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Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I

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Running head: COMFORT-I 2-year follow-up

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ABSTRACT

COMFORT-I is a randomized, double-blind, placebo-controlled trial of the Janus kinase 1/Janus kinase 2 inhibitor ruxolitinib in 309 patients with intermediate-2 or high-risk myelofibrosis. This analysis of COMFORT-I describes the long-term efficacy and safety of ruxolitinib (median follow-up, 2 years). Spleen volume was measured by magnetic resonance imaging, and quality of life was evaluated using the EORTC QLQ-C30. Overall survival was determined according to randomized treatment group. At the time of this analysis, 100 of 155 patients randomized to ruxolitinib were still receiving treatment. All patients randomized to placebo crossed over to ruxolitinib or discontinued within 3 months of the primary analysis (median time to crossover, 41 weeks). Mean spleen volume reductions in the ruxolitinib group were 31.6% at week 24 and 34.9% at week 96; improvements in quality of life measures were also maintained. Improved survival was observed for ruxolitinib (n=27 deaths) *versus* placebo (n=41 deaths) (hazard ratio=0.58; 95% confidence interval: 0.36, 0.95; *P*=.03). The incidence of new-onset grade 3 or 4 anemia and thrombocytopenia decreased over time to levels observed in patients receiving placebo. These data indicate that ruxolitinib treatment provides durable reductions in spleen volume and improvements in quality of life and suggest a continued survival advantage for ruxolitinib over placebo.

Trial registration: Clinicaltrials.gov identifier: NCT00952289

Key words: ruxolitinib, myelofibrosis, overall survival, splenomegaly

Introduction

Myeloproliferative neoplasms include primary myelofibrosis (PMF) as well as polycythemia vera (PV) and essential thrombocythemia (ET)—both of which can progress to MF (i.e. post PV-MF and post ET-MF).[1,2] Patients with MF often present with splenomegaly, burdensome symptoms (e.g. night sweats, fever, fatigue, bone pain and pruritus) and cytopenias.[3,4]

The pathogenesis of MF is linked, in part, to overactive signaling of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, resulting from various mechanisms and mutations. Although the most common and most recognized mutation in MF is *JAK2V617F*, this mutation is not required for the disease or overactive JAK-STAT activity. Some patients have other mutations that activate JAK-STAT signaling (such as *MPL* and mutations in *JAK2* exon 12), and it is thought that as yet unidentified mechanisms are responsible for JAK-STAT activation in the remaining patients. Elevated proinflammatory cytokines (signaling through JAK1 and JAK2) are a consistent feature of patients with MF.[5,6] Consequently, the development of agents that inhibit the JAK-STAT pathway has been a focus of current MF research.

Until recently, no approved treatments were available for MF and, with the exception of allogeneic stem cell transplantation, treatment involved nonspecific management of symptoms and signs with limited benefit.[2] Ruxolitinib is an oral JAK1 and JAK2 inhibitor approved by the US Food and Drug Administration for the treatment of intermediate or high-risk MF, including PMF, post PV-MF and post ET-MF. Approval was based in part on the results of 2 phase III clinical trials—the COntrolled MyeloFibrosis Study with ORal JAK Inhibitor Therapy (COMFORT)-I (www.clinicaltrials.gov NCT00952289)[7] and COMFORT-II (www.clinicaltrials.gov NCT00934544).[8] These studies compared ruxolitinib treatment with placebo and best available therapy, respectively, and both achieved their primary endpoint: significantly more patients receiving ruxolitinib experienced a ≥35% reduction in spleen volume from baseline as measured by magnetic resonance imaging (MRI) or computed tomography (CT) at week 24 in COMFORT-

I and at week 48 in COMFORT-II. In addition, ruxolitinib was superior to placebo and best available therapy in improving MF-related symptoms and measures of quality of life (QoL). Improved survival for patients treated with ruxolitinib over placebo was also observed at a median follow-up of 51 weeks (hazard ratio [HR]=0.50; 95% confidence interval [CI]: 0.25, 0.98; *P*=.04).[7] The objective of the current analysis was to describe the longer-term outcomes associated with ruxolitinib treatment in COMFORT-I, with 1 year of additional follow-up beyond previously published data.

Methods

Patients

Inclusion and exclusion criteria have been described elsewhere.[7] Briefly, eligible patients were ≥18 years of age with PMF, post PV-MF or post ET-MF according to the 2008 World Health Organization criteria[1] and intermediate-2 or high-risk MF by International Prognostic Scoring System.[3]

The protocol was approved by the institutional review board at each participating site. The study was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent. Data were collected by the investigators and analyzed by the sponsor, Incyte Corporation. All authors had access to the data.

Study design

Patients were randomized 1:1 to receive ruxolitinib or placebo orally twice daily (BID). Ruxolitinib starting doses were determined according to baseline platelet count: for patients with baseline platelets 100-200×10^9/L, the starting dose of ruxolitinib was 15 mg BID; for patients

with baseline platelets >200×10^9/L, the starting dose of ruxolitinib was 20 mg BID. Doses were individualized during the study to ensure safety and enhance efficacy.[7]

Patients receiving placebo were eligible for crossover to ruxolitinib during the primary analysis period based on specific criteria as previously described.[7] All patients were eligible for crossover following completion of the primary analysis, when all patients had completed 24 weeks and at least half had completed 36 weeks of randomized treatment, at which time the study was unblinded.

Evaluations

Imaging (MRI or CT) for spleen volume assessment was obtained at baseline and weeks 12, 24, 36, 48, 60 and 72, and every 24 weeks thereafter.[7] MF symptom burden was measured daily up to week 24 with the modified MF Symptom Assessment Form version 2.0 electronic diary. QoL was evaluated with the self-administered European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) at baseline and each study visit.[7] Adverse events were reported using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

The data cutoff for this analysis of the ongoing COMFORT-I study was March 1, 2012 (1 year after a prospectively defined safety follow-up). Kaplan-Meier analysis was used to evaluate the durability of the spleen response and to assess overall survival (OS) (intention-to-treat analysis). The Cox proportional hazards model was used to calculate HR and 95% CI and log-rank test for *P* value (unadjusted for repeat analyses).

Percentage changes in spleen volume from baseline to weeks 24 and 48 and percentage change in Total Symptom Score (TSS) from baseline to week 24 were evaluated by

titrated dose, which was the average dose in the last 12 weeks prior to the assessment: <10 mg BID (average total daily dose ≤15 mg), 10 mg BID (>15-25 mg), 15 mg BID (>25-35 mg), 20 mg BID (>35-45 mg) and >20 mg BID (>45 mg).

Percentage changes from baseline in hemoglobin, platelet count and the proportion of patients who received RBC transfusions during the previous 4 weeks were assessed. The incidence of worsening grade 3 and grade 4 anemia and thrombocytopenia, as defined by laboratory values, was assessed at 6-month intervals.

Results

Patients

Patient baseline characteristics have been reported previously; all were similar between randomized groups with the exception of age (median age: ruxolitinib, 66 years; placebo, 70 years; *P*<.05).[7] Patient disposition is shown in *Online Supplementary Figure 1*. At the time of this analysis (median follow-up, 102 weeks), 100 of the 155 (64.5%) patients originally randomized to receive ruxolitinib were still receiving treatment, 111 of the 154 (72.1%) patients originally randomized to receive placebo had crossed over to ruxolitinib, and no patient was receiving placebo. The median follow-up for the 100 patients in the ruxolitinib arm who were still on treatment was 103 weeks (range, 94-126 weeks), and 90% had a follow-up of more than 96 weeks. All patients randomized to receive placebo crossed over to ruxolitinib or discontinued the study within 3 months of the primary analysis, with a median time to crossover of 41.1 weeks. The discontinuation rate in the placebo group was 16.3% in the first 6 months. In the ruxolitinib group, rates of discontinuation decreased over time (10.3% in the first 6 months and 6.0% in the last 6 months of the 2-year follow-up).

Starting and titrated doses

Most ruxolitinib dose adjustments were implemented because of changes in platelet counts and occurred early in the course of treatment. Seventy percent of patients had at least one dose adjustment (increase or decrease) in the first 12 weeks of ruxolitinib therapy; the majority of patients had a dose reduction (52%) within this time frame. By week 24, patients initiating ruxolitinib at doses of 15 mg BID (n=55) and 20 mg BID (n=100) were titrated to a mean dose of ~10 and 15-20 mg BID, respectively (median doses, 10 mg and 20 mg BID, at which time mean doses began to stabilize) (Figure 1).

Efficacy

Mean spleen volume reduction in patients randomized to receive ruxolitinib observed at week 24 was maintained over time: 31.6% reduction at week 24 and 34.9% at week 96. Among the ruxolitinib-treated patients who achieved at least a 35% reduction in spleen volume at some point during the study (90/155 [58%] patients), 64% maintained this response for at least 2 years (Figure 2A). Most patients (>80%) who reached the threshold of a 35% reduction maintained at least a 10% reduction in spleen volume throughout the follow-up period—a reduction associated with clinically meaningful improvements in MF-related symptoms and QoL measures.[9] Consistent with this observation, improvements in functional and symptom subscales of the EORTC QLQ-C30 observed at week 24 were also maintained with long-term ruxolitinib therapy (*Online Supplementary Figure 2*). TSS was not collected beyond week 24.

