VOLUME 31 · NUMBER 10 · APRIL 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Effect of Ruxolitinib Therapy on Myelofibrosis-Related Symptoms and Other Patient-Reported Outcomes in COMFORT-I: A Randomized, Double-Blind, Placebo-Controlled Trial

*Ruben A. Mesa, Jason Gotlib, Vikas Gupta, John V. Catalano, Michael W. Deininger, Alan L. Shields, Carole B. Miller, Richard T. Silver, Moshe Talpaz, Elliott F. Winton, Jimmie H. Harvey, Thomas Hare, Susan Erickson-Viitanen, William Sun, Victor Sandor, Richard S. Levy, Hagop M. Kantarjian, and Srdan Verstovsek*

Ruben A. Mesa, Mayo Clinic, Scottsdale, AZ; Jason Gotlib, Stanford Cancer Institute, Stanford, CA; Vikas Gupta, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; John V. Catalano, Frankston Hospital and Monash University, Frankston, Victoria, Australia; Michael W. Deininger, Oregon Health and Science University, Portland, OR, and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Alan L. Shields, Adelphi Values, Boston, MA; Carol B. Miller, Saint Agnes Cancer Institute, Baltimore, MD; Richard T. Silver, Weill Medical College of Cornell University, New York, NY; Moshe Talpaz, University of Michigan, Ann Arbor, MI; Elliott F. Winton, Emory University School of Medicine, Atlanta, GA; Jimmie H. Harvey, Birmingham Hematology and Oncology Associates, Birmingham, AL; Thomas Hare, Susan Erickson-Viitanen, William Sun, Victor Sandor, and Richard S. Levy, Incyte, Wilmington, DE; and Hagop M. Kantarjian and Srdan Verstovsek, University of Texas MD Anderson Cancer Center, Houston, TX.

Published online ahead of print at www.jco.org on February 19, 2013.

Written on behalf of all COMFORT-I investigators.

All of the authors have approved this article and accept responsibility for the integrity of this work. This article is original and has not been published elsewhere in whole or in part.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00952289.

Corresponding author: Ruben A. Mesa, MD, Division of Hematology-Oncology, Mayo Clinic Arizona, 13400 E. Shea Blvd, Scottsdale, AZ 85259; e-mail: mesa.ruben@mayo.edu.



0732-183X/13/3110-1285/$20.00

DOI: 10.1200/JCO.2012.44.4489

## ABSTRACT

### Purpose
To assess the effects of ruxolitinib on symptom burden and quality of life (QoL) and to evaluate the ability of the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 to measure meaningful changes in myelofibrosis-related symptoms in patients with myelofibrosis.

### Patients and Methods
COMFORT-I (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment–I) is a double-blind, placebo-controlled phase III study evaluating ruxolitinib in patients with intermediate-2 or high-risk myelofibrosis. Exploratory analyses were conducted on the following patient-reported outcomes (PROs) assessments: modified MFSAF v2.0 (individual symptoms and Total Symptom Score [TSS]), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale, and Patient Global Impression of Change (PGIC).

### Results
Patients receiving ruxolitinib experienced improvements in individual myelofibrosis-related symptoms, although patients receiving placebo experienced worsening ($P < .001$). The majority (91%) of ruxolitinib-treated patients designated as ≥ 50% TSS responders (≥ 50% TSS improvement) self-reported their condition as either "Much improved" or "Very much improved" on the PGIC. These patients achieved significant improvements in the EORTC QLQ-C30 functional domains and Global Health Status/QoL versus patients receiving placebo, who experienced worsening on these measures ($P \leq .0135$). Ruxolitinib-treated patients with a lesser degree of symptom improvement (< 50% TSS responders) also achieved improvements over placebo on these measures. The degree of spleen volume reduction with ruxolitinib correlated with improvements in TSS, PGIC, PROMIS Fatigue Scale, and EORTC Global Health Status/QoL. Ruxolitinib-treated patients who achieved a ≥ 35% reduction in spleen volume experienced the greatest improvements in these PROs.

