ORIGINAL ARTICLE

A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis

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ABSTRACT

BACKGROUND

Ruxolitinib, a selective inhibitor of Janus kinase (JAK) 1 and 2, has clinically significant activity in myelofibrosis.

METHODS

In this double-blind trial, we randomly assigned patients with intermediate-2 or high-risk myelofibrosis to twice-daily oral ruxolitinib (155 patients) or placebo (154 patients). The primary end point was the proportion of patients with a reduction in spleen volume of 35% or more at 24 weeks, assessed by means of magnetic resonance imaging. Secondary end points included the durability of response, changes in symptom burden (assessed by the total symptom score), and overall survival.

RESULTS

The primary end point was reached in 41.9% of patients in the ruxolitinib group as compared with 0.7% in the placebo group ($P<0.001$). A reduction in spleen volume was maintained in patients who received ruxolitinib; 67.0% of the patients with a response had the response for 48 weeks or more. There was an improvement of 50% or more in the total symptom score at 24 weeks in 45.9% of patients who received ruxolitinib as compared with 5.3% of patients who received placebo ($P<0.001$). Thirteen deaths occurred in the ruxolitinib group as compared with 24 deaths in the placebo group (hazard ratio, 0.50; 95% confidence interval, 0.25 to 0.98; $P=0.04$). The rate of discontinuation of the study drug because of adverse events was 11.0% in the ruxolitinib group and 10.6% in the placebo group. Among patients who received ruxolitinib, anemia and thrombocytopenia were the most common adverse events, but they rarely led to discontinuation of the drug (in one patient for each event). Two patients had transformation to acute myeloid leukemia; both were in the ruxolitinib group.

CONCLUSIONS

Ruxolitinib, as compared with placebo, provided significant clinical benefits in patients with myelofibrosis by reducing spleen size, ameliorating debilitating myelofibrosis-related symptoms, and improving overall survival. These benefits came at the cost of more frequent anemia and thrombocytopenia in the early part of the treatment period. (Funded by Incyte; COMFORT-I ClinicalTrials.gov number, NCT00952289.)

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Investigators and participating centers in the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment I (COMFORT-I) are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2012;366:799-807.

Myelofibrosis, a myeloproliferative neoplasm, is manifested by abnormal blood counts (anemia, thrombocytosis or thrombocytopenia, and leukocytosis or leukopenia), splenomegaly, and debilitating symptoms (e.g., fatigue, weakness, abdominal pain, cachexia, weight loss, pruritus, night sweats, and bone pain), which are thought to be caused by the combined effects of massive splenomegaly and elevated levels of proinflammatory cytokines.[1] Survival ranges from approximately 2 to 11 years, depending on defined prognostic factors.[2] Traditional therapeutic options, including splenectomy, have limited benefit.[3] Although allogeneic stem-cell transplantation may cure myelofibrosis, few patients are eligible for this treatment.

Although the gain-of-function mutation in the gene encoding Janus kinase (JAK) 2 (*JAK2* V617F) is present in approximately 50% of patients with primary myelofibrosis, other mechanisms of direct or indirect activation of the intracellular JAK–signal transducer and activator of transcription (STAT) pathway are known,[4] suggesting that dysregulation of this pathway is a central pathogenic component in myelofibrosis, regardless of the mutational status of JAK2. Also, proinflammatory cytokines that play an important role in myelofibrosis signal through JAK 1 (JAK1) and JAK2.[5] In a phase 1–2 trial of ruxolitinib (INCB018424, Incyte), a potent inhibitor of JAK1 and JAK2,[6,7] patients with myelofibrosis had durable reductions in splenomegaly and improvements in myelofibrosis-related symptoms, regardless of their status with respect to the *JAK2* V617F mutation. To further evaluate the efficacy and safety of ruxolitinib, we conducted the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment I (COMFORT-I), a randomized, double-blind, placebo-controlled trial involving patients with intermediate-2 or high-risk myelofibrosis.

Methods

Patients

Patients were eligible for the study if they were 18 years of age or older and had primary myelofibrosis, post–polycythemia vera myelofibrosis, or post–essential thrombocythemia myelofibrosis according to 2008 World Health Organization criteria,[8] with a life expectancy of 6 months or longer, an International Prognostic Scoring System (IPSS) score[2] (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) of 2 (intermediate-2 risk) or 3 or more (high risk), an Eastern Cooperative Oncology Group performance status[9] of 3 or less (on a scale from 0 to 5, with higher scores indicating greater disability; see the Supplementary Appendix for further details), less than 10% peripheral-blood blasts, an absolute peripheral-blood CD34+ cell count of more than 20×10^6 per liter, a platelet count of 100×10^9 per liter or more, and palpable splenomegaly (≥5 cm below the left costal margin). Patients had disease that was refractory to available therapies, had side effects requiring their discontinuation, or were not candidates for available therapies and had disease requiring treatment. The trial protocol, which describes in detail the inclusion and exclusion criteria and other information about the trial design, as well as the statistical analysis plan, is available at NEJM.org.