At the time of their last assessment during the follow-up period, most patients in the ruxolitinib group had some reduction in spleen volume from baseline (Figure 2B; mean reduction, 27.5%).[7] Patients who crossed over from placebo to ruxolitinib (median follow-up on ruxolitinib after crossover, ~14 months) also experienced similar percentage reductions in spleen volume from the time of crossover to last assessment (mean, 30.0%); however, because patients in the crossover group experienced spleen growth prior to receipt of ruxolitinib, spleen

volume changes relative to their original baseline values were not as robust (mean reduction, 18.0%).

Because the majority of patients had some adjustment of their ruxolitinib dose early in the course of therapy (mainly in the first 8-12 weeks), the changes in spleen volume and TSS were evaluated by titrated dose at week 24. Changes in spleen volume by titrated dose were also assessed at week 48. Patients titrated to doses of 10 mg BID and higher experienced similar improvements in MF-related symptoms, whereas those titrated to doses of ≥15 mg BID (or continued on their starting dose) had moderately greater improvements in spleen volume than those titrated to 10 mg BID (Figure 3).

Survival

At the time of this analysis, 27 deaths were reported in the ruxolitinib group and 41 in the placebo group. The causes of death are listed in the *Online Supplementary Table 1.* Consistent with the OS analysis reported previously (median follow-up, 51 weeks),[7] ruxolitinib treatment continued to be associated with an OS advantage relative to placebo with 1 additional year of follow-up (HR=0.58; 95% CI: 0.36, 0.95; *P*=.03) (Figure 4). The 1- and 2-year survival probabilities for patients randomized to ruxolitinib were 92% (95% CI: 87%, 95%) and 82% (95% CI: 75%, 88%), respectively. In contrast, the 1- and 2-year survival probabilities for patients randomized to placebo (including those who crossed over to ruxolitinib) were 85% (95% CI: 79%, 90%) and 73% (95% CI: 65%, 80%), respectively. Because baseline age differed between the 2 treatment arms (median age: ruxolitinib, 66 years; placebo, 70 years), an age-adjusted survival analysis was also performed. The results (HR=0.61; 95% CI: 0.37, 0.99; *P*=.04) were similar to those of the unadjusted analysis.

Safety

Dose-dependent anemia and thrombocytopenia were the most common adverse events in the ruxolitinib group, but these events rarely led to discontinuation. At the time of the primary analysis, there was 1 discontinuation for each event in the ruxolitinib group and in the placebo group[7]; in the subsequent follow-up during ruxolitinib treatment, there was 1 discontinuation for anemia (median exposure, 107 weeks). The incidence of new-onset grade 3 or 4 anemia and thrombocytopenia decreased over time (Figure 5) to levels observed with placebo treatment (prior to crossover).

Mean platelet counts decreased over the first 8-12 weeks of the study and remained relatively stable over the course of long-term therapy (Figure 6A). Mean hemoglobin values reached a nadir of 10-12% below baseline between weeks 8 and 12 and stabilized over time to a new steady state slightly below baseline by week 24, and then remained stable throughout the remaining follow-up (Figure 6B). This pattern of hemoglobin recovery to a new steady state over time was also observed in patients who did not receive RBC transfusions post-baseline (*Online Supplementary Figure 3*). Consistent with these changes in hemoglobin over time, the proportion of ruxolitinib-treated patients receiving RBC transfusions decreased to the level seen with placebo by week 36 and remained stable thereafter (*Online Supplementary Figure 4*).

In the first 6 months of treatment, the most common nonhematologic adverse events that occurred more frequently in the ruxolitinib group compared with the placebo group were ecchymosis, headache and dizziness (Table 1). In the ruxolitinib group, the incidence of new-onset nonhematologic adverse events in the subsequent 6-month intervals was lower than that observed in the initial 6-month time frame. Most events were grade 1 or 2 (*Online Supplementary Table 2*).

Two patients originally randomized to receive ruxolitinib developed acute myeloid leukemia (AML) at the time of the primary analysis, as described previously[7]; no further cases of AML were reported in this group. Of the patients originally randomized to placebo, 2 developed AML. In one patient with a history of squamous cell carcinoma, bone marrow biopsy at the time

of crossover showed 11% blasts and loss of chromosome 5 and deletion of 17p; this patient developed AML 21 days later. The second patient with a history of cervical cancer entered the study with abnormal cytogenetics and had a blast cell count of 4% prior to crossover; this patient developed AML 174 days after crossover.

As reported in the primary analysis, an evaluation of grade 3 and 4 adverse events and serious adverse events upon treatment discontinuation or interruption (including assessment of cardiac or respiratory events) showed no pattern of a withdrawal syndrome (*Online Supplementary Tables 3-4*).

Discussion

In this 2-year follow-up of COMFORT-I, ruxolitinib treatment was generally well tolerated in patients with MF and provided durable and clinically meaningful reductions in spleen volume and improvements in QoL. Furthermore, these data suggest a continued survival advantage for ruxolitinib over placebo. Similar findings were reported from a 2-year follow-up of patients in COMFORT-II, showing consistent reductions in spleen volume over time with ruxolitinib therapy and a survival benefit compared with best available therapy.[10]

Because all patients in the placebo group had discontinued or were receiving ruxolitinib at the time of this analysis, the COMFORT-I study provides insight into potential consequences of delayed ruxolitinib therapy. The analysis of OS evaluated patients by randomized treatment group regardless of crossover status. With a median time to crossover of 41 weeks, those originally randomized to receive placebo had shortened survival compared with those randomized to receive ruxolitinib (HR=0.58). Based on these data, patients with MF who have symptoms or splenomegaly may benefit from earlier intervention with ruxolitinib.

Thrombopoietin and erythropoietin signal exclusively through JAK2 and, consequently, dose-dependent thrombocytopenia and anemia were expected with ruxolitinib treatment. These cytopenias were manageable with dose adjustments and RBC transfusions and rarely led to

treatment discontinuation. Dose reductions were mandated for protocol-defined decreases in platelet counts, and most dose reductions occurred over the first 8-12 weeks of treatment. During this time frame, mean platelet counts declined and subsequently remained stable. Also, initial decreases in hemoglobin levels in the first 8-12 weeks recovered to near baseline levels, and RBC transfusion requirements followed a similar pattern. In a separate study of patients with MF and baseline platelet counts 50-100×10^9/L, a starting dose of 5 mg BID with subsequent titration to 10 mg BID resulted in stable platelet counts and mean hemoglobin values over time.[11,12] Therefore, it is likely that dose reductions contributed to the recovery in hemoglobin values observed in COMFORT-I.

Mean titrated doses for patients in the 15-mg (baseline platelet count 100-200×10^9/L) and 20-mg (>200×10^9/L) BID groups were ~10 mg and 15-20 mg BID, respectively, by week 24—a time at which most patients started to maintain a stable dose. At week 24, patients titrated to doses of 10 mg BID experienced improvements in symptoms similar to those receiving higher titrated doses, whereas spleen volume reductions were slightly less than those observed at higher doses. Titrated doses at less than 10 mg BID resulted in smaller improvements in spleen volume and symptoms but provided greater benefit than placebo.

MF is a progressive chronic myeloproliferative neoplasm that has a profound impact on the daily lives of patients. In the absence of a cure for MF, some patients will require chronic therapy. The results of this long-term follow-up of patients in COMFORT-I underscore the importance of appropriate patient monitoring and individualized dose adjustments, particularly early in the course of treatment, to achieve long-term benefits with ruxolitinib therapy. Consistent with earlier reports, these data reinforce the durable efficacy and tolerability of ruxolitinib in patients with MF and suggest a continued survival advantage for ruxolitinib over placebo.

Authorship and Disclosures

SV, RAM and HMK performed the research and contributed to concept design, data collection and data interpretation. JG, VG, JFD, JVC, MWND, CBM, RTS, MT, EFW, JHH, MOA, EOH, RML, RP and AR performed research and contributed to data collection and interpretation. RSL and VS contributed to research design and data interpretation. WS performed statistical analyses. KV contributed to research design. SE-V contributed to data interpretation. All authors assisted with drafting the manuscript and/or critical revision of the content and approved the final manuscript submitted. Author conflict of interests are as follows**:** SV has received grant support through his institution from Incyte Corporation, Exelixis, Celgene, NS Pharma, Infinity Pharmaceuticals, SBIO, Lilly Oncology, AstraZeneca, Geron, Bristol-Myers Squibb, YM BioSciences, Gilead and Roche. RAM has received research funding from Incyte Corporation, Lilly, Sanofi, NS Pharma and YM Bioscience. JG has received consultancy, honoraria and support for travel to meetings for the study from Incyte Corporation. RSL is an employee of Incyte Corporation and owns stock in Incyte Corporation. VG has received grant support through his institution from Incyte Corporation and Novartis, consulting fees from Incyte Corporation and Novartis and lecture fees from Novartis. JFD has no potential conflicts of interest. JVC has received consulting fees from Incyte Corporation. MWND has received consulting fees from Bristol-Myers Squibb, Novartis, Incyte Corporation, Teva and Ariad and grant support through his institution from Bristol-Myers Squibb, Gilead and Novartis. CBM has received grant support through her institution, consulting fees and lecture fees from Novartis, and payments for development of educational presentations from Incyte Corporation and Novartis. RTS has received grant support through his institution from Incyte Corporation, Ariad, Sanofi and Novartis and lecture fees from Incyte Corporation and holds stock in Incyte Corporation, both individually and through his institution. MT has received membership on an entity's board of directors or advisory committees from Novartis, Bristol-Myers Squibb, Sanofi, Teva and Pfizer and research funding from Novartis, Bristol-Myers Squibb, Ariad, Sanofi and

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Table 1. Incidence of new-onset nonhematologic adverse events regardless of causality.