### Conclusion
Ruxolitinib-treated patients achieved clinically meaningful improvements in myelofibrosis-related symptoms and QoL, but patients receiving placebo reported worsening of symptoms and other PROs.

*J Clin Oncol 31:1285-1292. © 2013 by American Society of Clinical Oncology*

## INTRODUCTION

Myelofibrosis is characterized by splenomegaly,[1] cytopenias,[1] and symptoms that may be debilitating, such as fatigue, pruritus, night sweats, fever, bone pain, and weight loss.[2] These symptoms are highly prevalent among patients with myelofibrosis and can adversely affect quality of life (QoL).[2] The presence of myelofibrosis-related constitutional symptoms (unexplained fever, drenching night sweats, weight loss) has been identified as a risk factor for shortened survival.[3] Splenomegaly and myelofibrosis symptoms are thought to be driven by dysregulation of the Janus kinase (JAK) –STAT pathway resulting from mutations that lead to constitutively active JAK2[4,5] or increased proinflammatory cytokines that signal through JAK1 and JAK2.[6]

There are many types of patient-reported outcome (PRO) tools used in oncology; until recently, none were specifically designed to evaluate the symptoms of myelofibrosis.[7] The Myelofibrosis Symptom Assessment Form (MFSAF) was developed to evaluate the presence and severity of myelofibrosis-related symptoms.[7] In a phase II study of patients with myelofibrosis treated with ruxolitinib, a JAK1/JAK2 inhibitor, the MFSAF proved sensitive to ruxolitinib-associated improvements in symptoms over time, and symptom improvements correlated with objective measures of efficacy.[8] Subsequently, a more streamlined version of the MFSAF, the modified MFSAF v2.0, was developed and was used in a phase III, double-blind, placebo-controlled study (COMFORT-I; Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment–I).[9] In this analysis, we evaluated the ability of the modified MFSAF v2.0 to measure meaningful changes in myelofibrosis-related symptoms and the effects of ruxolitinib on symptom burden and other PROs in COMFORT-I.

## PATIENTS AND METHODS

### Patients

Adult patients who were diagnosed with primary myelofibrosis, postpolycythemia vera myelofibrosis, or postessential thrombocythemia myelofibrosis[10]; were classified as International Prognostic Scoring System[3] high risk or intermediate 2 risk; had palpable splenomegaly ($\geq$ 5 cm below left costal margin); and were resistant or refractory to, intolerant of, or not candidates for available therapy (in the investigator's opinion) were enrolled. Full inclusion and exclusion criteria have been previously reported.[9]

### Study Design

In this multicenter, double-blind phase III trial, patients were randomly assigned 1:1 to receive placebo or ruxolitinib (starting doses of 15 mg twice daily for platelet counts 100 to 200 $\times$ $10^9$/L and 20 mg twice daily for platelet counts $>$ 200 $\times$ $10^9$/L). Dose modification occurred in a blinded fashion for both arms on the basis of predefined criteria. Dose increases for lack of efficacy were permitted, and dose reductions for declining platelet or absolute neutrophil counts were required. The minimum recommended dose was 5 mg twice per day and the maximum permitted dose was 25 mg twice per day.[9] Before week 24, patients receiving placebo were eligible for early unblinding and crossover to ruxolitinib if they had a $\geq$ 25% increase from baseline in spleen volume along with worsening early satiety accompanied by weight loss or worsening splenic pain with increased narcotic requirements. After week 24, patients receiving placebo with asymptomatic spleen growth $\geq$ 25% could also cross over to ruxolitinib. The primary end point was the proportion of patients who achieved a $\geq$ 35% reduction in spleen volume by magnetic resonance imaging or computed tomography scans from baseline to week 24. The comparative secondary end point controlled for type I error was the proportion of patients who achieved $\geq$ 50% reduction (improvement) in the Total Symptom Score (TSS) from baseline to week 24 by using the modified MFSAF v2.0 electronic diary.[9]

This study was conducted in accordance with local regulatory requirements and Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent.

