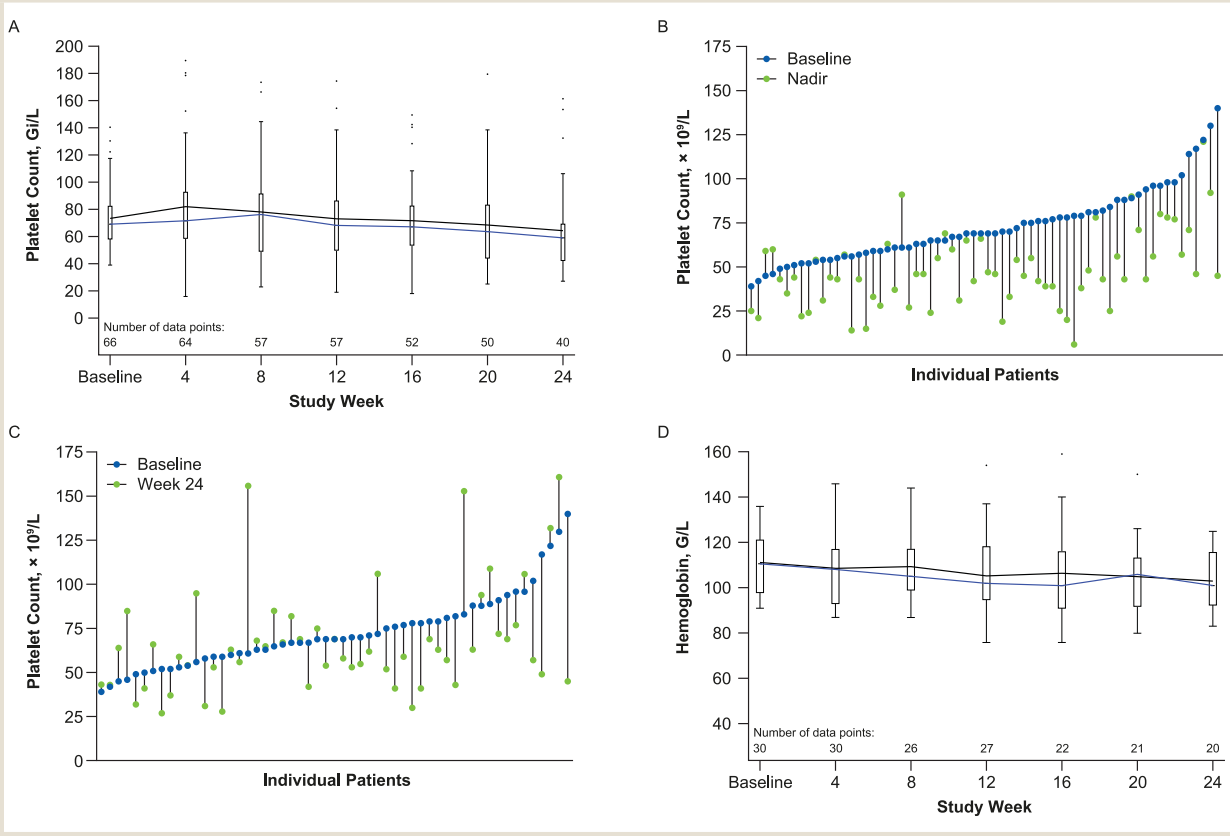
The most common nonhematologic TEAEs (incidence ≥20%) were peripheral edema (30.3%), diarrhea (25.8%), fatigue (25.8%), and nausea (21.2%); new-onset any-grade hematologic AEs included thrombocytopenia (24.2%), anemia (22.7%), and bruising (21.2%). Grade 3/4 anemia and thrombocytopenia were each reported in 13 patients (19.7%). Grade 3/4 thrombocytopenia events led to dose reduction in 4 patients (6.1%), dose interruption in 3 patients (4.5%), and dose discontinuation in 1 patient (1.5%). Fourteen patients (21.2%) had hemorrhagic events, most commonly epistaxis ($n = 6$ [9.1%]). 6 patients had grade 2 or higher hemorrhagic events, including grade 2 epistaxis ($n = 3$ [4.5%]), grade 2 hematochezia ($n = 1$ [1.5%]), grade 2 rectal hemorrhage ($n = 1$ [1.5%]), and grade 4 retroperitoneal hemorrhage ($n = 1$ [1.5%]).

