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JAK Inhibition with Ruxolitinib versus Best Available Therapy for Myelofibrosis

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ABSTRACT

BACKGROUND

Treatment options for myelofibrosis are limited. We evaluated the efficacy and safety of ruxolitinib, a potent and selective Janus kinase (JAK) 1 and 2 inhibitor, as compared with the best available therapy, in patients with myelofibrosis.

METHODS

We assigned 219 patients with intermediate-2 or high-risk primary myelofibrosis, post–polycythemia vera myelofibrosis, or post–essential thrombocythemia myelofibrosis to receive oral ruxolitinib or the best available therapy. The primary end point and key secondary end point of the study were the percentage of patients with at least a 35% reduction in spleen volume at week 48 and at week 24, respectively, as assessed with the use of magnetic resonance imaging or computed tomography.

RESULTS

A total of 28% of the patients in the ruxolitinib group had at least a 35% reduction in spleen volume at week 48, as compared with 0% in the group receiving the best available therapy ($P<0.001$); the corresponding percentages at week 24 were 32% and 0% ($P<0.001$). At 48 weeks, the mean palpable spleen length had decreased by 56% with ruxolitinib but had increased by 4% with the best available therapy. The median duration of response with ruxolitinib was not reached, with 80% of patients still having a response at a median follow-up of 12 months. Patients in the ruxolitinib group had an improvement in overall quality-of-life measures and a reduction in symptoms associated with myelofibrosis. The most common hematologic abnormalities of grade 3 or higher in either group were thrombocytopenia and anemia, which were managed with a dose reduction, interruption of treatment, or transfusion. One patient in each group discontinued treatment owing to thrombocytopenia, and none discontinued owing to anemia. Nonhematologic adverse events were rare and mostly grade 1 or 2. Two cases of acute myeloid leukemia were reported with the best available therapy.

CONCLUSIONS

Continuous ruxolitinib therapy, as compared with the best available therapy, was associated with marked and durable reductions in splenomegaly and disease-related symptoms, improvements in role functioning and quality of life, and modest toxic effects. An influence on overall survival has not yet been shown. (Funded by Novartis Pharmaceuticals; ClinicalTrials.gov number, NCT00934544.)

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Myelofibrosis, which can present as a primary disease or can evolve from polycythemia vera or essential thrombocythemia,[1] is characterized by marrow fibrosis, progressive anemia, and extramedullary hematopoiesis, manifested primarily as splenomegaly. Severe constitutional symptoms (e.g., night sweats and weight loss), pruritus, fatigue, and sequelae of splenomegaly are common.[2] The median survival from the time of diagnosis is 4 years for patients with intermediate-2–risk disease and 2 years for patients with high-risk disease.[3] Apart from allogeneic stem-cell transplantation, treatment is palliative and does not address the characteristic abnormality identified in myelofibrosis, a dysregulation of Janus kinase (JAK)–mediated cytokine and growth-factor signal transduction.[4]

In 2005, the *JAK2* V617F mutation was identified as the most common molecular abnormality in myeloproliferative neoplasms.[5-8] Other mutations that activate the JAK pathway have been identified, including mutations in *JAK2* exon 12, myeloproliferative leukemia virus oncogene (*MPL*), and *LNK*.[9-11] Thus, dysregulation of the JAK signaling pathway is frequently noted in patients who have myelofibrosis, with or without the V617F mutation.[12]

Ruxolitinib (also known as INC424 or INCB18424) is an orally bioavailable, potent, and selective inhibitor of JAK1 and JAK2 that is approved for the treatment of intermediate- and high-risk myelofibrosis.[13,14] Ruxolitinib selectively inhibits the proliferation of *JAK2* V617F-driven Ba/F3 cells, and these effects are correlated with decreased levels of phosphorylated JAK2 and of signal transducer and activator of transcription 5 (STAT5).[13] In a phase 1–2 study of patients with myelofibrosis, ruxolitinib was associated with weight gain, prompt and marked reductions in spleen size, and reductions in debilitating symptoms.[15] We describe here results from the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment II (COMFORT-II), a randomized, phase 3 trial comparing ruxolitinib with the best available therapy in patients with primary myelofibrosis, post–polycythemia vera myelofibrosis, or post–essential thrombocythemia myelofibrosis.

METHODS

ELIGIBILITY CRITERIA

Patients 18 years of age or older who had primary myelofibrosis, post–polycythemia vera myelofibrosis, or post–essential thrombocythemia myelofibrosis[16] and a palpable spleen 5 cm or more below the costal margin were eligible for the study, irrespective of their *JAK2* V617F mutation status. Eligible patients had two prognostic factors (intermediate-2 risk) or three or more prognostic factors (high risk) according to the International Prognostic Scoring System (in which the prognostic factors are age >65 years, hemoglobin level of <10 g per deciliter, leukocyte count of $>25\times10^9$ per liter, ≥1% circulating myeloblasts, and presence of constitutional symptoms),[3] a peripheral-blood blast count of less than 10%, a platelet count of 100×10^9 or more per liter, an Eastern Cooperative Oncology Group (ECOG) performance status[17] of 3 or less (on a scale from 0 to 5, with 0 indicating that the patient is fully active, higher scores indicating increasing disability, and 5 indicating death; see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), and no prior treatment with a JAK inhibitor. In addition, eligible patients were not considered to be suitable candidates for allogeneic stem-cell transplantation at the time of enrollment.