### PRO Assessments

The PRO measures used in the COMFORT-I study have been previously described in detail[9]; a brief overview is provided here.

### Modified MFSAF v2.0 and TSS

The modified MFSAF v2.0, an electronic daily symptom diary, was developed for the COMFORT-I study on the basis of prior paper versions of myelofibrosis symptom assessment forms[7,8] along with feedback from the US Food and Drug Administration. Patients completed the modified MFSAF v2.0 every night from baseline through week 24 (25 weeks total) with electronic data downloaded to a central server. Patients rated the following myelofibrosis symptoms, at their worst as experienced in the 24 hours before assessment, by using a scale from 0 (absent) to 10 (worst imaginable): night sweats, pruritus/itching, abdominal discomfort, pain under the ribs (left side), early satiety, bone/muscle pain, and inactivity. The TSS reflects the sum of the scores of these symptoms except inactivity, for a maximum possible score of 60 (ie, most severe symptom experience). The baseline TSS was the average of seven daily measurements before baseline (at least four of which had to be non-missing), and the week 24 TSS was the average of 28 daily measurements before week 24 (at least 21 of which had to be non-missing).

### PGIC Scale

The Patient Global Impression of Change (PGIC) scale assessed patients' perceptions of change in their myelofibrosis symptoms over time. The PGIC has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial.[11] In this study, patients answered the following question at monthly study visits beginning at week 4: "Since the start of the treatment you've received in this study, your myelofibrosis symptoms are (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, (7) Very much worse."

### EORTC QLQ-C30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) is a 30-item questionnaire used to evaluate QoL and includes five functional domains (physical, cognitive, role, emotional, and social) and a global health status scale. Each subscale is evaluated on a standardized scale of 0 (worst) to 100 (best).[12] Patients completed the EORTC QLQ-C30 at the baseline visit and at each study visit.

### PROMIS Fatigue Scale: Short Form

This scale measures the frequency and impact of fatigue.[13] The Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale contains seven items with a recall period of 7 days. Each of the items uses a 5-point response option with scores of 1 (never) to 5 (always). An average score is calculated and transformed to a final score on a 100-point scale ranging from 0 (never fatigued) to 100 (always fatigued). Patients completed the instrument at the baseline visit and at each study visit.

### Statistical Analysis

Patient disposition and baseline PRO scores were summarized descriptively. Percent changes from baseline in individual symptom scores (average symptom scores from the previous 28 days, as measured by the modified MFSAF v2.0), EORTC QLQ-C30 subscale scores and PROMIS Fatigue Scale scores were calculated at weeks 4, 8, 12, 16, 20 (individual symptom scores only), and 24. Treatment comparisons (ruxolitinib *v* placebo) in these percent changes were performed by using Wilcoxon rank sum test at each time point. Percent changes were calculated at the patient level before descriptive statistics were derived.

Previous data[14] suggested that ruxolitinib doses as low as 10 mg twice per day were associated with symptom benefits similar to those of higher doses in patients with myelofibrosis. To confirm this, we also assessed the effect of dose on symptom improvements. Median percent change from baseline in TSS at week 24 was calculated across groups on the basis of final titrated ruxolitinib dose at week 24 (average ruxolitinib dose during weeks 21 to 24). Median percent change from baseline in TSS at week 24 in ruxolitinib-treated patients with and without new onset/worsening of grade 3 to 4 anemia or grade 3 to 4 thrombocytopenia were also calculated. These TSS analyses were descriptive.