Study Oversight

The protocol was approved by the institutional review board at each participating site. The study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice. All patients provided written informed consent.

Data were collected by the academic investigators and analyzed by the sponsor of the study, Incyte. The sponsor, in collaboration with the academic investigators, interpreted the data. The first author and an author who was an employee of the sponsor wrote the initial draft of the manuscript, with assistance from a medical writer who was paid by the sponsor. All the authors contributed to subsequent drafts and made the decision to submit the article for publication. All the authors vouch for the accuracy and completeness of the reported data and for the fidelity of this report to the protocol.

Study Design and Treatment

This randomized, double-blind, placebo-controlled, phase 3 trial was conducted at 89 sites in the United States, Australia, and Canada. Patients were randomly assigned in a 1:1 ratio to receive oral ruxolitinib phosphate tablets or matched placebo. The starting dose of ruxolitinib depended on the baseline platelet count: 15 mg twice daily for a platelet count of 100×10^9 to 200×10^9 per liter and 20 mg twice daily for a count that exceeded 200×10^9 per liter. The dose was adjusted for lack of efficacy or excess toxicity as specified in the protocol (see the Supplementary Appendix). Unblinding of the study-drug assignments and crossover from

placebo to ruxolitinib were permitted for protocol-defined worsening splenomegaly (see the Supplementary Appendix). The prospectively defined cutoff point for data analysis occurred when half the patients remaining in the study had completed the week 36 visit and when all the patients had completed the week 24 evaluation or discontinued treatment. After crossover, data for patients who were initially assigned to placebo were not included in the analyses, except for the intention-to-treat analysis of overall survival.

The primary end point was the proportion of patients with a reduction of 35% or more in spleen volume from baseline to week 24, measured by means of magnetic resonance imaging or computed tomography. Secondary end points included the duration of the reduction in spleen volume; the proportion of patients with a reduction in the total symptom score of 50% or more from baseline to week 24, as assessed with the modified Myelofibrosis Symptom Assessment Form (MFSAF), version 2.0 (see the Supplementary Appendix)[10,11]; the change in the total symptom score from baseline to week 24; and overall survival. The analysis of overall survival was updated at the time of a planned data-collection cutoff 4 months after the primary analysis. Patients completed the MFSAF every night; this electronic diary was used to evaluate symptoms of night sweats, itching, abdominal discomfort, pain under the ribs on the left side, a feeling of fullness (early satiety), muscle or bone pain, and inactivity. Scores ranged from 0 ("absent" symptoms) to 10 ("worst imaginable" symptoms), and the total symptom score was the sum of the individual scores, excluding inactivity. Exploratory end points included changes in body weight and the *JAK2* V617F allele burden, achievement of independence from transfusions,[12] and additional patient-reported outcomes (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The study was designed to enroll 240 patients, providing 97% power to detect a treatment difference in spleen-volume response at a two-sided alpha level of 0.05, assuming a response rate of 30% or more for ruxolitinib and a response rate of 10% or less for placebo. Analyses were conducted in accordance with the intention-to-treat principle. For all applicable variables, however, patients with missing baseline values were excluded from the analyses of change and percent change from baseline. In the analyses of change from baseline to week 24, patients who discontinued the study drug or crossed over before week 24 were counted as not having a response (for response measures of a reduction in spleen volume and symptom improvement). Secondary efficacy variables were tested in a fixed-sequence testing procedure at an alpha level of 0.05. The durability of spleen response and survival were analyzed with the use of the Kaplan–Meier method.

RESULTS

PATIENTS

From September 2009 through April 2010, a total of 309 patients were enrolled: 155 were randomly assigned to ruxolitinib, and 154 were randomly assigned to placebo. Baseline characteristics were similar in the two groups (Table 1). The median spleen volume was more than 2500 cm^3 (>10 times the median normal spleen volume of 200 cm^3).[13-15] A total of 38.2% of the patients had IPSS intermediate-2–risk disease, and 61.2% had high-risk disease.

At the time of the prospectively defined data cutoff (median follow-up, 32 weeks), 134 patients in the ruxolitinib group (86.5%) and 78 in the placebo group (50.6%) were receiving the randomly assigned study drug. Thirty-six patients in the placebo group (23.4%) crossed over to ruxolitinib (16 before and 20 after week 24; see the Supplementary Appendix.)