STUDY DESIGN

Patients were stratified according to prognostic score[3] at enrollment and were randomly assigned, in a 2:1 ratio, to receive ruxolitinib or the best available therapy, which included any commercially available agents (as monotherapy or in combination) or no therapy at all and which could be changed during the treatment phase. The starting dose of ruxolitinib tablets was 15 mg twice daily if the baseline platelet count was 200×10^9 per liter or less and 20 mg orally twice daily if the baseline platelet count was greater than 200×10^9 per liter. A protocol-specified dosing regimen required reductions of the dose for reasons of safety (if neutropenia or thrombocytopenia developed) and permitted escalation of the dose to increase efficacy, although the dose could not exceed 25 mg twice daily.[15] Patients received ruxolitinib or the best available therapy until the criteria for disease progression were met. At any time, patients who met protocol-specified criteria (underwent splenectomy or had an increase in spleen volume of >25% from the nadir during the study period, which could include the baseline volume) discontinued the randomized treatment phase of the study and could enter an extension phase. In the extension phase, patients who had been randomly assigned to the best available therapy could re-

ceive ruxolitinib if they met protocol-specified safety criteria, and patients who had been randomly assigned to ruxolitinib could continue to receive ruxolitinib if they were still deriving a clinical benefit. Patients who had leukemic transformation or underwent splenic irradiation were withdrawn from the study.

END POINTS

The primary end point was a reduction of 35% or more in spleen volume from baseline at week 48. This end point was selected on the basis of the international response criterion of a reduction of 50% or more in spleen length as assessed by palpation[18] and prior data showing a correlation of that measurement with a 33% reduction in spleen volume as measured by magnetic resonance imaging (MRI).[15] Spleen volume was assessed by MRI or by computed tomography (CT) (in the case of patients who were not suitable candidates for MRI) every 12 weeks; the images were read by a reader at a central location who was unaware of the group assignments. Spleen and liver volumes were assessed by outlining the circumference of the organ and determining the volume using a least-squares analysis. Spleen length was assessed by manual palpation at every study visit. Throughout this report, measurements of spleen volume were performed by MRI or CT, whereas measurements of spleen length were performed by palpation.

The key secondary end point was a reduction of 35% or more in spleen volume from baseline at week 24. Additional secondary end points included the length of time that a reduction in spleen volume of at least 35% was maintained, the time to a reduction in spleen volume of 35% or more from baseline, progression-free survival, leukemia-free survival, overall survival, and change in marrow histomorphologic features. Information regarding other secondary and exploratory end points and the definition of disease progression are provided in the Supplementary Appendix.

SYMPTOMS AND QUALITY OF LIFE

Symptoms and quality of life were assessed with the use of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire core model (QLQ-C30) and the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) scale. The EORTC QLQ-C30 includes five scales related to functioning, nine scales related to symptoms, and a global health status and quality-of-life scale. The FACT-Lym consists of a general core questionnaire (FACT-G), a disease-specific questionnaire (Lymphoma Subscale [LymS]), and a trial outcome index (FACT-TOI), which is a summary index of physical, functional, and symptom outcomes.

SAFETY

The safety population consisted of all patients in the ruxolitinib group who received at least one dose of study drug and all patients in the best-available-therapy group. Adverse events were monitored continuously during the study and were graded according to the National Cancer Institute's Common Toxicity Criteria, version 3. Throughout the study, patients provided blood samples at specified times, and the samples were analyzed by the same laboratory throughout the study to ensure consistency in values.

STUDY OVERSIGHT

The study was sponsored by Novartis Pharmaceuticals and designed by Incyte. It was approved by the institutional review board at each participating institution, and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent. Data were analyzed and interpreted by the sponsor's clinical and statistical teams in collaboration with authors who were not affiliated with the sponsor. An independent data and safety monitoring board reviewed the trial data and made recommendations regarding the continuation of the study. The first author prepared the first draft of the manuscript, with assistance from a medical writer who was funded by Novartis Pharmaceuticals, and made the final decision to submit the manuscript for publication. All the authors and representatives of the sponsor reviewed and amended the manuscript. All the authors vouch for the accuracy and completeness of the data and verify that the study as reported conforms to the protocol and statistical analysis plan (both of which are available at NEJM.org).

STATISTICAL ANALYSIS

The efficacy analysis was performed according to the intention-to-treat principle, with data from all patients who underwent randomization. The database cutoff date was January 4, 2011, the date on which the last patient completed the week 48 study visit. Patients who did not undergo an assessment of spleen volume at week 48 were considered not to have had a response. The two groups were com-

pared with the use of the exact Cochran–Mantel–Haenszel test, stratified according to prognostic category (intermediate-2 risk or high risk). The family-wise alpha level was controlled at 0.05 overall for two prespecified comparisons (the primary and key secondary end points). The key secondary end point was to be tested only if the primary end point showed significance at a two-sided alpha level of 0.05. No formal adjustment for multiple comparisons has been made. Survival curves for leukemia-free survival, overall survival, and progression-free survival were estimated with the use of the Kaplan–Meier method. Hazard ratios and the corresponding 95% confidence intervals were estimated with the use of the Cox proportional-hazards model, stratified according to baseline prognostic category; the between-group treatment difference was tested with the use of a stratified two-sided log-rank test.