Patients (%)	0 to less than 6 mo		6 to less than 12 mo	12 to less than 18 mo	18 to less than 24 mo	24 mo or more
	RUX	PBO	RUX	RUX	RUX	RUX
Fatigue	25.7	31.9	5.8	7.9	8.4	5.4
Diarrhea	23.2	22.9	5.7	5.7	3.4	10.3
Ecchymosis	18.1	9.2	5.5	4.3	1.6	0
Dyspnea	16.8	16.1	4.5	6.4	4.8	4.9
Peripheral edema	16.7	23.2	5.3	6.3	4.8	5.1
Headache	15.5	5.0	0.9	2.1	1.5	0
Dizziness	14.2	6.5	5.3	6.5	3.2	4.5
Nausea	12.8	17.0	5.2	3.0	0	8.0
Constipation	12.0	12.1	4.2	5.9	4.3	8.7
Vomiting	12.0	10.8	2.5	1.0	0	4.0
Pain in extremity	11.4	10.7	8.5	4.3	1.6	0
Pyrexia	11.3	6.4	2.4	3.7	6.7	8.2
Insomnia	10.7	10.7	4.2	2.0	2.8	4.1
Abdominal pain	10.1	40.7	5.0	4.9	0	8.2
Arthralgia	10.1	7.9	2.5	5.0	0	4.4

PBO: placebo; *RUX:* ruxolitinib.

For each time interval, the effective sample size of the interval was used as the denominator. The effective sample size=the number of patients at risk at the beginning of the interval plus half of the censored patients during the time interval. Because all patients receiving placebo had either crossed over to ruxolitinib treatment or discontinued from the study after the primary analysis and therefore only a subset of these patients had data beyond 6 months, the incidence of adverse events after 6 months was summarized only for patients originally randomized to receive ruxolitinib.

Figure 1. **Mean daily dose of ruxolitinib over time in all patients randomized to ruxolitinib and by initial ruxolitinib dose.** *BID*: twice daily; BL; baseline.

Figure 2. Durability of spleen volume reduction and individual percentage changes from baseline with ruxolitinib therapy. (A) Kaplan-Meier curve of durability of spleen volume reduction. In patients maintaining at least a 35% reduction in spleen volume (dark green line), duration of response was defined as the time from first 35% reduction to less than 35% reduction and 25% increase from nadir. Among patients achieving a 35% reduction in spleen volume, most patients maintained at least a 10% reduction from baseline (light green line), with duration defined as the time from first 35% reduction to less than 10% reduction from baseline. (B) Percentage change in spleen volume in individual patients from original baseline to last available spleen volume measurement in the ruxolitinib group (median follow-up, 24 months) and placebo group after crossover to ruxolitinib treatment (median follow-up after crossover, 14 months).

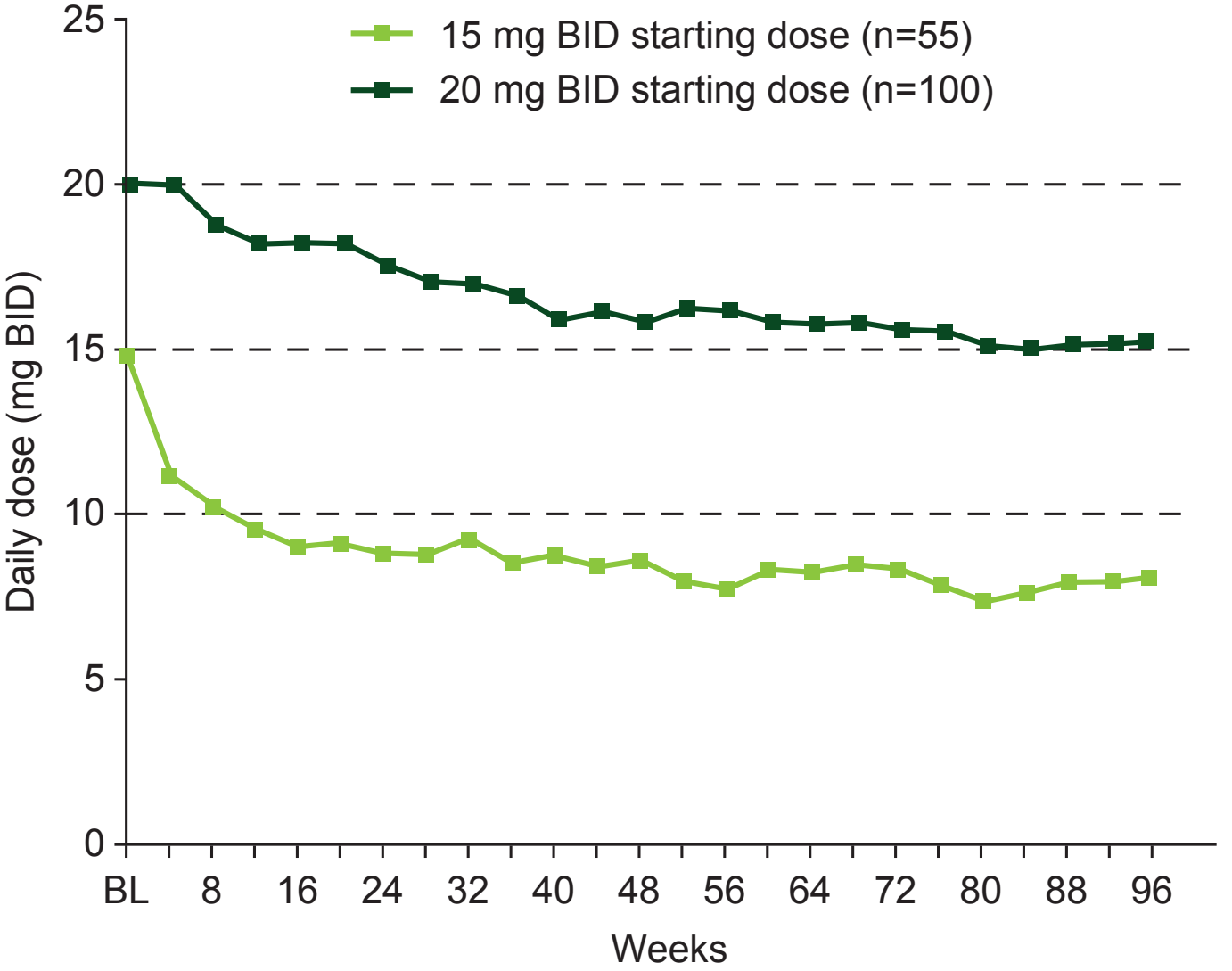
Figure 3. Mean percentage changes from baseline in spleen volume at weeks 24 and 48 and mean percentage changes in Total Symptom Score by titrated dose. Titrated dose was defined as the average dose patients received in the last 12 weeks before the time of assessment. *BID:* twice daily.

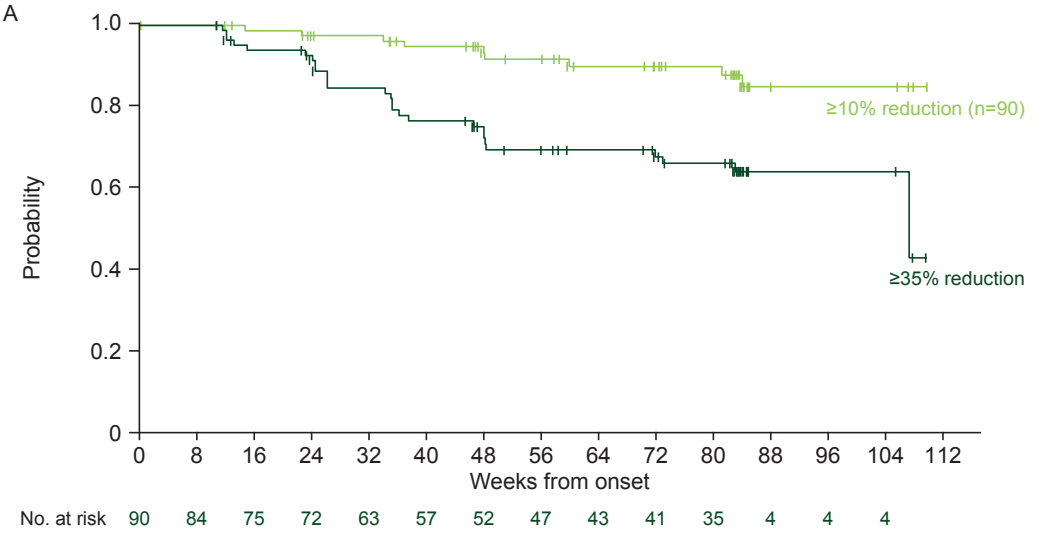
Figure 4. Overall survival by randomized treatment group (intent-to-treat population). *CI:* confidence interval; *HR:* hazard ratio.