EFFICACY

Spleen Size

The proportion of patients with a reduction of 35% or more in spleen volume at week 24 (primary end point) was 41.9% in the ruxolitinib group as compared with 0.7% in the placebo group (odds ratio, 134.4; 95% confidence interval [CI], 18.0 to 1004.9; P<0.001) (Fig. 1A). Additional prespecified analyses showed that among the patients for whom baseline and week 24 data were available, the 139 patients receiving ruxolitinib had a mean reduction in spleen volume of 31.6% (median, 33.0%) at week 24; the 106 patients receiving placebo had a mean increase of 8.1% (median, 8.5%). Almost all patients receiving ruxolitinib had some degree of reduction in spleen volume (Fig. 1B). The majority of patients receiving placebo had spleen growth. Changes in palpable spleen length in the ruxolitinib and placebo groups mirrored the changes in spleen volume. The reduction in spleen volume was durable with continued

Table 1. Baseline Characteristics of the Patients.*

Variable	Ruxolitinib (N = 155)	Placebo (N = 154)
Median age (range) — yr	66 (43–91)	70 (40–86)
Male sex — % of patients	51.0	57.1
Myelofibrosis subtype — % of patients		
Primary myelofibrosis	45.2	54.5
Post–polycythemia vera myelofibrosis	32.3	30.5
Post–essential thrombocythemia myelofibrosis	22.6	14.3
IPSS risk status — % of patients		
High	58.1	64.3
Intermediate 2	41.3	35.1
Previous hydroxyurea use — % of patients	67.1	56.5
Median platelet count (range) — $\times 10^{-9}$/liter	262 (81–984)	238 (100–887)
Median hemoglobin (range) — g/liter	105 (66–170)	105 (35–173)
Median palpable spleen length (range) — cm	16 (0–33)†	16 (5–34)
Median spleen volume (range) — cm^3	2598 (478–7462)	2566 (521–8881)
JAK2 V617F–positive — % of patients	72.9	79.9

* There were no significant differences between the two groups with the exception of age ($P<0.05$). IPSS denotes International Prognostic Scoring System.
† One patient had a baseline spleen length recorded as nonpalpable in error but had a prior measurement of 16 cm and a baseline spleen volume of 2450 cm^3.

therapy (Fig. 1C). For this secondary end point, among patients who had a reduction of 35% or more in spleen volume, 67.0% (95% CI, 46.4 to 81.1) had a reduction in spleen volume that was maintained for 48 weeks or more (loss of response was defined as a reduction of <35% from baseline and an increase of ≥25% from the nadir).

Symptoms and Other Patient-Reported Outcomes

The proportion of patients with a reduction of 50% or more in the total symptom score from baseline to week 24, a prespecified secondary end point, was significantly higher in the ruxolitinib group than in the placebo group (45.9% vs. 5.3%; odds ratio, 15.3; 95% CI, 6.9 to 33.7; $P<0.001$). Additional prespecified analyses showed that among the patients for whom baseline and week 24 data were available, the 129 patients receiving ruxolitinib had a mean improvement of 46.1% (median, 56.2%) in the total symptom score at week 24; the 103 patients receiving placebo had a mean worsening of 41.8% (median, 14.6%) in the score ($P<0.001$). The improvement was rapid and was maintained over the 24-week period during which symptom data were collected (Fig. 2A). Most patients who received ruxolitinib had improvement in symptoms; the majority of patients who received placebo had worsening of symptoms (Fig. 2B).

A post hoc analysis showed that patients who received ruxolitinib had improvement in each individual symptom assessed on the MFSAF (Fig. 2C), whereas symptoms worsened in the placebo group ($P<0.01$ for all comparisons with placebo).

Prespecified analyses were conducted to cross-validate the modified MFSAF, version 2.0. The Patient Global Impression of Change and other patient-reported outcomes mirrored changes in symptom scores (Fig. S3A, S3B, and S3C in the Supplementary Appendix). Patients who received ruxolitinib had weight gain, whereas those receiving placebo had weight loss (Fig. S4 in the Supplementary Appendix). In the ruxolitinib group, 62.7% of patients with a reduction in spleen volume of 35% or more had improvement of 50% or more in spleen-related symptoms (as indicated by the sum of MFSAF scores for abdominal discomfort, pain under the ribs on the left side, and a feeling of fullness [early satiety]); however, this level of improvement also occurred in 46.9% of patients with a reduction in spleen volume of less than 35%. An additional post hoc analysis showed an improvement of 50% or more in nonabdominal symptoms (night sweats, bone or muscle pain, and pruritus) in 58.6% of patients with reductions in spleen volume of 35% or more and in 54.1% of patients with reductions in spleen volume of less than 35%.