RESULTS

CHARACTERISTICS OF THE PATIENTS

During the period from July 1, 2009, through January 22, 2010, a total of 219 patients underwent randomization, of whom 146 were assigned to receive ruxolitinib and 73 were assigned to receive the best available therapy. The baseline charac-

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Ruxolitinib (N=146)	Best Available Therapy (N=73)
Age (yr)		
Median	67	66
Range	35–83	35–85
Sex (%)		
Male	57	58
Female	43	42
Risk category (%)†		
Intermediate-2	40	40
High	60	59
Not determined	0	1
ECOG performance status (%)‡		
0	40	36
1	53	51
2	7	12
3	1	1
Myelofibrosis subtype (%)		
Primary	53	53
Post–polycythemia vera	33	27
Post–essential thrombocythemia	14	19
Previous myelofibrosis therapy (%)	76	73
Hydroxyurea	75	68
Radiotherapy	0	5
Palpable spleen length below costal margin (cm)		
Median	14	15
Range	5–30	5–37
Spleen volume (cm^3)§		
Median	2408	2318
Range	451–7766	728–7701

Table 1. (Continued.)

Characteristic	Ruxolitinib (N=146)	Best Available Therapy (N=73)
Presence of constitutional symptoms (%)¶	69	63
Hemoglobin <10 g/dl (%)	45	52
Median neutrophil count ($\times 10^{-9}$/liter)	11.3	9.4
Median platelet count ($\times 10^{-9}$/liter)	244	228
History of leukocyte count >25×10^9/liter (%)	38	36
Circulating blasts ≥1% (%)	76	74
JAK2 V617F mutation status at screening (%)		
Positive	75	67
Negative	24	27
Unknown	1	6

* There were no significant differences between the two groups in any of the baseline characteristics listed here.
† Risk was classified as "not determined" if any one of the five International Prognostic Scoring System risk factors (age >65 years, hemoglobin level <10 g per deciliter, leukocyte count >25x10^9 per liter, ≥1% circulating myeloblasts, and presence of constitutional symptoms) was not available. No data on assessment of prognostic factors were entered for one patient in the best-available-therapy group.
‡ The Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5. An ECOG status of 0 indicates that the patient is fully active and able to carry on all predisease activities without restriction, 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work), 2 indicates that the patient is ambulatory and capable of all self-care but unable to carry out any work activities and is up and about more than 50% of waking hours, and 3 indicates that the patient is capable of only limited self-care and is confined to a bed or chair more than 50% of waking hours.
§ The median normal spleen volume is approximately 200 cm^3.
¶ Constitutional symptoms included weight loss, fever, and night sweats.

teristics were balanced between the groups (Table 1). Approximately half the patients had primary myelofibrosis, approximately one third had post–polycythemia vera myelofibrosis, and the remainder had post–essential thrombocythemia myelofibrosis. Approximately 40% of the patients in each study group were classified as having disease of intermediate-2 risk, and 60% were classified as having high-risk disease.

Treatment with ruxolitinib was initiated at a dose of 15 mg twice daily in 38% of the patients and at a dose of 20 mg twice daily in 62%. The median dose intensity of ruxolitinib was 30 mg per day (range, 10 to 49). Among patients receiving the best available therapy, the most common therapies were antineoplastic agents (in 51%) — most frequently hydroxyurea (47%) — and glucocorticoids (16%); a total of 33% of patients received no therapy (Table 2 in the Supplementary Appendix). As of the data cutoff date (January 4, 2011), a smaller percentage of patients in the ruxolitinib group than in the best-available-therapy group had discontinued the randomized treatment phase of the study (38% vs. 58%). Of the 55 patients who had been randomly assigned to receive ruxolitinib and who discontinued the randomized treatment phase owing to protocol-specified criteria, 29 (53%) entered the extension phase and continued to receive ruxolitinib because they were still deriving clinical benefits. Of the 42 patients who had originally been assigned to receive the best available therapy and who discontinued the randomized treatment phase for any reason, 18 (43%) met protocol-specified criteria for crossover to ruxolitinib in the extension phase. Information on patient disposition is provided in Figure 1 and Table 3 in the Supplementary Appendix. The data included in this article are those from the randomized treatment phase only.

EFFICACY ANALYSIS

Assessments of Spleen Volume and Length

The efficacy analyses included all 219 patients who underwent randomization (146 in the ruxolitinib group and 73 in the group receiving the best available therapy). Three patients (two in the ruxolitinib group and one in the group receiving the best available therapy) underwent baseline MRI

assessments of spleen volume after randomization and were not included in the efficacy analyses of spleen volume. At week 48, most of the patients in the ruxolitinib group had a reduction in spleen volume (Fig. 1A). Only patients in the ruxolitinib group met the criterion for the primary end point, at least a 35% reduction in spleen volume from baseline at 48 weeks (28%, vs. 0% in the group receiving the best available therapy; P<0.001). Similarly, only patients in the ruxolitinib group met the criterion for the key secondary end point: a reduction of at least 35% in spleen volume at 24 weeks (32%, vs. 0% in the group receiving the best available therapy; P<0.001).