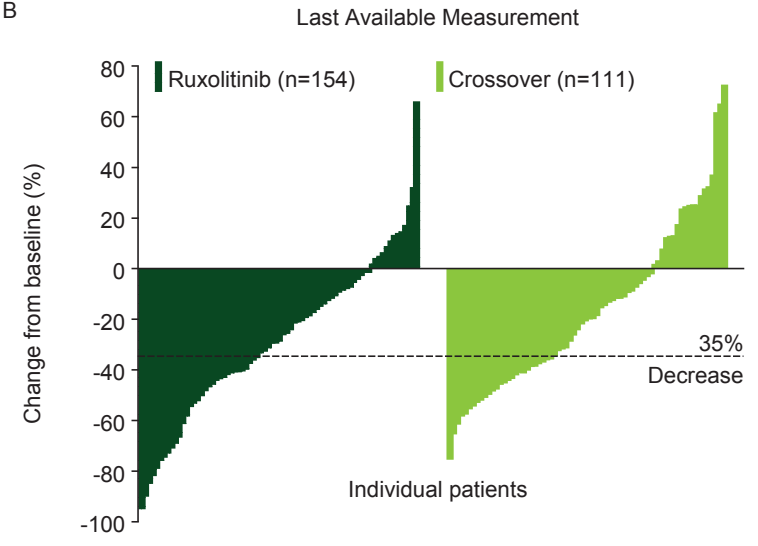
Figure 5. **Incidence of new-onset grade 3 and 4 anemia and thrombocytopenia over time.** The incidence of anemia and thrombocytopenia after 6 months was summarized only for patients originally randomized to receive ruxolitinib because all patients receiving placebo had

either crossed over to ruxolitinib or discontinued from the study after the primary analysis. Incidence was calculated using the life table method based on the time to first worsening grade 3 or 4 event censored at the time of discontinuation or data cutoff (earlier of the two); the effective sample size was used as the denominator.

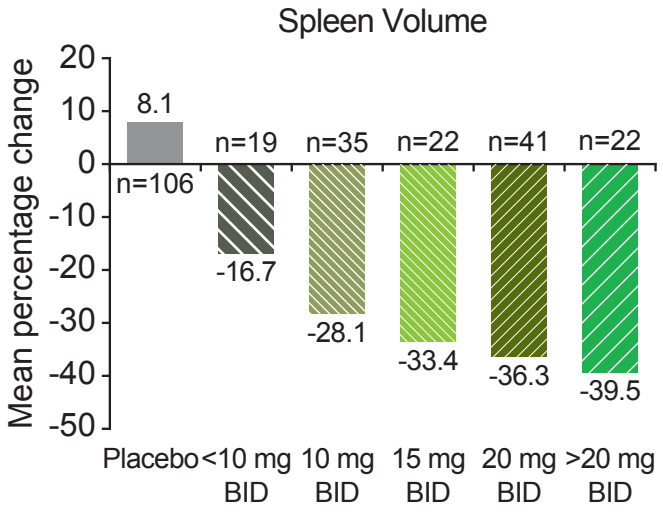
Figure 6. Mean percentage change (± standard error of the mean) in (A) platelet counts and (B) hemoglobin levels from baseline over time. *BL:* baseline.

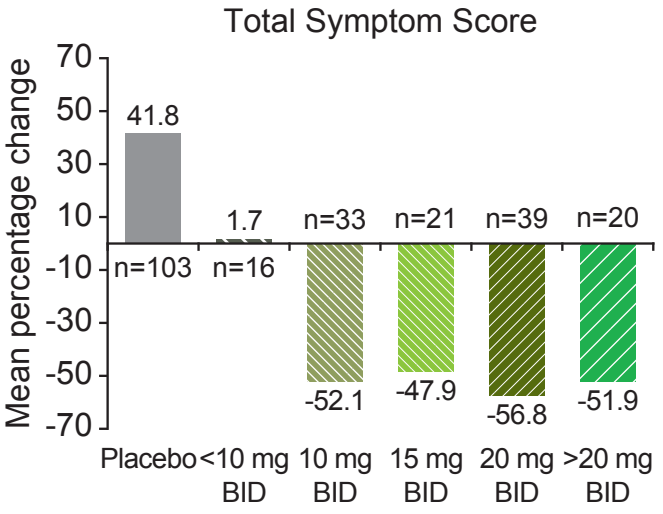

15 mg BID starting dose (n=55)
20 mg BID starting dose (n=100)
Daily dose (mg BID)
25
20
15
10
5
0
BL
8
16
24
32
40
48
56
64
72
80
88
96
Weeks


A
1.0
0.8
0.6
0.4
0.2
0
Probability
≥10% reduction (n=90)
≥35% reduction
0
8
16
24
32
40
48
56
64
72
80
88
96
104
112
Weeks from onset
No. at risk
90
84
75
72
63
57
52
47
43
41
35
4
4
4

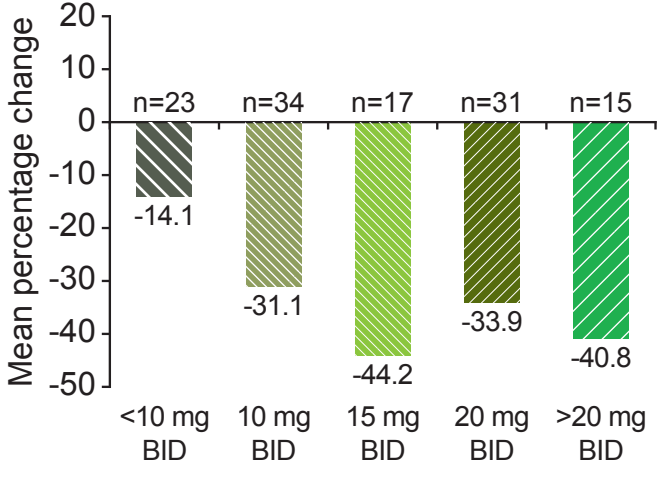

B
Last Available Measurement
Ruxolitinib (n=154)
Crossover (n=111)
80
60
40
20
0
-20
-40
-60
-80
-100
Change from baseline (%)
35%
Decrease
Individual patients