The relationships between the following variables were also evaluated: (1) improvement in TSS ($\geq$ 50% or $<$ 50% TSS response) with the PGIC score and change from baseline in EORTC QLQ-C30 scores at week 24 and (2) spleen volume reductions ($<$ 10%, 10% to 35%, $\geq$ 35%) with the PGIC, percent change from baseline in TSS, and changes from baseline in PROMIS Fatigue Scale and EORTC QLQ-C30 Global Health Status/QoL scores at week 24. For the relationship between TSS response and EORTC QLQ-C30 subscale score, an analysis of covariance was used with the baseline EORTC QLQ-C30 subscale as the covariate, the TSS response as the main effect, and the all-placebo group as the reference level for comparisons. For the relationship between spleen volume reduction and improvement on the PROs, analysis

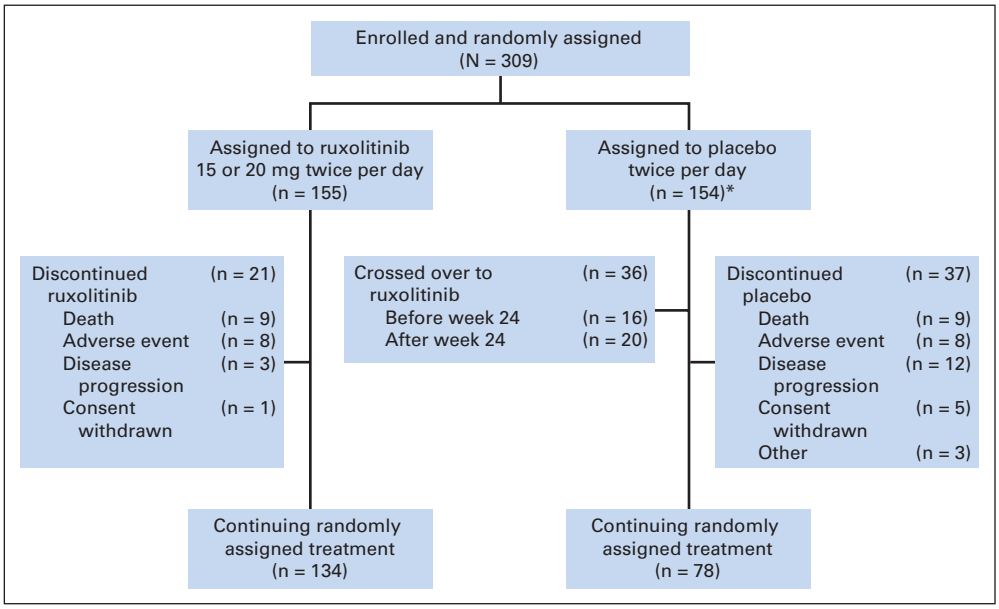


**Fig 1.** CONSORT diagram illustrating the disposition of the 309 enrolled patients at the time of primary analysis data cutoff. (*) Three patients not evaluable for safety but included in the intent-to-treat analysis of efficacy.

of covariance was used with the baseline value as the covariate, the spleen volume reduction group as the main effect, and with the all-placebo group as the reference level for comparisons. Because these analyses were exploratory and descriptive, no adjustments were made for multiple comparisons. These analyses were based on observed data (no missing value imputation was performed).

The interpretability of the modified MFSAF v2.0 was explored as described in the Appendix (online only). Test-retest reliability between week 7 and week 8 was measured by using intraclass correlation coefficients.

## RESULTS

### *Patient Disposition and Baseline PRO Measures*

Patient disposition (N = 309) at the time of the primary analysis, when all patients completed at least 24 weeks of treatment or discontinued and at least half the remaining patients completed 36 weeks of treatment, is shown in Figure 1. As reported previously, baseline characteristics were generally similar in the two treatment arms.[9] The primary and secondary efficacy end points were also previously reported.[9] Briefly, by week 24, a significantly greater proportion of ruxolitinib-treated patients had a $\geq$ 35% reduction in spleen volume compared with patients in the placebo group (41.9% *v* 0.7%; odds ratio, 134.4; 95% CI, 18.0 to 1,004.9; $P < .001$).[9] Ruxolitinib treatment also provided improvement in symptom burden, with 45.9% of patients achieving a $\geq$ 50% reduction in TSS from baseline to week 24 versus 5.3% of the placebo arm (odds ratio, 15.3; 95% CI, 6.9 to 33.7; $P < .001$).[9] Only 3.9% of ruxolitinib-treated patients showed a significant worsening of TSS from baseline to week 24 (ie, > 50% increase in TSS) compared with 33.0% of patients receiving placebo.