Analyses of prespecified exploratory end points showed that there were significant differences in the mean percentage change in spleen volume from baseline between the group assigned to ruxolitinib and the group assigned to the best available therapy, at week 24 (–29.2% vs. 2.7%, P<0.001) and at week 48 (–30.1% vs. 7.3%, P<0.001). During the 48-week period, almost all patients who were treated with ruxolitinib (97%), as compared with 56% given the best available therapy, had a measurable reduction in spleen volume (Fig. 1B). Among the 136 patients in the ruxolitinib group and 63 in the best-available-therapy group who had a baseline measurement and at least one subsequent measurement, only 4 patients (3%) in the ruxolitinib group — 3 of whom were V617F-positive — as compared with 28 (44%) in the group receiving the best available therapy had an increase in spleen volume as the best percentage change from baseline.

In secondary analyses, reductions in spleen volume with ruxolitinib were seen across all patient subgroups, including subgroups defined according to sex, myelofibrosis subtype, and prognostic category (all prespecified analyses) and *JAK2* V617F mutation status (a post hoc analysis). The rates of response (i.e., reduction in spleen volume of ≥35%) in the V617F-positive subgroup were 33% (95% confidence interval [CI], 25 to 43) with ruxolitinib and 0% (95% CI, 0 to 7) with the best available therapy; the corresponding rates in the V617F-negative subgroup were 14% (95% CI, 5 to 30) and 0% (95% CI, 0 to 17).

Prespecified secondary analyses also showed that ruxolitinib resulted in rapid and durable reductions in spleen volume. The median time to the first observation on MRI or CT of a reduction from baseline of 35% or more in spleen volume was 12.3 weeks in the ruxolitinib group (Table 4 in the Supplementary Appendix). Among the 69 patients who had a reduction in spleen volume of at least 35% at any time during the study, the reduction was observed at the first assessment (12 weeks) in 44 patients (64%). The median duration of response among patients treated with ruxolitinib was not reached, with 80% of patients still having a response at a median of 12 months of follow-up (Fig. 1C). Only 1 patient who received the best available therapy had a reduction of at least 35% in spleen volume at week 12, but data from that patient could not be assessed further owing to censoring.

At the first prespecified assessment of palpable spleen length (week 4), the mean length had decreased from baseline in patients receiving ruxolitinib but had increased in patients receiving the best available therapy (Fig. 1D). At week 48, patients treated with ruxolitinib had a mean decrease in spleen length from baseline of 56%, as compared with a mean increase of 4% in patients receiving the best available therapy.

Survival Assessments

By the data cutoff date at a median of 12 months of follow-up, 124 patients who had been randomly assigned to the ruxolitinib group and 50 patients who had been randomly assigned to the best-available-therapy group were alive and still being followed for the prespecified secondary survival end points beyond 48 weeks. In a time-to-event analysis, conducted at week 48, there were 44 patients in the ruxolitinib group (30%) who had progression events, as compared with 19 (26%) in the group receiving the best available therapy (hazard ratio for progression with ruxolitinib, 0.81; 95% CI, 0.47 to 1.39). In the analyses of leukemia-free survival and overall survival, there were 10 events in total (all of which were deaths): 6 events (4%) with ruxolitinib, as compared with 4 events (5%) with the best available therapy (hazard ratio for leukemia-free survival with ruxolitinib, 0.65; 95% CI, 0.18 to 2.31; hazard ratio for overall survival, 0.70; 95% CI, 0.20 to 2.49). In an analysis performed for a planned safety update with approximately 2 months of additional follow-up (median, 61.1 weeks), a total of 11 deaths (8%) were reported in the ruxolitinib group and 4 (5%) in the group receiving the best available therapy (hazard ratio, 1.01; 95% CI, 0.32 to 3.24). The median survival time has not been reached. The study was not powered to