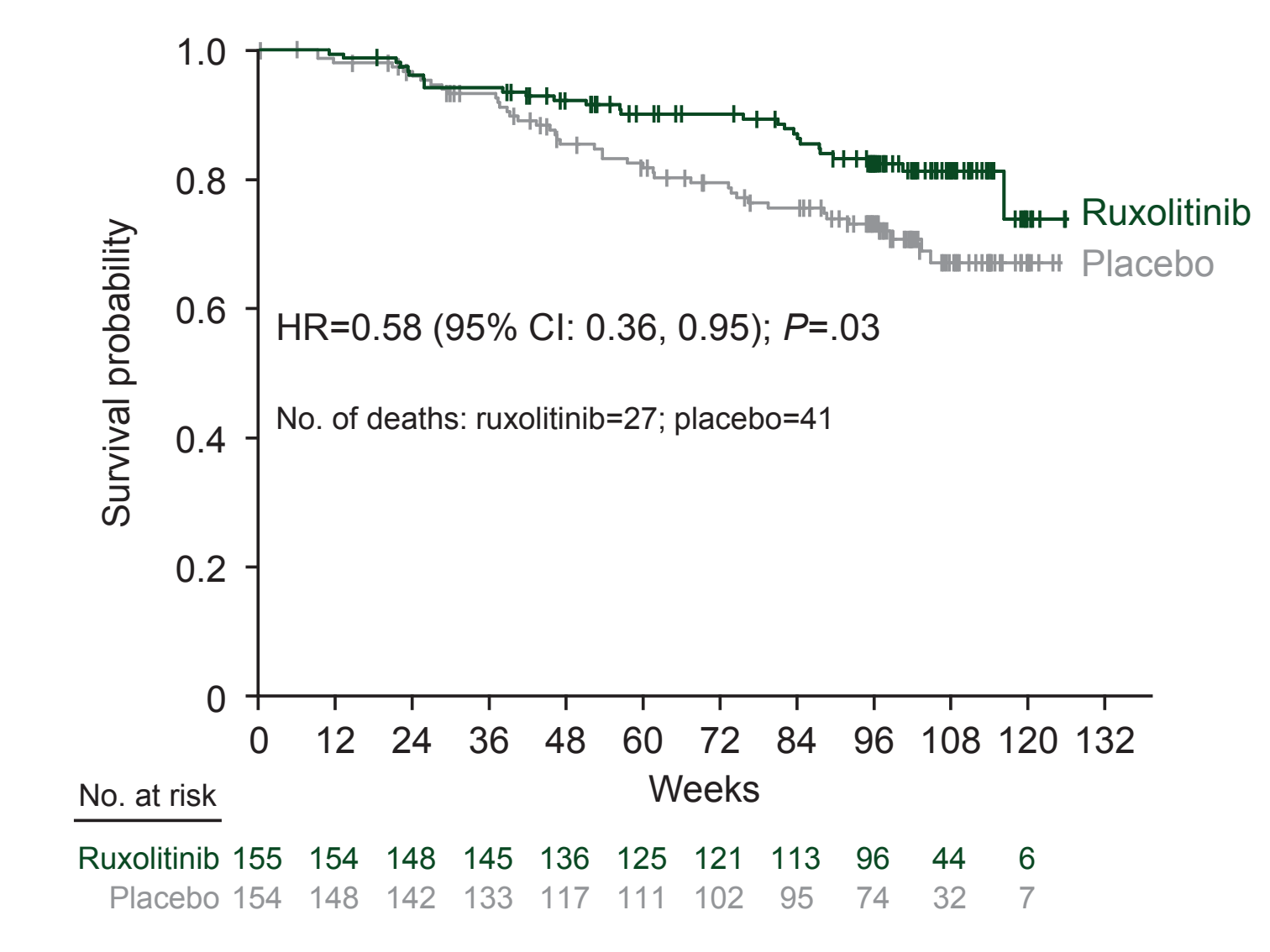
Week 24

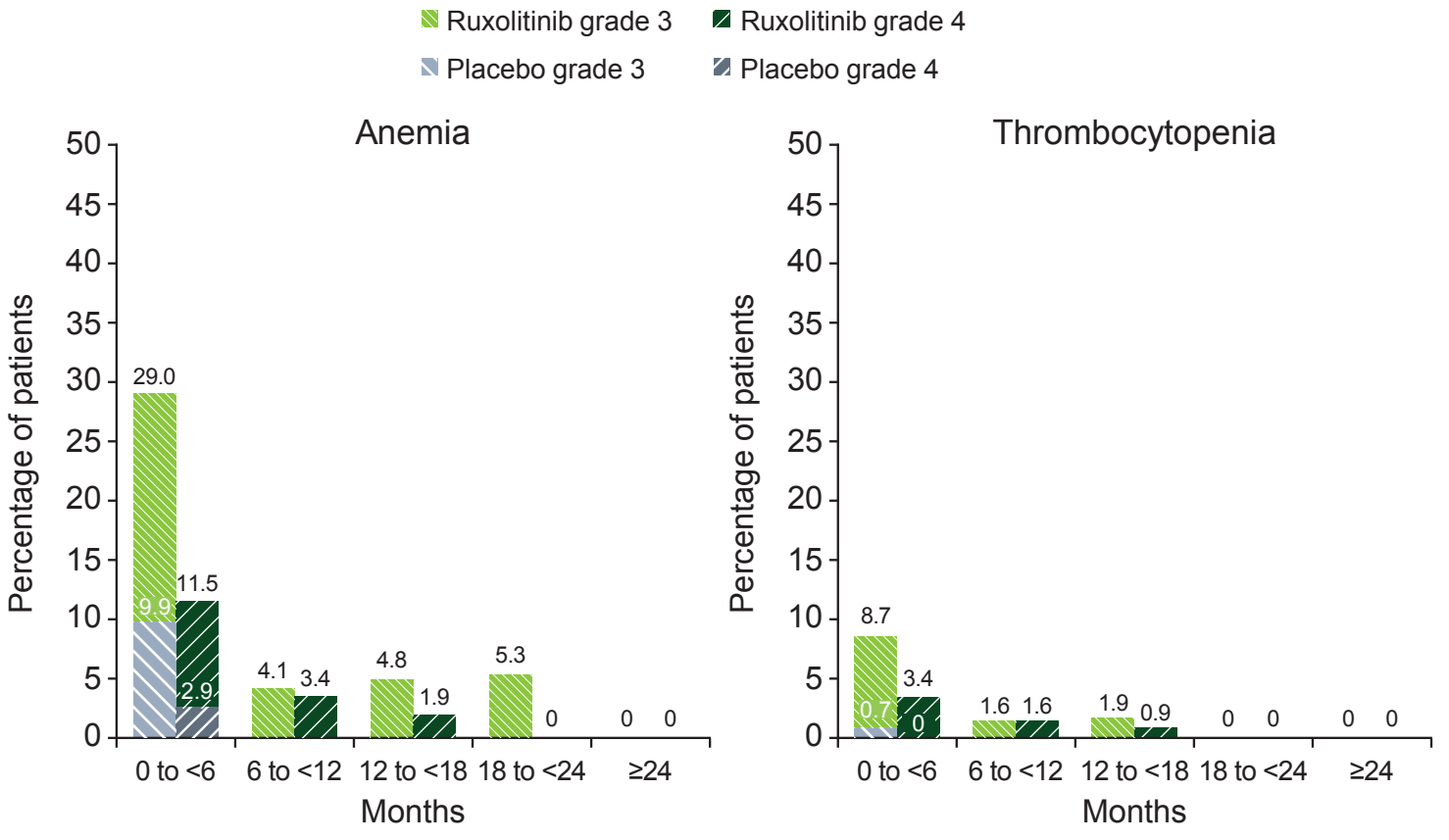


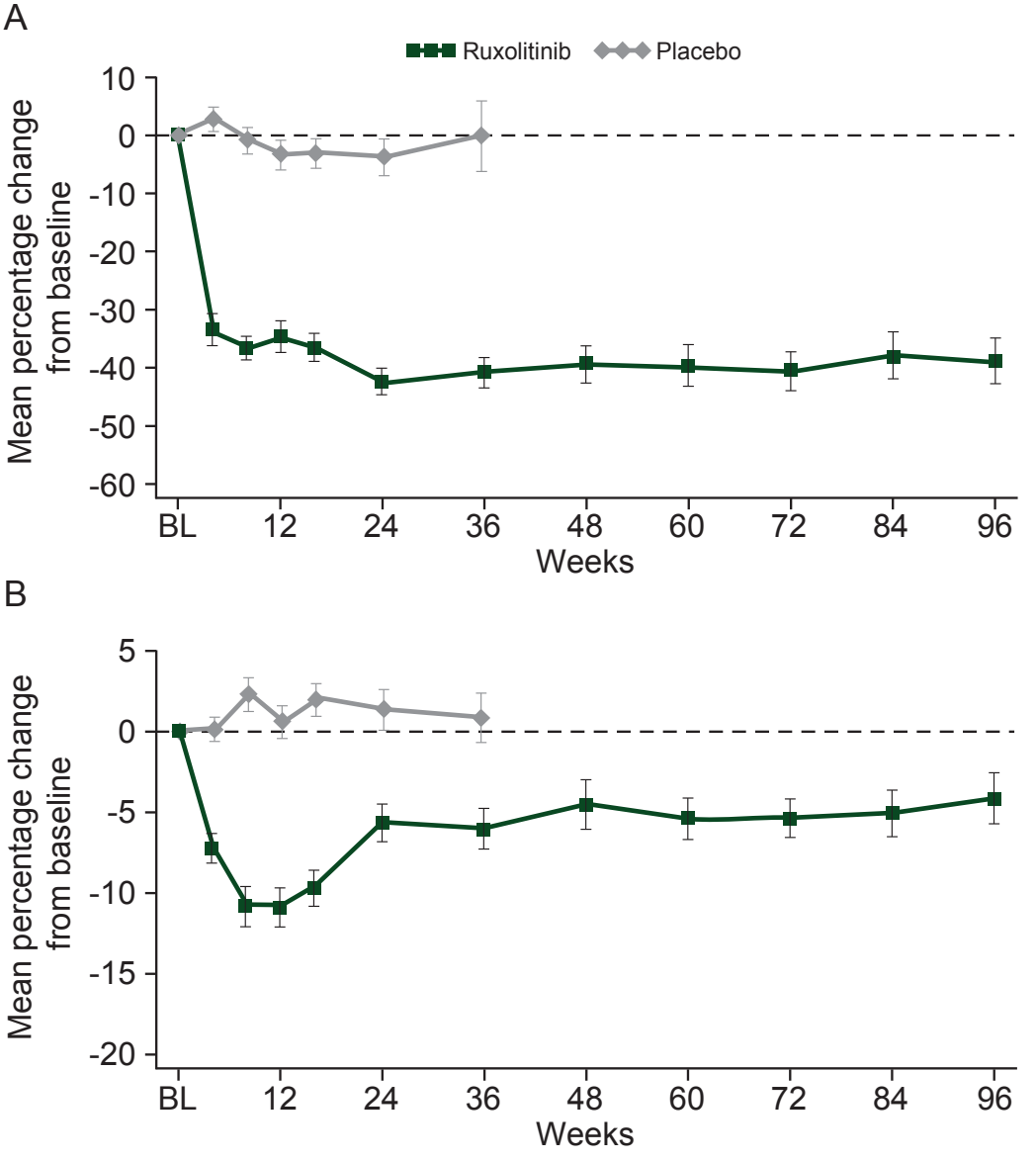


Week 48




1.0
0.8
0.6
0.4
0.2
0
Survival probability
HR=0.58 (95% CI: 0.36, 0.95); P=.03
No. of deaths: ruxolitinib=27; placebo=41
Ruxolitinib
Placebo
0 12 24 36 48 60 72 84 96 108 120 132
Weeks
No. at risk
Ruxolitinib 155 154 148 145 136 125 121 113 96 44 6
Placebo 154 148 142 133 117 111 102 95 74 32 7