The majority of patients completed the EORTC QLQ-C30, PGIC, and PROMIS Fatigue Scale at each study visit (Appendix Table A1, online only), and the electronic daily data capture for the modified MFSAF v2.0 resulted in high compliance rates for completion of this PRO and almost no missing data. Completion of the electronic daily diary required 1 minute or less for 94% of patients, and test-retest reliability intraclass correlation coefficients (week 7 to week 8) were 0.97 for patients treated with placebo and 0.98 for patients treated with ruxolitinib.

Mean scores at baseline in the PRO measures were similar between treatment groups (Table 1). Moreover, all individual myelofibrosis-related symptoms assessed by the modified MFSAF v2.0 were prevalent in the majority of patients in the COMFORT-I study population at baseline. The most prevalent symptoms (reported by > 90% of patients receiving ruxolitinib and placebo) were abdominal discomfort, early satiety, and inactivity. Of note, these same symptoms ranked greatest in severity (Fig 2). EORTC QLQ-C30 subscales reflected poor QoL at baseline and were similar to scores of other populations with advanced cancer and another patient population with myeloproliferative neoplasms.[15,16] Of the five functional domains, patients suffered the greatest burden in role functioning.

### *Changes in Individual Myelofibrosis-Related Symptoms, QoL, and Fatigue*

Overall, individual symptom scores as assessed by the modified MFSAF v2.0 at each 4-week time point in patients receiving ruxolitinib showed improvement relative to baseline (Fig 3). There was approximately linear worsening in symptom scores for patients receiving placebo over the entire 24 weeks. The differences between ruxolitinib- and placebo-treated groups were significant at all time points for all symptoms ($P < .001$; Fig 3). Improvements relative to baseline and placebo in PROMIS Fatigue Scale score and most EORTC QLQ-C30 subscales were also seen with ruxolitinib treatment (Appendix Table A2, online only).

### *Improvement in TSS by Average Total Daily Ruxolitinib Dose and Effect of Anemia or Thrombocytopenia on TSS in Ruxolitinib-Treated Patients*

Although patients in the study began dosing at either 15 or 20 mg twice per day, individualized dose optimization resulted in an overall average dose exposure for ruxolitinib-treated patients of 15.5 mg twice per day. Median improvements from baseline at week 24 in TSS

**Table 1.** Baseline Scores on Patient-Reported Outcome Measures

| Parameter Measured | Ruxolitinib Mean | Ruxolitinib Range | Placebo Mean | Placebo Range | Maximum Score Possible |
|---|---|---|---|---|---|
| Modified MFSAF v2.0, TSS | 18.2 | 0-50.1 | 16.9 | 0-52.7 | 60 (worst possible) |
| EORTC QLQ-C30 Subscales | | | | | |
| Global Health Status/QoL | 52.7 | 0-100 | 52.9 | 0-100 | 100 (best possible) |
| Physical Functioning | 69.7 | 0-100 | 67.2 | 20-100 | 100 (best possible) |
| Role Functioning | 64.5 | 0-100 | 63.2 | 0-100 | 100 (best possible) |
| Emotional Functioning | 73.3 | 0-100 | 75.5 | 0-100 | 100 (best possible) |
| Cognitive Functioning | 80.7 | 0-100 | 80.1 | 16.7-100 | 100 (best possible) |
| Social Functioning | 68.0 | 0-100 | 66.1 | 0-100 | 100 (best possible) |
| PROMIS Fatigue Scale | 43.7 | 10.7-85.7 | 43.3 | 0-89.3 | 100 (worst possible) |

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MFSAF, Myelofibrosis Symptom Assessment Form; PROMIS, Patient Reported Outcomes Measurement Information System; QoL, quality of life; TSS, Total Symptom Score.