The median (range) platelet count over time (Figure 5A) generally remained stable through week 24 (baseline [$n = 66$], 69.0 [39.0 – 140.0] × 10^9/L; at week 24 [$n = 55$], 62.0 [27.0 –161.0] × 10^9/L). Changes in platelet counts for individual patients from baseline to nadir ($n = 66$) and baseline to week 24 ($n = 55$) are presented in Figure 5B and 5C. Mean hemoglobin levels over time were also stable through week 24 in patients who did not receive red blood cell transfusions during the study (Figure 5D).

An ad hoc analysis demonstrated nonsignificant differences in baseline hemoglobin, baseline DIPSS, and week 24 percentage change in spleen volume between patients with a ≥20 × 10^9/L increase in platelet count at week 24 ($n = 8$) and all other patients ($n = 58$).

Serious TEAEs were reported in 21 patients (31.8%), most commonly pneumonia ($n = 4$), anemia ($n = 3$), abdominal pain ($n = 2$), and dizziness ($n = 2$). 2 patients died during the study; causes of death were chronic obstructive pulmonary disease ($n = 1$

Figure 5 Changes in hematologic parameters. (A) Platelet count over time. (B, C) Changes in individual platelet counts from baseline to nadir and baseline to week 24, respectively. (D) Hemoglobin levels over time in patients who did not receive red blood cell transfusions during the study. For panels A and D, blue lines indicate median over time and the gray lines indicate mean over time; only selected study weeks are shown and are calculated based on laboratory assessment dates not on normal study weeks.



[day 154]) and natural causes ($n = 1$ [day 67]); neither death was deemed treatment-related.

Discussion

In this final analysis of study INCB 18424-258, patients with MF ($n = 66$) and a low baseline platelet count (median, 69.0 × 10^9/L) were treated with the JAK1/2 inhibitor ruxolitinib starting at 5 mg BID with gradual titration based on response and hematologic parameters. By week 24, ruxolitinib 10 mg BID was the most common titrated dose schedule (38.5% [20/52]); most patients receiving this dose achieved clinically meaningful reductions in spleen volume (72.7% [8/11] achieved ≥35% reduction) and improvements in MF-related symptoms (44.1% [15/34] achieved ≥50% improvement in TSS). Notably, an ad hoc analysis indicated that improvement in platelets ≥20 × 10^9/L from baseline to week 24 did not seem to correlate with baseline hemoglobin, baseline DIPSS, or change in spleen volume at week 24. Observed AEs were consistent with the established safety profile from prior clinical trials of ruxolitinib.[20,27] Grade 3/4 events of thrombocytopenia were infrequent (13/66; 19.7%) and most were manageable with dose adjustments; no patient discontinued the study because of thrombocytopenia. Although an extended treatment phase was included to collect 3 years of data per the FDA, only 23 patients entered the extension phase, as most patients discontinued from the study (per the original protocol wherein the trial was to end at week 24) and transitioned to commercial ruxolitinib.

In the current study, final titrated doses of ≥10 mg BID resulted in clinically meaningful reductions in spleen volume and improvements in symptom burden. These results are consistent with findings from other clinical trials evaluating the use of ruxolitinib in patients with MF with baseline thrombocytopenia. The 48-week analysis of EXPAND (phase 1b, dose-finding study) in 69 patients with MF and with a baseline platelet count of 50 –99 × 10^9/L, identified a maximum safe starting dose of ruxolitinib 10 mg BID.[28] Similarly, in EXPAND, improvements were observed from baseline to week 24 in spleen and symptom assessments with the 10-mg BID dose.[28]

A post hoc analysis of the JUMP study (phase 3b, open-label, single-arm expanded access study) showed that although patients with MF and low baseline platelet counts (<100 × 10^9/L; $n = 138$) experienced improvements in spleen length and MF symptoms, response rates were lower than those with a higher baseline platelet

count because of the lower dose received by these patients (up-titration from the 5-mg BID starting dose were not protocol-mandated).[29] Similarly, the current study demonstrated greater improvements in spleen length and symptom burden in patients titrated to the 10-mg BID dose than the 5-mg BID dose.