Ruxolitinib grade 3
Ruxolitinib grade 4
Placebo grade 3
Placebo grade 4
Anemia
Percentage of patients
50
45
40
35
30
25
20
15
10
5
0
29.0
9.9
11.5
2.9
4.1
3.4
4.8
1.9
5.3
0
0
0
0 to <6
6 to <12
12 to <18
18 to <24
≥24
Months
Thrombocytopenia
Percentage of patients
8.7
0.7
3.4
0
1.6
1.6
1.9
0.9
0
0
0
0
0 to <6
6 to <12
12 to <18
18 to <24
≥24
Months


A
Ruxolitinib
Placebo
Mean percentage change from baseline
10
0
-10
-20
-30
-40
-50
-60
BL
12
24
36
48
60
72
84
96
Weeks
B
Mean percentage change from baseline
5
0
-5
-10
-15
-20
BL
12
24
36
48
60
72
84
96
Weeks

COMFORT-I 2-Year Follow up

Online Supplement

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Detailed Methods

Patients

Inclusion and exclusion criteria have been described elsewhere.(1) Briefly, eligible patients were 18 years of age or older with PMF, post PV-MF or post ET-MF according to the 2008 World Health Organization criteria(2) and intermediate-2 or high-risk MF by International Prognostic Scoring System.(3) Patients also had to have a palpable spleen length ≥5 cm, platelet count ≥100×10^9/L and were refractory to or not candidates for available therapy.(1)

The protocol was approved by the institutional review board at each participating site. The study was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent. Data were collected by the investigators and analyzed by the sponsor, Incyte Corporation. All authors had access to the data.

Study design

Patients were randomized 1:1 to receive ruxolitinib or placebo orally twice daily. Ruxolitinib starting doses were determined according to baseline platelet count: for patients with baseline platelets 100-200×10^9/L, the starting dose of ruxolitinib was 15 mg twice daily; for patients with baseline platelets >200×10^9/L, the starting dose of ruxolitinib was 20 mg twice daily. Doses were individualized to ensure safety and enhance efficacy. Doses could be increased for inadequate efficacy in patients with adequate platelet and absolute neutrophil counts. Dose holds were required for platelet counts <50×10^9/L or absolute neutrophil count <0.5×10^9/L, and dose adjustments were required for platelet counts <125×10^9/L (depending on the dose at the time of platelet count decline). Dose holds or adjustments were not required for anemia, although dose

adjustments and red blood cell (RBC) transfusions were permitted. Patients receiving placebo were eligible for crossover to ruxolitinib before week 24 if they had a ≥25% increase from baseline in spleen volume accompanied by worsening early satiety with weight loss or worsening spleen-related pain requiring narcotic analgesics; after week 24, an asymptomatic increase in spleen volume ≥25% alone was sufficient for crossover. All patients were eligible for crossover following completion of the primary analysis, when all patients had completed 24 weeks and at least half had completed 36 weeks of randomized treatment, at which time the study was unblinded.(1)

Evaluations

Spleen volume was measured by MRI or CT (for patients in whom MRI was contraindicated or not available). Imaging for spleen volume assessment was obtained at baseline and weeks 12, 24, 36, 48, 60 and 72, and every 24 weeks thereafter. MF symptom burden was measured daily up to week 24 with the modified MF Symptom Assessment Form version 2.0 electronic diary. The following symptoms were assessed on a scale of 0 (absent) to 10 (worst imaginable): night sweats, itching (pruritus), abdominal discomfort, pain under the ribs on the left side, feeling of fullness (early satiety), muscle/bone pain and inactivity. The sum of the individual symptom scores, excluding the score for inactivity, was used to determine the total symptom score (TSS). Patient QoL was evaluated with the self-administered European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) at baseline and each study visit. Adverse events were reported using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.(1)

Statistical analysis

The data cutoff for this analysis of the ongoing COMFORT-I study was March 1, 2012 (1 year after a prospectively defined safety follow-up). Kaplan-Meier analysis was used to evaluate the durability of the spleen response and to assess OS. The analysis of durability of spleen volume reduction included all patients who had at least one spleen volume assessment demonstrating a ≥35% reduction from baseline. Duration of spleen volume response was defined as the time from first reduction of at least 35% from baseline to time of <35% reduction from baseline that was also a 25% increase over nadir. OS was determined according to original randomized treatment regardless of treatment crossover for all patients in the intent-to treat population and was censored at last known date alive. The Cox proportional hazards model was used to calculate HR and 95% CI and log-rank test for *P* value (unadjusted for repeat analyses).

Percentage changes in spleen volume from baseline to week 24 and 48 and percentage change in TSS from baseline to week 24 were evaluated by titrated dose. Titrated dose was defined as the average dose in the last 12 weeks prior to the assessment: <10 mg twice daily (average total daily dose ≤15 mg), 10 mg twice daily (>15-25 mg), 15 mg twice daily (>25-35 mg), 20 mg twice daily (>35-45 mg) and >20 mg twice daily (>45 mg).

Percentage changes from baseline in hemoglobin and platelet count as well as the proportion of patients who received any units of RBC transfusions during the previous 4 weeks were also assessed. In patients randomized to receive ruxolitinib, percentage changes from baseline in hemoglobin levels were also evaluated, including only patients who did not receive post-baseline RBC transfusions before week 36. The incidence of worsening grade 3 and grade 4 anemia and thrombocytopenia, as defined by laboratory values, was assessed at 6-month intervals (0-<6, 6-<12, 12-<18, 18-<24 and ≥24 months). Because all patients receiving placebo

had either crossed over to ruxolitinib treatment or discontinued from the study after the primary analysis and therefore only a subset of these patients had data beyond 6 months, the incidence of anemia and thrombocytopenia after 6 months was summarized only for patients originally randomized to receive ruxolitinib. Incidence was calculated using the life table method based on the time to first worsening grade 3 or 4 event censored at the time of discontinuation or data cutoff (earlier of the two); the effective sample size was used as the denominator. The incidence of overall and grade ≥3 nonhematologic events and treatment discontinuation rates by exposure interval were calculated in a similar manner. Median exposure time was calculated based on time to discontinuation using reverse Kaplan-Meier method.

References

1. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012 Mar 1;366(9):799-807.
2. Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organizaiton criteria and point-of-care diagnostic algorithms. Leukemia. 2008 Jan;22(1);14-22.
3. Cervantes F, Dupriez B, Pereira A, Passamonti F, Reilly JT, Morra E, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009 Mar 26;113(13);2895-901.

Supplementary Table 1. Causes of death by randomized treatment allocation.*

Cause of Death	**Ruxolitinib (N=155)**	**Placebo (N=154)**
Acute myeloid leukemia	2	3
Anastomotic hemorrhage		1
Cerebral hemorrhage		1
Completed suicide		1
Congestive heart failure resulting from pneumonia		1
Death	1	
Disease progression	4	7
Graft versus host disease	1	
Gastrointestinal hemorrhage		2
Leukemia or underlying leukemia	1	1
Intestinal perforation		1
Intra-abdominal hemorrhage		1
Muscular weakness	1	
MDS disease progression		1
Metastatic colon cancer		1
Multi-organ failure		1
Myelofibrosis	1	3
Myelofibrosis with possible transformation to acute myelogenous leukemia and pneumonia		1
Myeloproliferative disease		1

Non-small cell lung cancer metastatic	1	
Pneumonia	1	1
Pneumonia; septic shock	1	
Pneumonia, multi organ failure	1	
Renal failure	1	
Respiratory failure	1	
Road traffic accident		1
Shock hemorrhagic		1
Shock, respiratory and cardiac failure; hemorrhage following splenectomy	1	
Sepsis or septic shock	3	3
Splenic infarction	1	
Staphylococcal infection		1
Subdural hematoma	1	1
Surgical complications		1
Unknown	4	5
Total	**27**	**41**

*Documentation of cause of death was not available for all patients.

Supplementary Table 2. Incidence of new-onset grade 3/4 nonhematologic adverse events regardless of causality.