exceeding 50% were observed for all dose groups in which the dose was ≥ 10 mg twice per day: 71.1% (n = 30), 59.6% (n = 23), 67.7% (n = 38), and 66.2% (n = 20) for dose groups of 10 mg twice per day, 15 mg twice per day, 20 mg twice per day, and 25 mg twice per day, respectively. Ruxolitinib-treated patients who developed new-onset or worsening of grade 3 or 4 anemia achieved TSS improvements at week 24 that were similar in magnitude to improvements in those who did not experience grade 3 or 4 anemia (median, −46.4% [n = 47] and −58.3% [n = 82], respectively). Ruxolitinib-treated patients with and without new-onset or worsening of grade 3 or 4 thrombocytopenia also experienced TSS improvements (median, −26.8% [n = 13] and −62.5% [n = 116], respectively). Although there was an apparent difference in the magnitude of the improvements between these groups, the number of patients with grade 3 or 4 thrombocytopenia was too small to draw a clear conclusion. In contrast, patients receiving placebo showed worsening TSS scores (median, 14.6% [n = 103]).

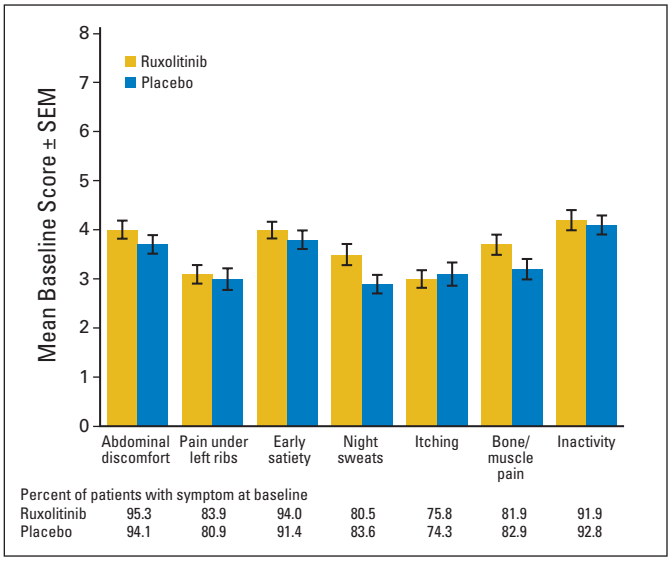


**Fig 2.** Individual symptom scores at baseline (in patients with symptoms at baseline) as measured by the modified Myelofibrosis Symptom Assessment Form v2.0. The most prevalent symptoms (reported in > 90% of patients in both treatment groups) and most severe symptoms were abdominal discomfort, early satiety, and inactivity. Scale range: 0, absent to 10, worst imaginable.

### *Relationship Between TSS Improvement and PGIC*

As detailed in Table 2, 62 (91.2%) of ruxolitinib patients who were ≥ 50% TSS responders characterized their condition as either "Much improved" or "Very much improved." In addition, 67 (73.7%) of the placebo group who were less than 50% TSS responders characterized their condition as "unchanged" or "worsening." These results suggest a relationship between the TSS and the PGIC in that the individual patient perceived and reported meaningful benefit from the treatment in terms of an overall improvement in myelofibrosis symptoms, which further supports the use of the modified MFSAF v2.0.

### *Relationship Between TSS Improvement and EORTC QLQ-C30*

For each subscale of the EORTC QLQ-C30, ruxolitinib-treated patients reported increases (improvements) from baseline, whereas patients receiving placebo reported decreases (worsening). Ruxolitinib-treated patients defined as ≥ 50% TSS responders achieved significantly greater improvements in the EORTC QLQ-C30 subscales versus patients receiving placebo who continued to show deterioration in their QoL ($P \leq .0135$; Fig 4). Notably, ruxolitinib-treated patients with a lesser degree of symptom response (< 50% TSS responders) also achieved significant improvements over placebo for all EORTC QLQ-C30 subscales ($P \leq .0075$), with the exception of the Emotional Functioning and Cognitive Functioning domains (Fig 4).