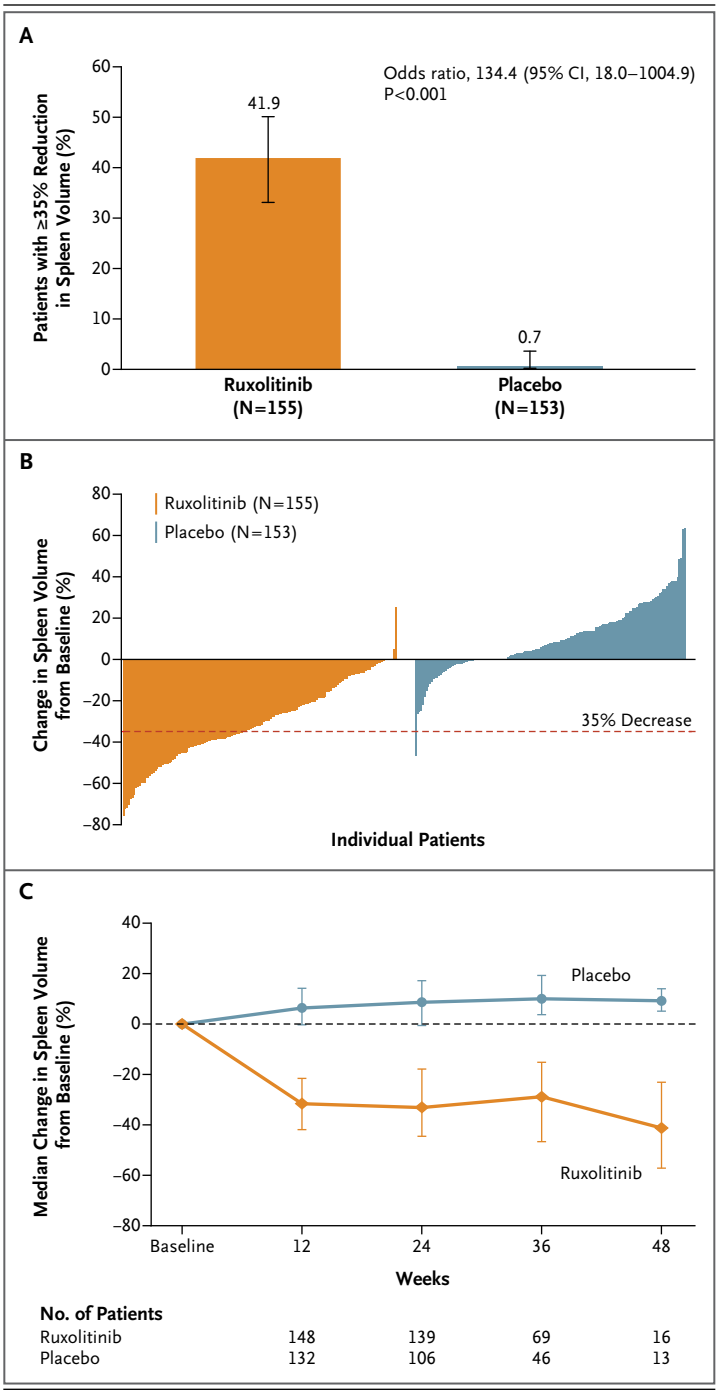

Figure 1. Change in Spleen Volume.

Panel A shows the results of the intention-to-treat analysis of the percentage of patients in each study group who reached the primary end point of a reduction of 35% or more in spleen volume as assessed by means of magnetic resonance imaging (MRI) or computed tomography (CT). Patients who discontinued the study drug before week 24 or crossed over before week 24 were counted as not having had a response. Only patients with baseline data were included in this analysis. I bars denote 95% confidence intervals. CI denotes confidence interval. Panel B shows the percent change from baseline in spleen volume at week 24 (in 139 patients in the ruxolitinib group and 106 in the placebo group) or at the last evaluation before week 24 (in 16 patients in the ruxolitinib group and 47 in the placebo group). Data for 1 patient with a missing baseline value are not included on the graph. Most patients in the ruxolitinib group (150 of 155) had a reduction in spleen volume, whereas most patients in the placebo group had either an increase in spleen volume (102 of 153 patients) or no change (15 of 153 patients). Panel C shows the median percent change in spleen volume as assessed by means of MRI or CT over time. Reductions in spleen volume were apparent at the first on-study measurement at 12 weeks and were maintained over the course of the study. The upper edge of each I bar corresponds to the 75th percentile, and the lower edge to the 25th percentile.