Patients (%)	0 to less than 6 months		6 to less than 12 months	12 to less than 18 months	18 to less than 24 months	24 months or more
	RUX	PBO	RUX	RUX	RUX	RUX
Fatigue	6.1	6.4	0	0.9	0	0
Pneumonia	4.1	3.6	1.6	3.6	1.3	0
Abdominal pain	2.7	9.9	1.6	0	1.2	3.6
Arthralgia	2.0	0	0	0	0	0
Diarrhea	2.0	0	0	0	0	0
Dyspnea	1.4	2.9	0.8	0	2.5	0
Fall	1.4	1.4	0	0.9	0	0
GI hemorrhage	1.4	0.7	0.8	0	0	0
Hyperuricemia	1.4	2.2	0	0	0	0
Muscular weakness	1.4	0	0	0	0	0
Septic shock	1.4	0	0	0	0	0
Hypotension	0.7	0.7	0	0	2.4	0
Hypoxia	0.7	0.7	0.8	0	2.5	0
Pain in extremity	0.7	0	1.5	0	0	0
Acute renal failure	0.7	2.2	0	0	2.5	3.6
Sepsis	0.7	0.7	0	0.9	2.5	0

Hyperglycemia	0	0	0	0	2.4	0

GI: gastrointestinal; *PBO:* placebo; *RUX:* ruxolitinib.

For each time interval, the effective sample size of the interval was used as the denominator. The effective sample size = the number of patients at risk at the beginning of the interval, plus half of the censored patients during the time interval.

Supplementary Table 3. Adverse events (grade 3/4 and serious) reported during treatment interruption.

Adverse event	Ruxolitinib (N=89)		Placebo (N=62)	
	Grade 3/4	**Serious**	**Grade 3/4**	**Serious**
Total patients with AEs, n (%)	8 (9.0)	3 (3.4)	7 (11.3)	2 (3.2)
Anemia	5 (5.6)	1 (1.1)	0	0
Abdominal pain	1 (1.1)	0	0	0
Delirium	1 (1.1)	0	0	0
Disseminated intravascular coagulation	1 (1.1)	0	0	0
Fatigue	1 (1.1)	0	0	0
GI hemorrhage	1 (1.1)	1 (1.1)	0	0
Renal failure acute	1 (1.1)	0	1 (1.6)	0
Thrombocytopenia	1 (1.1)	0	1 (1.6)	0
Nausea	1 (1.1)	0	0	0
Urosepsis	0	1 (1.1)	0	0
Asthenia	0	0	1 (1.6)	0
Atrial fibrillation	0	0	1 (1.6)	0
Gastric varices	0	0	1 (1.6)	0
Gout	0	0	1 (1.6)	1 (1.6)
Hepatic encephalopathy	0	0	1 (1.6)	1 (1.6)
Hyperbilirubinemia	0	0	1 (1.6)	0

Splenic infarction	0	0	1 (1.6)	0
Ventricular dysfunction	0	0	1 (1.6)	0
Vomiting	1 (1.1)	1 (1.1)	1 (1.6)	1 (1.6)
Ascites	0	0	1 (1.6)	0
Hydronephrosis	0	0	1 (1.6)	0
Febrile neutropenia	0	1 (1.1)	0	0
Pulmonary edema	0	0	0	1 (1.6)

AE: adverse event; *GI:* gastrointestinal.

Numbers reported are percentages of those who had a treatment interruption (not the total study population).

Supplementary Table 4. Adverse events (grade 3/4 and serious) reported after study discontinuation*.

Adverse event	Ruxolitinib (N=55)		Placebo (N=40)	
	Grade 3/4	**Serious**	**Grade 3/4**	**Serious**
Total patients with AEs, n (%)	20 (36.4)	20 (36.4)	20 (50)	15 (30)
Thrombocytopenia	4 (7.3)	2 (3.6)	2 (5.0)	0
Acute myeloid leukemia	2 (3.6)	2 (3.6)	0	0
Dyspnea	2 (3.6)	1 (1.8)	2 (5.0)	0
Pneumonia	2 (3.6)	3 (5.5)	4 (10.0)	2 (5.0)
Splenic infarction	2 (3.6)	2 (3.6)	0	0
Abdominal pain	1 (1.8)	0	4 (10.0)	2 (5.0)
Cardiac arrest	1 (1.8)	0	0	0
Clostridial infection	1 (1.8)	1 (1.8)	0	0
Death	1 (1.8)	1 (1.8)	0	0
Disease progression	1 (1.8)	1 (1.8)	2 (5.0)	2 (5.0)
Disseminated intravascular coagulation	1 (1.8)	0	0	0
Edema	1 (1.8)	0	0	0
Epistaxis	1 (1.8)	0	0	0
Fatigue	1 (1.8)	1 (1.8)	3 (7.5)	0
Hemoglobin decreased	1 (1.8)	0	0	0
Hepatosplenomegaly	1 (1.8)	1 (1.8)	0	0

Hyperglycemia	1 (1.8)	0	0	0
Hypokalemia	1 (1.8)	0	0	0
Hypotension	1 (1.8)	0	0	0
Hypoxia	1 (1.8)	0	2 (5.0)	0
Lactic acidosis	1 (1.8)	0	0	0
Malnutrition	1 (1.8)	0	1 (2.5)	0
Muscular weakness	1 (1.8)	1 (1.8)	0	0
Myocardial infarction	1 (1.8)	1 (1.8)	0	0
Platelet count increased	1 (1.8)	0	0	0
Portal vein thrombosis	1 (1.8)	0	0	0
Pulmonary edema	1 (1.8)	0	1 (2.5)	1 (2.5)
Pyrexia	1 (1.8)	2 (3.6)	0	0
Renal failure	1 (1.8)	1 (1.8)	2 (5.0)	2 (5.0)
Renal failure acute	1 (1.8)	0	0	0
Respiratory failure	1 (1.8)	1 (1.8)	0	0
Sepsis	1 (1.8)	1 (1.8)	1 (2.5)	1 (2.5)
Septic shock	1 (1.8)	1 (1.8)	0	0
Splenic hemorrhage	1 (1.8)	1 (1.8)	0	0
Subdural hematoma	1 (1.8)	1 (1.8)	2 (5.0)	2 (5.0)
Transaminases increased	1 (1.8)	0	0	0
Transient ischemic attack	1 (1.8)	1 (1.8)	0	0
Abdominal pain upper	0	1 (1.8)	0	0
Agitation	0	0	1 (2.5)	0

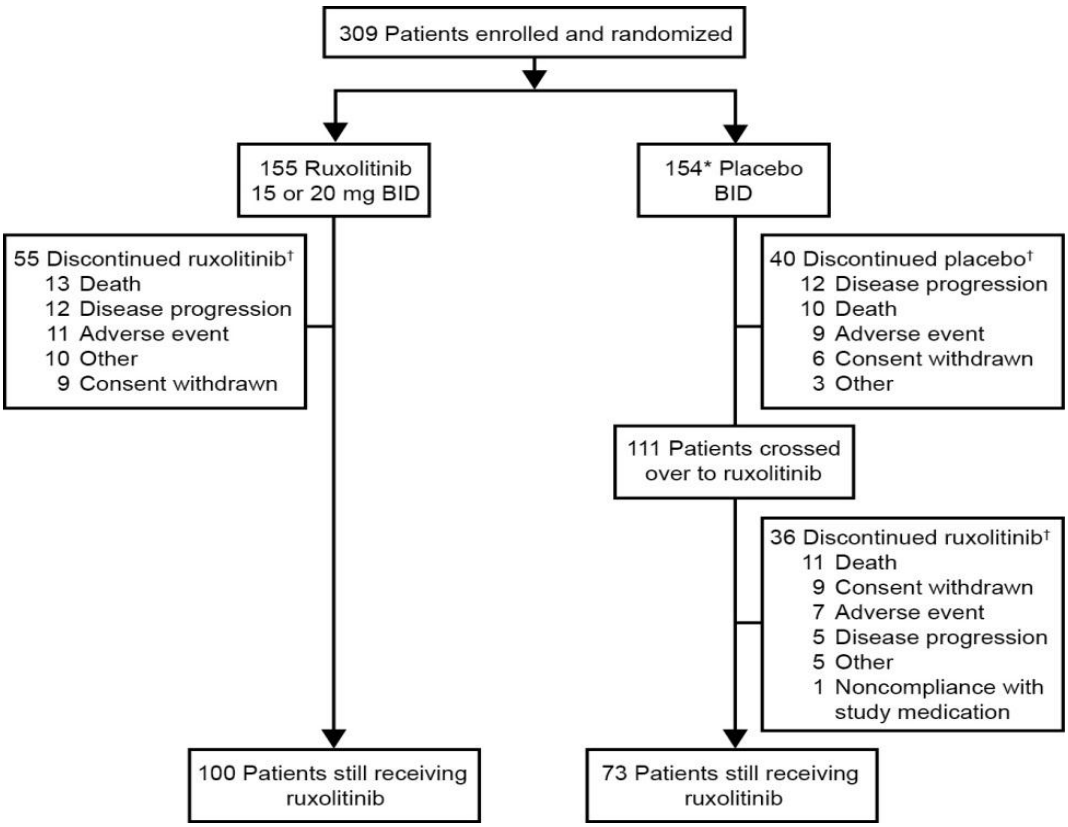
Anemia	0	1 (1.8)	0	0
Arthralgia	0	0	1 (2.5)	0
Atrial fibrillation	0	0	1 (2.5)	1 (2.5)
Blood amylase increased	0	0	1 (2.5)	0
Blood magnesium decreased	0	0	1 (2.5)	0
Cardiac failure	0	0	1 (2.5)	1 (2.5)
Cellulitis	0	1 (1.8)	0	0
Chronic obstructive pulmonary disease	0	0	1 (2.5)	0
Colitis	0	0	1 (2.5)	1 (2.5)
Dehydration	0	1 (1.8)	2 (5.0)	1 (2.5)
Diarrhea	0	1 (1.8)	0	0
Fall	0	1 (1.8)	2 (5.0)	1 (2.5)
Febrile neutropenia	0	0	1 (2.5)	0
GI hemorrhage	0	0	1 (2.5)	1 (2.5)
Hyponatremia	0	0	2 (5.0)	0
Intestinal ischemia	0	0	1 (2.5)	1 (2.5)
Leukocytosis	0	0	1 (2.5)	1 (2.5)
Lipase increased	0	0	1 (2.5)	0
Loss of consciousness	0	0	1 (2.5)	0
Multi-organ failure	0	0	1 (2.5)	1 (2.5)
Musculoskeletal pain	0	0	1 (2.5)	0
Myelofibrosis	0	0	1 (2.5)	1 (2.5)