Fedratinib is the only other approved treatment for patients with intermediate-2 or high-risk primary or secondary MF, with a recommended dose of 400 mg QD for patients with a baseline platelet count $\geq 50 \times 10^9$/L.[30] The phase 3, placebo-controlled JAKARTA study evaluated the efficacy and safety of first-line fedratinib in patients with MF ($n = 96$), and included 14 patients with a low baseline platelet count ($<100 \times 10^9$/L).[31,32] Treatment with fedratinib 400 mg QD yielded a symptom response rate (≥50% improvement from baseline to end of cycle 6) of 31% (4/13 patients) and a spleen volume response rate (≥35% improvement from baseline to end of cycle 6) of 36% (5/14 patients).[32,33]

Thrombocytopenia is an expected on-target hematologic AE of both ruxolitinib and fedratinib due to JAK2 inhibition, and similar rates of grade 3/4 thrombocytopenia have been observed for ruxolitinib and fedratinib (13% and 12%, respectively).[15,30] However, the toxicity profiles of ruxolitinib and fedratinib are different, possibly as a result of fedratinib's broader kinase inhibition profile,[34] including FMS-like tyrosine kinase 3 and thiamine transporter-2 inhibitory activity.[34,35] High rates of gastrointestinal toxicity (including nausea, vomiting, and diarrhea), anemia, and transaminase elevations are reported with fedratinib.[31] Fedratinib also has a boxed warning regarding the risk of serious and fatal encephalopathy, including Wernicke's encephalopathy.[30]

Gradual dose titration from 5 mg BID in the current study appeared to have avoided the initial drop in hemoglobin levels observed in COMFORT-I, in which patients commenced therapy with ruxolitinib 15 mg or 20 mg BID.[18] Additionally, a dose of 10 mg BID in the current study was not associated with significant changes in hemoglobin levels through week 24 in patients who did not receive transfusions.

Conclusion

In conclusion, the results from this study suggest that a lower starting dose of ruxolitinib with gradual up-titration and subsequent dose optimization based on hematologic parameters and response is safe and efficacious in patients with MF and platelet counts of $50 – 100 \times 10^9$/L.

Clinical Practice Points

- Based on an interim analysis of the phase 2 study INCB 18424-258, the ruxolitinib label includes a recommended starting dose of ruxolitinib 5 mg twice daily (BID) for patients with myelofibrosis (MF) with baseline platelet count of 50 to $< 100 \times 10^9$/L, with recommendations for dose modifications for thrombocytopenia and upward dose titration for insufficient response.
- In this final analysis of study INCB 18424-258, involving patients with MF ($n = 66$) and low baseline platelet count (median, 69.0×10^9/L), ruxolitinib 10 mg BID was the most common titrated dose schedule (38.5% [20/52]) by week 24. Improvements in spleen length and symptom burden were greater in patients titrated to the 10 mg BID dose, compared to patients receiving the 5 mg BID dose.
- A dose of 10 mg BID was not associated with significant changes in hemoglobin levels through week 24 in patients who did not receive transfusions. Grade 3/4 events of thrombocytopenia were infrequent (19.7% [13/66]) and most were manageable with dose adjustments; no patient discontinued the study because of thrombocytopenia.
- Results from this study suggest that a starting dose of ruxolitinib 5 mg BID, with gradual up-titration and subsequent dose optimization based on hematologic parameters and response, is safe and efficacious in patients with MF and platelet counts of $50 – 100 \times 10^9$/L.

Authors' Contributions

Moshe Talpaz: Conceptualization, Design. Moshe Talpaz, Josef Prchal, Lawrence Afrin, Murat Arcasoy, Solomon Hamburg, Srdan Verstovsek: Data acquisition. Jason Clark, Deanna Kornacki, Philomena Colucci: Data analysis. All authors: Writing – original draft, review & editing.

Data Availability Statement

Incyte Corporation (Wilmington, DE) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase 1 studies) for which the product and indication have been approved on or after January 1, 2020 in at least 1 major market (eg, US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2021.10.016.

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