Subgroups

In a post hoc analysis of subgroups, mean changes in spleen volume among patients with the *JAK2* V617F mutation were −34.6% in the ruxolitinib group and 8.1% in the placebo group; the corresponding changes among patients without the mutation were −23.8% and 8.4% (P value for interaction, 0.07). The changes in the total symptom score among patients with the *JAK2* V617F mutation were −52.6% (improvement) in the ruxolitinib group and 42.8% (worsening) in the placebo group, and the changes among those without the mutation were −28.1% and 37.2%, respectively (P=0.11 for interaction). Across myelofibrosis subtypes (primary myelofibrosis, post–polycythemia vera myelofibrosis, and post–essential thrombocythemia myelofibrosis), patients who received ruxolitinib had a decrease in spleen volume and improvement in the total symptom score; patients receiving placebo had increases in spleen volume (P=0.52 for interaction) and worsening of the total symptom score (P=0.46 for interaction) (Fig. S5A and S5B in the Supplementary Appendix).

Biomarkers

In a prespecified analysis of biomarkers, patients who received ruxolitinib had mean reductions in the *JAK2* V617F allele burden of 10.9% at week 24 and 21.5% at week 48; patients who received placebo had a mean increase of 3.5% at week 24 and 6.3% at week 48 (Fig. S6 in the Supplementary Appendix). Furthermore, patients receiving ruxolitinib had reductions in plasma levels of C-reactive protein and the proinflammatory cytokines tumor necrosis factor α and interleukin-6, and they had increases in levels of plasma leptin and erythropoietin (Fig. S7 in the Supplementary Appendix).

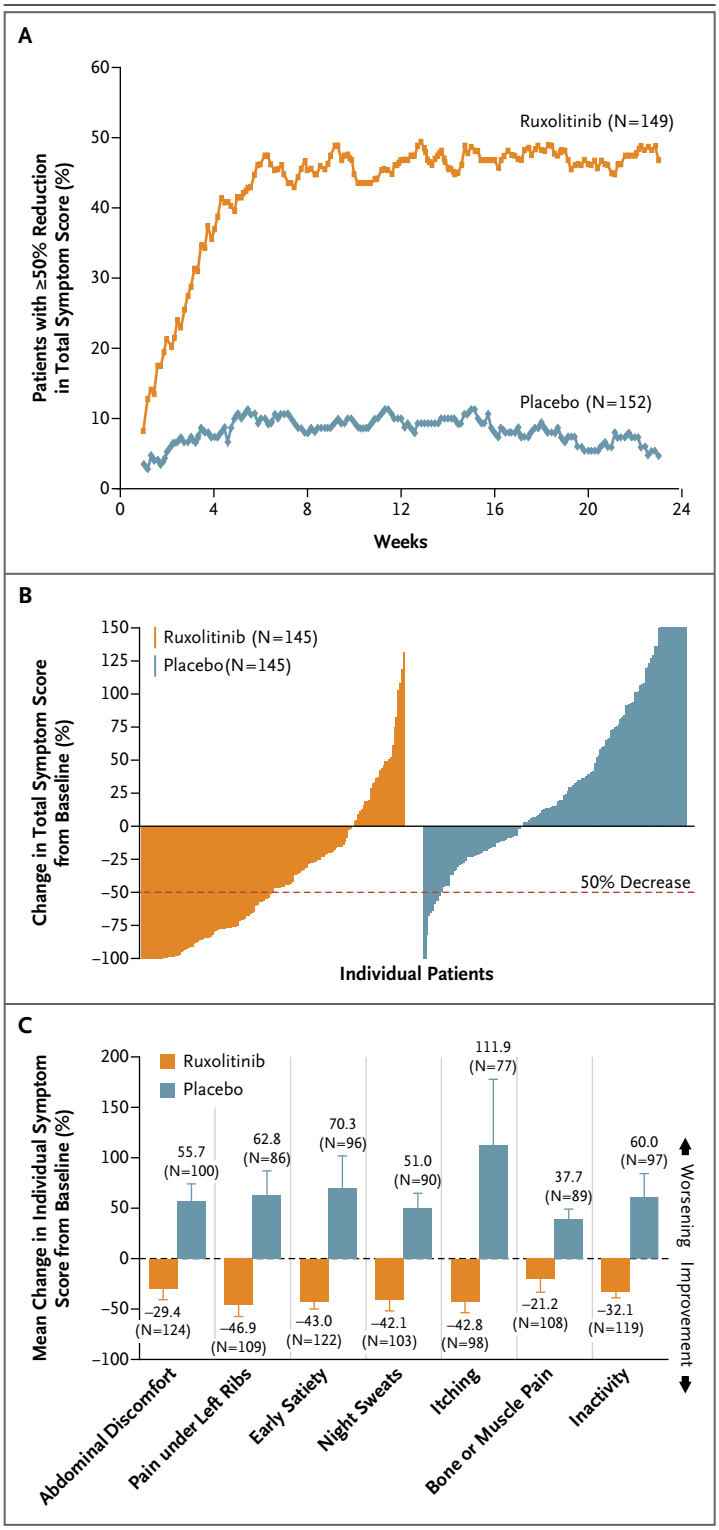

Figure 2. Change in Symptom Scores.