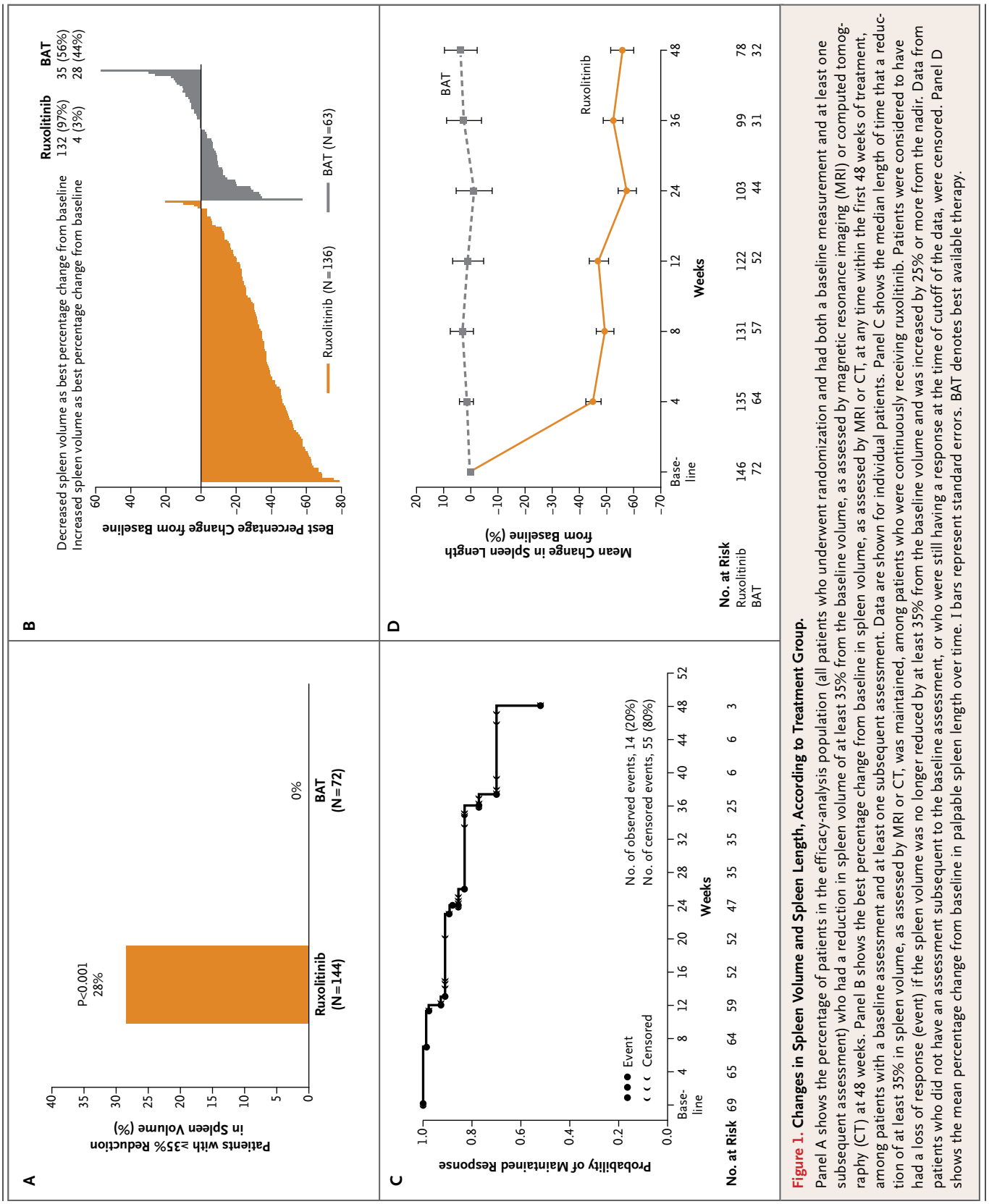

Figure 1. Changes in Spleen Volume and Spleen Length, According to Treatment Group.

Panel A shows the percentage of patients in the efficacy-analysis population (all patients who underwent randomization and had both a baseline measurement and at least one subsequent assessment) who had a reduction in spleen volume of at least 35% from the baseline volume, as assessed by magnetic resonance imaging (MRI) or computed tomography (CT) at 48 weeks. Panel B shows the best percentage change from baseline in spleen volume, as assessed by MRI or CT, at any time within the first 48 weeks of treatment, among patients with a baseline assessment and at least one subsequent assessment. Data are shown for individual patients. Panel C shows the median length of time that a reduction of at least 35% in spleen volume, as assessed by MRI or CT, was maintained, among patients who were continuously receiving ruxolitinib. Patients were considered to have had a loss of response (event) if the spleen volume was no longer reduced by at least 35% from the baseline volume and was increased by 25% or more from the nadir. Data from patients who did not have an assessment subsequent to the baseline assessment, or who were still having a response at the time of cutoff of the data, were censored. Panel D shows the mean percentage change from baseline in palpable spleen length over time. I bars represent standard errors. BAT denotes best available therapy.