### *Relationship Between Spleen Volume Reductions and PROs*

In the ruxolitinib arm, improvements in TSS, abdominal symptoms, nonabdominal symptoms, and the PGIC score correlated with reductions in spleen size; patients who had a ≥ 35% reduction in spleen volume had the greatest improvement in symptoms and perceived change in condition (Figs 5A to 5D). Of note, however, ruxolitinib-treated patients who exhibited even small spleen volume reductions (< 10%) achieved meaningful improvements in these PRO measures compared with patients in the placebo group. In addition, ruxolitinib-treated patients who achieved a ≥ 10% reduction in spleen volume had significant improvements versus placebo in both the PROMIS Fatigue Scale ($P < .001$; Fig 5E) and EORTC QLQ-C30 Global Health Status ($P < .001$; Fig 5F). Indeed, the improvements in

  

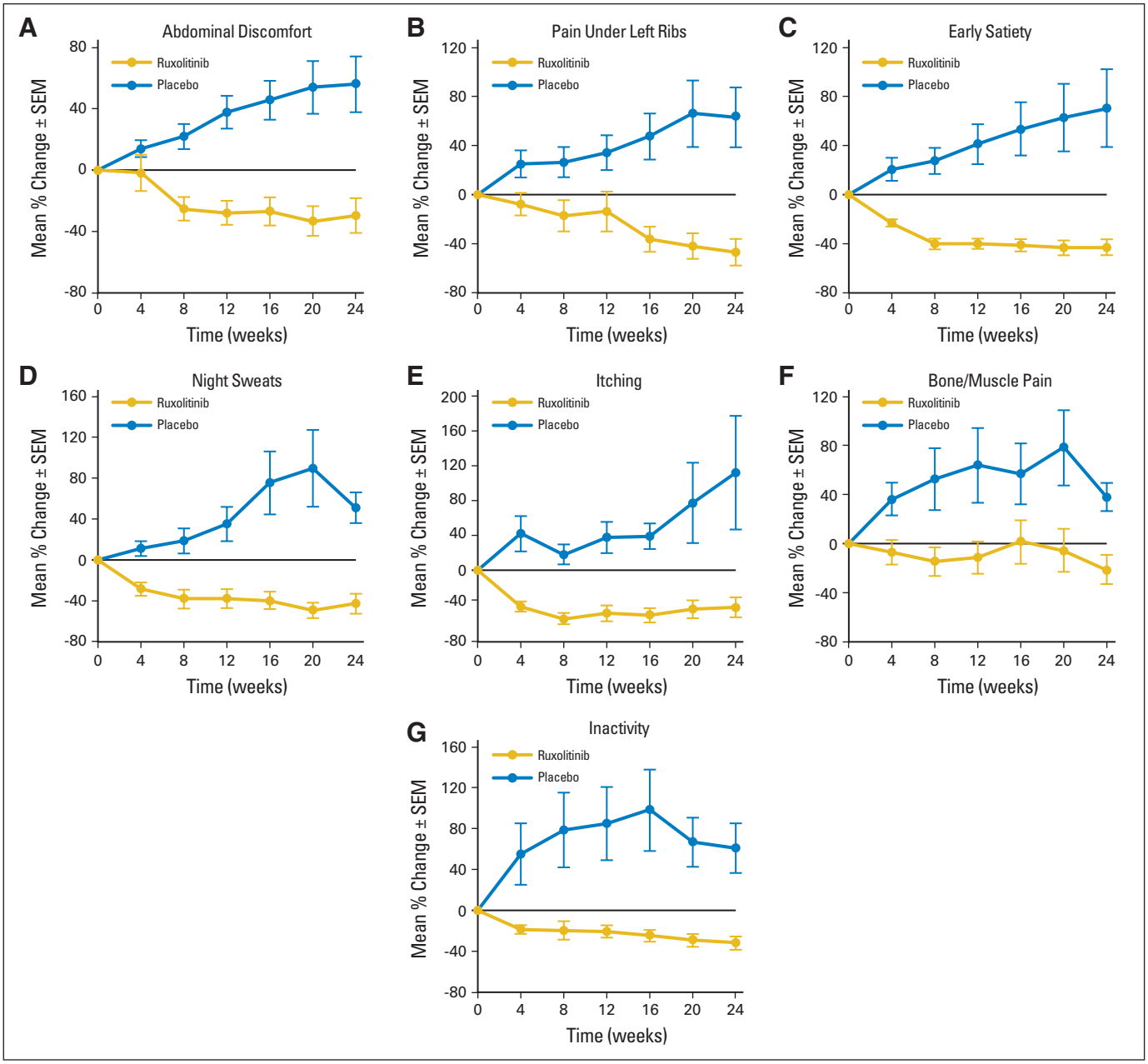


**Fig 3.** (A-G) Assessment of individual symptom burden by using the modified Myelofibrosis Symptom Assessment Form v2.0. Individual symptom scores at each 4-week time point improved in patients receiving ruxolitinib, whereas patients who received placebo experienced a worsening of symptoms. $P < .001$ for all comparisons between ruxolitinib and placebo at all time points (weeks 4, 8, 12, 16, 20, and 24). Individual symptom scores at each 4-week time point were calculated by averaging the daily individual symptom scores from the previous 28 days.

PRO parameters for ruxolitinib-treated patients who achieved ≥ 35% reduction in spleen volume versus those who achieved a 10% to less than 35% reduction in spleen volume were not significantly different (all $P \geq .07$).