Panel A shows the results of an intention-to-treat analysis of the proportion of patients with at least a 50% reduction in the total symptom score over time (each value plotted represents the moving average for the previous 7 days). Patients who discontinued the study drug or for whom data were missing were considered not to have had a response. The majority of responses occurred rapidly, within the first 4 weeks after treatment. Only patients with baseline data were included in this analysis. Panel B shows the percent change from baseline in the total symptom score at week 24 (in 129 patients in the ruxolitinib group and 103 patients in the placebo group) and at the last evaluation during receipt of the randomly assigned study drug (in 16 patients in the ruxolitinib group and 42 patients in the placebo group). Five patients with a baseline score of 0, 8 patients with missing baseline values, and 6 patients with insufficient data after baseline are not included. Whereas most patients who received ruxolitinib had a reduction in the total symptom score, the majority of patients who received placebo had a worsening of symptoms (worsening in the total symptom score of ≥150% is shown as 150%). Panel C shows the mean percent change in the score for each symptom in the modified Myelofibrosis Symptom Assessment Form, version 2.0. All symptoms improved in the ruxolitinib group and worsened in the placebo group ($P<0.01$ for all comparisons with placebo). T bars denote standard errors.

Overall Survival

For the secondary end point of overall survival, at the time of data cutoff, 10 deaths were reported in the ruxolitinib group (6.5%) as compared with 14 deaths in the placebo group (9.1%) (hazard ratio, 0.67; 95% CI, 0.30 to 1.50; $P=0.33$). Subsequently, a survival analysis based on a planned data cutoff with 4 additional months of follow-up (median follow-up, 51 weeks) revealed a significant survival advantage for patients who received ruxolitinib, with 13 deaths in the ruxolitinib group (8.4%) and 24 deaths in the placebo group (15.6%) (hazard ratio, 0.50; 95% CI, 0.25 to 0.98; $P=0.04$) (Fig. 3).

SAFETY

A total of 155 patients in the ruxolitinib group and 151 in the placebo group received at least one dose of the study medication and were included in the analysis of safety. The number of patient-years of exposure was 105 in the ruxolitinib group and 87 in the placebo group; study discontinuation and crossover to ruxolitinib accounted for lower exposure in the placebo group. Seventeen patients who received ruxolitinib (11.0%) and 16 patients who received placebo (10.6%) discontinued the study treatment because of adverse events (of any grade). Twenty deaths occurred during the study or within 28 days after the last dose was administered (9 deaths in the ruxolitinib group and 11 deaths in the placebo group, including 1 death after crossover) (see the Supplementary Appendix for more

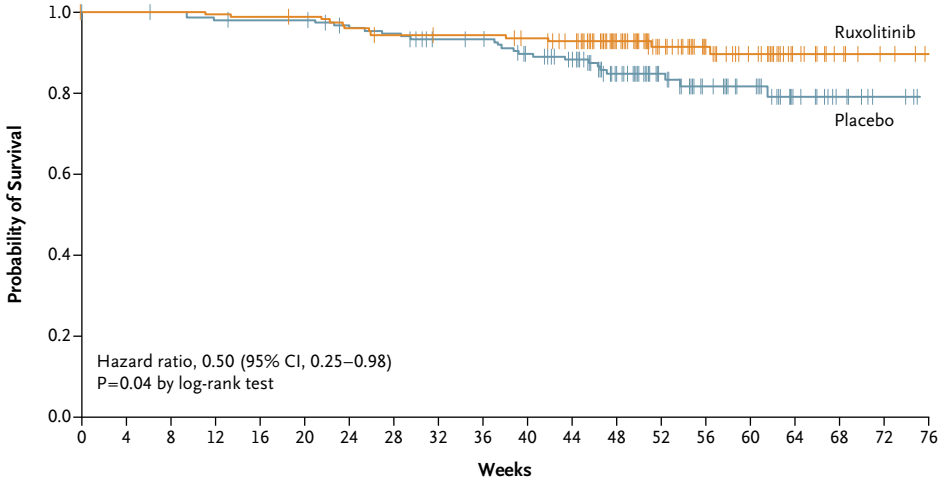

Figure 3. Overall Survival.