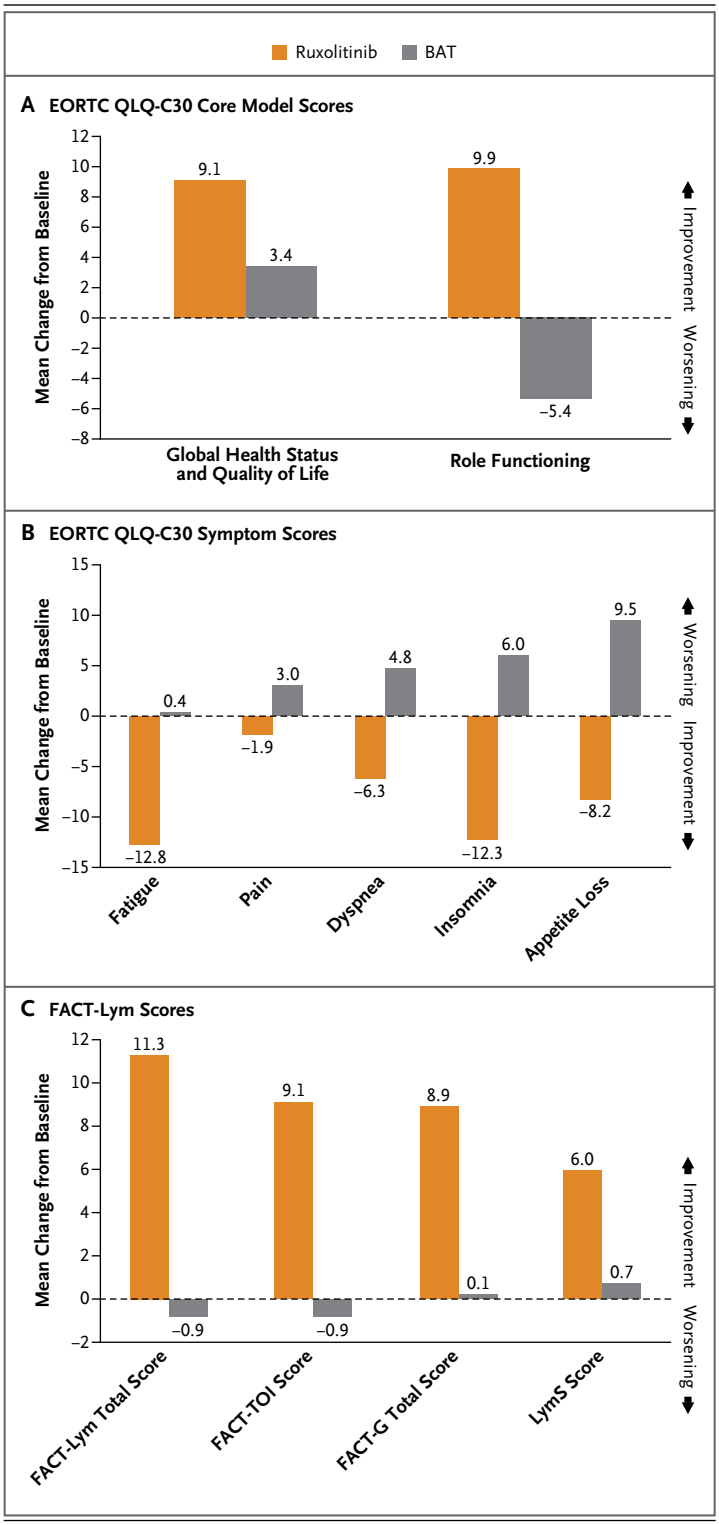

Figure 2. Changes in Quality-of-Life and Symptom-Assessment Scores, According to Treatment Group.

Mean changes from baseline at week 48 are shown for scores on the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire core model (QLQ-C30) global health status–quality of life and selected functioning scores (Panel A); selected EORTC QLQ-C30 symptom scores (Panel B); and Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) scores, including total scores, disease-specific subscale (FACT-LymS) scores, Trial Outcome Index (FACT-TOI) scores (a summary of physical, functional, and disease-specific outcomes), and general (FACT-G) scores (Panel C). In Panels A and C, improvement is represented by positive numbers, whereas in Panel B, improvement is represented by negative numbers (reduction in symptoms). For EORTC QLQ-C30 functioning and symptom subscales that are not shown, there only were minimal between-group differences (i.e., a difference of <10 points in the mean change in scores between the ruxolitinib group and the best-available-therapy [BAT] group at weeks 24 and 48). The ranges for minimal clinically important differences for the FACT-Lym are as follows: FACT-Lym total score, 6.5 to 11.2; FACT-TOI score, 5.5 to 11; FACT-G total score, 3 to 7; and LymS score, 2.9 to 5.4.[19,20]

detect differences in time-to-event end points, and a limited number of patients remain in the group receiving the best available therapy for further time-to-event end-point analyses.

Marrow Histomorphologic and Biomarker Assessments

No major changes in marrow histomorphologic features were observed in a prespecified secondary analysis of data from patients receiving any therapy. In a prespecified exploratory analysis, ruxolitinib treatment was associated with changes in plasma biomarkers (Table 5 in the Supplementary Appendix); levels of several proinflammatory cytokines, including interleukin-6, tumor necrosis factor alpha, and C-reactive protein were reduced, whereas erythropoietin and leptin levels were increased.

Symptoms and Other Patient-Reported Outcomes

In prespecified exploratory analyses of patient-reported outcomes (as assessed by means of the EORTC QLQ-C30 and FACT-Lym subscales), patients in the ruxolitinib group, as compared with patients receiving the best available therapy, had improved quality-of-life and role functioning (Fig. 2A). At week 48, patients receiving ruxolitinib had marked reductions in myelofibrosis-associated symptoms, including appetite loss, dyspnea, fatigue, insomnia, and pain, whereas patients receiving the best available therapy had worsening symptoms (Fig. 2B). Similarly, substantial improvements in FACT-Lym scores indicated that patients receiving ruxolitinib had a reduction in myelofi-

brosis-associated symptoms (Fig. 2C). In the group receiving the best available therapy, FACT-Lym scores consistently worsened throughout the study, whereas they improved and then stabilized in the ruxolitinib group. Patients in the ruxolitinib group had a greater improvement in physical condition and functioning, as assessed by FACT-TOI scores, than did patients in the group receiving the best available therapy.

SAFETY

Both ruxolitinib and the best available therapy were associated with few grade 3 or 4 nonhematologic adverse events, regardless of whether they were thought to be related to the study drug (Table 2), and the percentage of patients who discontinued treatment owing to adverse events was small in both groups (8% in the ruxolitinib group and 5% in the best-available-therapy group). The most frequently reported nonhematologic adverse event of any grade in the ruxolitinib group was diarrhea (with diarrhea of any grade occurring in 23% of the patients and grade 3 or 4 diarrhea occurring in 1%); diarrhea was also the only adverse event with a difference in incidence of 10% or more between the ruxolitinib group and the best-available-therapy group. Peripheral edema was the most frequently reported adverse event in the group receiving the best available therapy. The most frequently reported grade 3 or 4 nonhematologic adverse events were abdominal pain in the ruxolitinib group (occurring in 3% of the patients) and dyspnea and pneumonia in the group receiving the best available therapy (each occurring in 4% of the patients). The patients in the ruxolitinib group had a mean gain in body weight of 4.43 kg by week 48, whereas the mean body-weight gain in the best-available-therapy group was minimal (0.03 kg).