Postoperative wound infection	0	1 (1.8)	0	0
Pulmonary embolism	0	0	2 (5.0)	1 (2.5)
Splenic hematoma	0	0	1 (2.5)	1 (2.5)
Splenomegaly	0	0	1 (2.5)	0
Staphylococcal infection	0	0	1 (2.5)	1 (2.5)
Tachycardia	0	0	1 (2.5)	0
Urinary tract infection	0	0	1 (2.5)	1 (2.5)
Weight increased	0	0	1 (2.5)	0

AE: adverse event; *GI:* gastrointestinal.

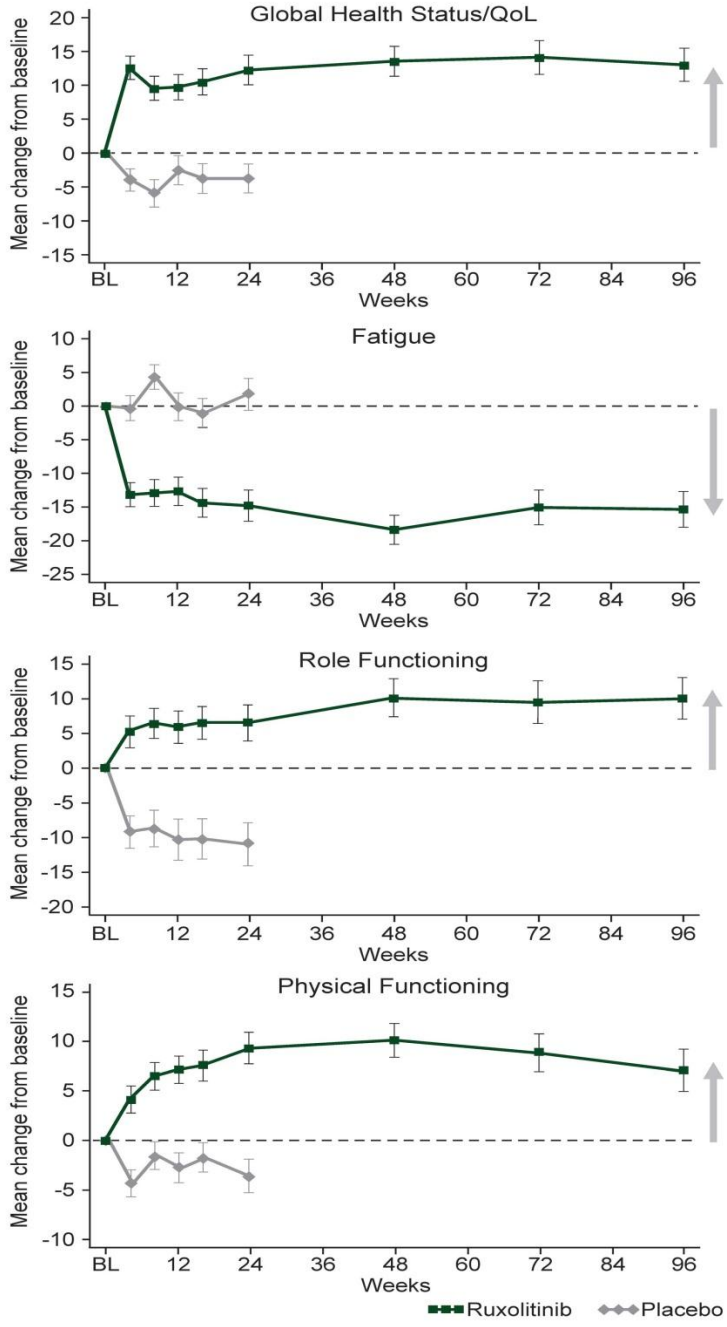
*Numbers reported are percentages of those who discontinued the study (not the total study population).

Supplementary Figure 1. Patient disposition.

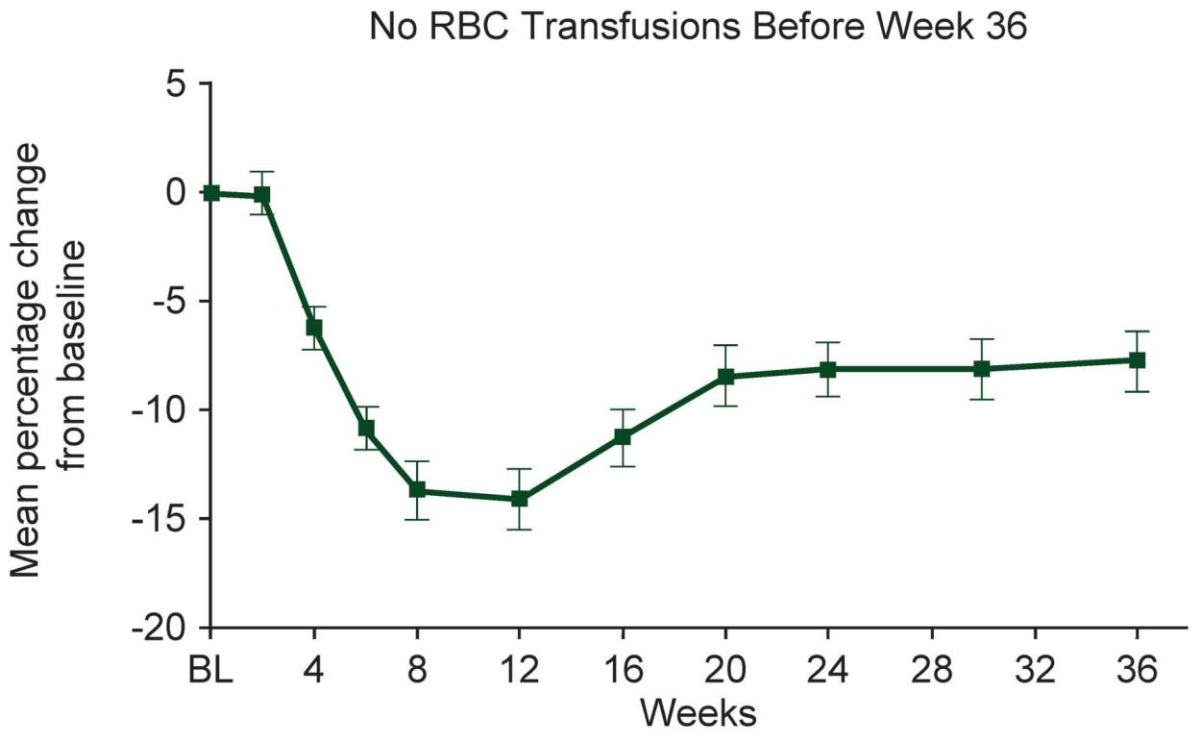


*Three patients were not evaluable for safety but were included in the intent-to-treat analysis of efficacy. †Discontinuations represent absolute numbers unadjusted for differences in exposure. “Other” reasons for discontinuation in the ruxolitinib group: decision to receive transplant (3), refractory to medication (2), patient choice to pursue different treatment, patient entered hospice, investigator decision, worsening symptoms, lack of efficacy; in the placebo group: patient choice (2), patient put on hydroxyurea; and in the crossover group: patient entered hospice, no improvement in blood counts, patient choice, refractory to medication, investigator decision. *BID*: twice daily.

Supplementary Figure 2. Mean changes (±SEM) in EORTC QLQ-C30 scores over time. (A) Global health status/QoL, (B) fatigue symptom score, (C) role functioning, and (D) physical functioning. Arrows indicate direction of improvement. *QoL:* quality of life.



Supplementary Figure 3. Mean percentage change (±SEM) from baseline in hemoglobin levels over time in patients randomized to receive ruxolitinib who completed first 36 weeks of treatment and did not received post-baseline RBC transfusions before week 36. *RBC:* red blood cell.



Supplementary Figure 4. **The proportion of patients receiving RBC transfusions in the prior month by randomized group over time.** *RBC:* red blood cell.