Kaplan–Meier estimates of overall survival, including 4 months of additional follow-up after the primary analysis, are shown. There were 13 deaths in the ruxolitinib group (8.4%) and 24 deaths in the placebo group (15.6%) during a median follow-up period of 51 weeks. Tick marks indicate censoring times for individual patients.

detailed information). Principal causes of death in the ruxolitinib group were muscle weakness and general deterioration, subdural hematoma, renal failure, non–small-cell lung cancer, acute myeloid leukemia (AML), pneumonia (in 2 patients), and sepsis (in 2 patients). Principal causes of death in the placebo group were staphylococcal infection, gastrointestinal hemorrhage, intestinal perforation, multiorgan failure, pneumonia, sepsis (in 2 patients), and disease progression (in 4 patients).

Overall, nonhematologic adverse events occurred at a similar rate in the two groups. Events that occurred more frequently in the ruxolitinib group were ecchymosis, dizziness, and headache (predominantly grade 1 or 2) (Table 2). The most common grade 3 or 4 nonhematologic adverse events (abdominal pain, fatigue, and dyspnea) occurred more frequently in the placebo group.

Anemia and thrombocytopenia were the most frequent hematologic adverse events (overall and grade 3 or 4 events) (Table 2) and a reason for treatment discontinuation in one patient in each study-drug group for each event. About half of all grade 3 or 4 adverse events of anemia in the ruxolitinib group occurred during the first 8 weeks of therapy. The mean hemoglobin level in patients who received ruxolitinib reached a nadir of 95 g per liter after approximately 8 to 12 weeks of therapy (Fig. S8 in the Supplementary Appendix), with an increase by week 24 to a new steady state (101 g per liter). The monthly prevalence of grade 3 or 4 anemia and the proportion of patients requiring transfusions (1 or more units of red cells) also followed a pattern that was consistent with changes in the hemoglobin level over time (Fig. S9A and S9B in the Supplementary Appendix). According to the response criteria of the International Working Group for Myelofibrosis Research and Treatment, 41.2% of patients in the ruxolitinib group and 46.9% of patients in the placebo group who were dependent on transfusions at baseline were classified as transfusion-independent during the study (Table S4 in the Supplementary Appendix). In the ruxolitinib group, patients with new-onset grade 3 or 4 anemia had improvements in symptoms and reductions in spleen volume that were similar to those in patients without anemia (Fig. 9C and 9D in the Supplementary Appendix).

Approximately half the grade 3 or 4 thrombocytopenia events (11 of 20) occurred during the first 8 weeks of treatment (Fig. S10 in the Supplementary Appendix) and led to dose adjustments or brief treatment interruptions. Five patients had more than one episode of grade 3 or 4 thrombocytopenia. Grade 3 episodes of bleeding (terms for bleeding events are described in the Supplementary Appendix) occurred in 2.6% of patients who received ruxolitinib and in 2.0% of patients who

Table 2. Adverse Events Observed in 10% or More of Patients Who Received Ruxolitinib.

Event	Ruxolitinib (N=155)		Placebo (N=151)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	percent of patients			
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

* Hematologic abnormalities are based on laboratory values. The data shown are for events of the worst grade during the study, regardless of whether this grade was a change from the baseline grade.

received placebo. Grade 4 episodes of bleeding occurred in 1.3% of patients who received ruxolitinib and in 1.3% of patients who received placebo. Bruising (bleeding events related to skin and subcutaneous tissue) (see the Supplementary Appendix) was assessed separately. A total of 23.2% of patients who received ruxolitinib and 14.6% of patients who received placebo had bruising; all events were grade 1 or 2 except for one grade 3 event in the ruxolitinib group.

Among patients in whom the study drug was interrupted, symptoms (assessed by means of the total symptom score) returned to baseline levels over a period of approximately 1 week (Fig. S11 in the Supplementary Appendix). Adverse events of grade 3 or higher developed in 8 of 49 patients in the ruxolitinib group (16.3%) and in 7 of 54 patients in the placebo group (13.0%) after interruption of the study drug and in 12 of 21 patients in the ruxolitinib group (57.1%) and 17 of 37 patients in the placebo group (45.9%) after discontinuation. There was no clear pattern in these events to suggest a specific withdrawal effect (Tables S5 and S6 in the Supplementary Appendix).

Two patients in the ruxolitinib group had a transformation to AML during the study: one patient with 7% bone marrow blasts at baseline and a history of breast cancer had AML transformation after 8 months in the study; the second patient entered the study with 2% bone marrow blasts and a trisomy 8 chromosomal abnormality at baseline and had AML transformation after 5 months in the study. There were no transformations in the placebo group.