Thrombocytopenia and anemia occurred more frequently in the patients receiving ruxolitinib than in those receiving the best available therapy (Table 3), a finding that is consistent with the known mechanism of action of ruxolitinib, but these events rarely led to treatment discontinuation (one patient in each group discontinued the study owing to thrombocytopenia) and were generally manageable with dose modifications, transfusions of packed red cells, or both. Mean hemoglobin levels in the ruxolitinib group declined from the baseline level of 109.3 g per liter to a nadir of 94.1 g per liter at approximately 12 weeks of therapy and then increased to a steady state (101.8 g per liter) by week 24 (Fig. 2 in the Supplementary Appendix). Modifications of the ruxolitinib dose were mandated if thrombocytopenia or neutropenia developed. Adverse events of any grade requiring dose reductions or interruptions occurred more frequently with ruxolitinib than with the best available therapy (in 63% of patients vs. 15%). Thrombocytopenia was the most common cause of dose modifications in both groups (in 41% of the pa-

Table 2. Nonhematologic and Serious Adverse Events, Regardless of Whether They Were Related to the Study Drug.*

Adverse Event	Ruxolitinib (N=146)	Best Available Therapy (N=73)
	number of patients (percent)	
Nonhematologic: all grades, grade 3 or 4		
Diarrhea	34 (23), 2 (1)	9 (12), 0
Peripheral edema	32 (22), 0	19 (26), 0
Asthenia	26 (18), 2 (1)	7 (10), 1 (1)
Dyspnea	23 (16), 1 (1)	13 (18), 3 (4)
Nasopharyngitis	23 (16), 0	10 (14), 0
Pyrexia	20 (14), 3 (2)	7 (10), 0
Cough	20 (14), 0	11 (15), 1 (1)
Nausea	19 (13), 1 (1)	5 (7), 0
Arthralgia	18 (12), 1 (1)	5 (7), 0
Fatigue	18 (12), 1 (1)	6 (8), 0
Pain in extremity	17 (12), 1 (1)	3 (4), 0
Abdominal pain	16 (11), 5 (3)	10 (14), 2 (3)
Headache	15 (10), 2 (1)	3 (4), 0
Back pain	14 (10), 3 (2)	8 (11), 0
Pruritus	7 (5), 0	9 (12), 0
Serious		
Anemia	7 (5)	3 (4)
Abdominal pain	3 (2)	1 (1)
Pyrexia	3 (2)	1 (1)
Esophageal varices	3 (2)	0
Dyspnea	2 (1)	3 (4)
Pneumonia	1 (1)	4 (5)
Actinic keratosis	0	2 (3)
Ascites	0	2 (3)
Peritoneal hemorrhage	0	2 (3)
Respiratory failure	0	2 (3)

* Included are nonhematologic adverse events that occurred in 10% or more of patients in either group and serious adverse events that occurred in 2% or more of patients in either group.

Table 3. Hemoglobin and Platelet–Count Abnormalities, According to Study Group and Grade.

Laboratory Test and Baseline Grade	At Baseline	During Study*			
		Grade 1	Grade 2	Grade 3	Grade 4
		number of patients (percent)†			
Hemoglobin					
Ruxolitinib					
Grade 0	43 (29)	17 (12)	17 (12)	4 (3)	0
Grade 1	50 (34)	6 (4)	29 (20)	12 (8)	3 (2)
Grade 2	42 (29)	1 (1)	8 (5)	28 (19)	5 (3)
Grade 3	11 (8)	0	1 (1)	6 (4)	4 (3)
Total	146 (100)	24 (16)	55 (38)	50 (34)	12 (8)
Best available therapy					
Grade 0	12 (17)	6 (9)	1 (1)	0	1 (1)
Grade 1	27 (39)	9 (13)	14 (20)	2 (3)	1 (1)
Grade 2	20 (29)	0	12 (17)	6 (9)	2 (3)
Grade 3	10 (14)	0	1 (1)	6 (9)	3 (4)
Grade 4	1 (1)	0	0	1 (1)	0
Total	70 (100)	16 (23)	28 (40)	15 (21)	7 (10)
Platelet count					
Ruxolitinib					
Grade 0	134 (92)	44 (30)	33 (23)	7 (5)	3 (2)
Grade 1	12 (8)	2 (1)	8 (5)	2 (1)	0
Total	146 (100)	46 (32)	41 (28)	9 (6)	3 (2)
Best available therapy					
Grade 0	62 (90)	10 (14)	1 (1)	1 (1)	1 (1)
Grade 1	7 (10)	1 (1)	3 (4)	2 (3)	1 (1)
Total	69 (100)	11 (16)	4 (6)	3 (4)	2 (3)

* Numbers and percentages refer to the highest grade documented during the study. Percentages may not total 100 because of rounding.
† The denominators for percentages during the study are the total numbers at baseline.

tients in the ruxolitinib group and 1% in the best-available-therapy group). Only 5% of the patients in the ruxolitinib group required dose interruptions or reductions owing to anemia and 1% owing to neutropenia; the corresponding percentages in the best-available-therapy group were 1% and 0%.