DISCUSSION

In this study, ruxolitinib therapy was significantly more effective than placebo with respect to all primary and secondary efficacy end points, as well as in an updated analysis of overall survival. In the ruxolitinib group, 41.9% of patients met the defined response threshold of a reduction of 35% or more in spleen volume, and nearly all the patients had some reduction in spleen volume. Reductions in spleen volume were durable; 67.0% of patients with a response had this response for 48 weeks or longer with continued therapy.

Improvements in symptoms were measured with the use of the modified MFSAF, version 2.0, diary, a tool designed specifically to assess symptoms of myelofibrosis. The majority of patients had improvements in symptoms, which occurred even in patients who did not have a reduction in spleen volume of 35% or more. In contrast, most patients who received placebo had progressive splenomegaly and worsening of myelofibrosis-related symptoms. Changes in symptoms recorded with the MFSAF were directionally consistent with the assessments made with other validated and common patient-reported outcome instruments used in this study.

Anemia and thrombocytopenia were more common in patients who received ruxolitinib than in patients who received placebo. These adverse events were manageable, as evidenced by the low discontinuation rate (one patient in each group for each event). Thrombocytopenia rarely recurred at a grade 3 or 4 level after appropriate dose modifications and was not associated with an increase in bleeding events, although bruising was more common in the ruxolitinib group. The prevalence of grade 3 or 4 anemia peaked after approximately 8 to 12 weeks of ruxolitinib therapy, subsequently

decreasing to levels similar to those in patients who received placebo. In the ruxolitinib group, patients with new-onset grade 3 or 4 anemia had symptomatic improvement similar to that in patients without anemia. In the placebo group, patients with and those without grade 3 or 4 anemia had worsening of symptoms, which was greater in patients with anemia.

Transformation to AML occurred in 2 patients in this study; both patients received ruxolitinib and had baseline characteristics that placed them at increased risk for transformation. In a separate phase 3 trial with a median follow-up of 61 weeks, there were no transformations to AML in 146 patients who received ruxolitinib and two transformations in 73 patients who received the best available therapy.[16] Longer-term follow-up will be required to better define rates of AML transformation.

After interruption of ruxolitinib therapy, myelofibrosis-related symptoms gradually returned to baseline levels. A between-group comparison of adverse events reported after interruption or permanent discontinuation of the study drug showed no clear pattern of a specific withdrawal effect.

In conclusion, ruxolitinib was associated with reductions in splenomegaly and symptoms that are prominent manifestations of myelofibrosis and appeared to be associated with an improvement in overall survival. Toxic effects were generally managed with dose modification. These findings show that ruxolitinib is an effective therapy for myelofibrosis.

Supported by Incyte.

Dr. Verstovsek reports receiving grant support through his institution from Incyte, Exelixis, Celgene, NS Pharma, Infinity Pharmaceuticals, SBIO, Lilly Oncology, AstraZeneca, Geron, Bristol-Myers Squibb, YM BioSciences, Gilead, and Roche; Dr. Levy, being an employee of Incyte and receiving stock options as part of his compensation; Dr. Gupta, receiving grant support through his institution from Incyte and Novartis, consulting fees from Incyte and Novartis, and lecture fees from Novartis; Dr. Catalano, receiving consulting fees from Incyte; Dr. Deininger, receiving consulting fees from Bristol-Myers Squibb, Novartis, and Ariad, and grant support through his institution from Bristol-Myers Squibb; Dr. Miller, receiving grant support through her institution, consulting fees, and lecture fees from Novartis, and payments for development of educational presentations from Incyte and Novartis; Dr. Silver, receiving grant support through his institution from Incyte and lecture fees from Incyte, and holding stock in Incyte both individually and through his institution; Dr. Lyons, receiving grant support through his institution from Incyte; Dr. Paquette, receiving consulting fees paid through his institution from Incyte; Dr. Vaddi, being an employee of Incyte and receiving stock or stock options as a part of his compensation; Dr. Erickson-Viitanen, being an employee of Incyte and receiving stock or stock options as part of her compensation; Dr. Sun, being an employee of Incyte and receiving stock options as part of his compensation; Dr. Sandor, being an employee of Incyte and receiving stock or stock options as part of his compensation; and Dr. Kantarjian, receiving grant support through his institution from Incyte. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Kelly Reith of Incyte for editorial assistance with an earlier version of the manuscript and Daniel Hutta, Ph.D., of Articulate Science for medical writing assistance with an early draft of the manuscript.

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