During the treatment period, more patients in the ruxolitinib group than in the best-available-therapy group received at least one transfusion of packed red cells (51% vs. 38%). The mean number of transfusions per month was similar in the two treatment groups (0.86 and 0.91, respectively). In the ruxolitinib group, the percentage of patients who required transfusions of packed red cells was higher among those who started ruxolitinib at a dose of 20 mg twice daily than among those who started at 15 mg twice daily (58% vs. 41%).

Serious adverse events were balanced between the two groups (Table 2). The most frequently reported serious adverse event in both groups was anemia (in 5% of the patients in the ruxolitinib group and 4% in the best-available-therapy group). Pneumonia was the only serious adverse event reported in 5% or more of patients in either group (1% in the ruxolitinib group and 5% in the best-available-therapy group).

Among the 32 patients who discontinued ruxolitinib, 19 had adverse events 2 weeks or less after discontinuation. Of these 19 patients, 6 patients had at least one symptom referable to myelofi-

brosis, including general deterioration in physical health (1 patient), pyrexia (2), anorexia (2), fatigue (1), weight loss (2), night sweats (1), and pruritus (1). Three of these events — general deterioration in physical health, pyrexia, and fatigue — were reported as grade 3 events. Among the remaining patients who discontinued ruxolitinib, there was no pattern with respect to the type or severity of the event.

At 12 months of follow-up, 10 deaths had been reported (6 in the ruxolitinib group [4%] and 4 in the best-available-therapy group, [5%]), of which 7 deaths (4 [3%] and 3 [4%] in the two groups, respectively) occurred within 28 days after discontinuation of the study treatment. With an additional 2 months of follow-up (median total follow-up, 61.1 weeks), an additional 5 deaths occurred in the ruxolitinib group. The causes of death in the ruxolitinib group were hepatic failure, cerebral hemorrhage, and portal-vein thrombosis after surgery for metastatic squamous-cell carcinoma of the head and neck (in 1 patient); pulmonary edema and cardiac arrhythmia (1); retroperitoneal hemorrhage after an orthopedic procedure (1); intestinal perforation associated with terminal ileitis (1); respiratory infection (1); cardiac arrest and myelofibrosis (1); cardiac failure (1); pulmonary extramedullary hematopoiesis and pulmonary failure (1); post-transplantation lymphoproliferative disorder and multiorgan failure (1); and myelofibrosis (2). The causes of death in the best-available-therapy group were pneumonia, septic shock, multisystem organ failure, and acute myeloid leukemia (in 1 patient); post-splenectomy *Klebsiella pneumoniae* sepsis (1); splenectomy, peritoneal hemorrhage, and respiratory failure (1); and renal failure and acute myeloid leukemia (1).

DISCUSSION

This randomized, phase 3 study shows the superiority of a JAK1 and JAK2 inhibitor over the best available therapy with respect to clinically relevant end points in patients with myelofibrosis. Ruxolitinib resulted in a rapid reduction in splenomegaly (at weeks 24 and 48). The meaningful overall reductions in debilitating symptoms of myelofibrosis and improvements in role functioning, which were observed by week 8 and continued through week 48, attest to the beneficial effects of ruxolitinib on quality of life in patients with myelofibrosis. In addition to these reductions in splenomegaly and myelofibrosis-associated symptoms, ruxolitinib resulted in changes in cytokine levels that were similar to those that have been reported previously[15] and that have been implicated in the clinical phenotype of myelofibrosis.[21] In contrast, the best available therapy was associated with a median increase in spleen volume and a worsening of symptoms.

Ruxolitinib was associated with increased frequencies of anemia and thrombocytopenia, findings that are consistent with the results of previous studies.[15,22,23] Anemia and thrombocytopenia could generally be managed with dose reductions or brief interruptions of ruxolitinib therapy, and treatment had to be discontinued in only one patient in the ruxolitinib group owing to thrombocytopenia and in none owing to anemia. More patients in the ruxolitinib group than in the best-available-therapy group required transfusions of packed red cells to treat anemia, though the mean number of units transfused per patient was similar in the two treatment groups.

Some differences in response rates were detected between patients with the wild-type allele and those with the *JAK2* V617F mutation. However, the overall similarity in responses across subgroups suggests that these factors may not be useful prerequisites for the consideration of ruxolitinib therapy. Longer follow-up will be needed to assess changes in marrow fibrosis and the *JAK2* V617F allele burden.

Although no benefit of ruxolitinib was observed with respect to overall survival, at the updated analysis, approximately 25% of the patients who had been assigned to receive the best available therapy had crossed over to ruxolitinib, and an additional 12% had withdrawn consent, with no additional follow-up for survival. This limits the interpretation of the survival analysis because of confounding survival data for one third of the patients in the best-available-therapy group.

In summary, this study shows that continuous oral ruxolitinib therapy can reduce splenomegaly and improve quality of life in patients with myelofibrosis. Further follow-up is needed to assess the long-term outcomes with respect to efficacy and safety.

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