## DISCUSSION

In this randomized, placebo-controlled study, patients showed a high prevalence and severity of individual myelofibrosis-related symptoms at baseline, and the modified MFSAF v2.0 was sensitive to differentiating responses in the placebo and ruxolitinib arms over time. Individual symptom scores with ruxolitinib showed improvement relative to baseline and to placebo early in the course of study treatment. The true magnitude of symptom response within 4 weeks of initiating ruxolitinib therapy may be underestimated in this analysis, because symptom scores calculated by using a 28-day average included scores from the initial days of treatment that may have potentially diluted the benefit seen later in the treatment period. Analysis of TSS in ruxolitinib-treated patients by using a 7-day moving average over time shows that the majority of TSS responses (≥ 50% reduction in TSS

**Table 2.** Relationship Between PGIC Scale and TSS

| | Ruxolitinib* (n = 127) | | | | Placebo* (n = 100) | | | | Total Sample* (N = 227) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≥ 50% TSS Responder (n = 68) | | < 50% TSS Responder (n = 59) | | ≥ 50% TSS Responder (n = 9) | | < 50% TSS Responder (n = 91) | | ≥ 50% TSS Responder (n = 77) | | < 50% TSS Responder (n = 150) | |
| PGIC Scale | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Very much improved | 35 | 51.5 | 8 | 13.6 | 1 | 11.1 | 0 | 0.0 | 36 | 46.8 | 8 | 5.3 |
| Much improved | 27 | 39.7 | 19 | 32.2 | 3 | 33.3 | 7 | 7.7 | 30 | 39.0 | 26 | 17.3 |
| Minimally improved | 3 | 4.4 | 22 | 37.3 | 3 | 33.3 | 17 | 18.7 | 6 | 7.8 | 39 | 26.0 |
| No change | 0 | 0.0 | 6 | 10.2 | 2 | 22.2 | 30 | 33.0 | 2 | 2.6 | 36 | 24.0 |
| Minimally worse | 2 | 2.9 | 3 | 5.1 | 0 | 0.0 | 19 | 20.9 | 2 | 2.6 | 22 | 14.7 |
| Much worse | 1 | 1.5 | 0 | 0.0 | 0 | 0.0 | 14 | 15.4 | 1 | 1.3 | 14 | 9.3 |
| Very much worse | 0 | 0.0 | 1 | 1.7 | 0 | 0.0 | 4 | 4.4 | 0 | 0.0 | 5 | 3.3 |

NOTE. ≥ 50% TSS responders are patients who achieved a ≥ 50% improvement in modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 Total Symptom Score (TSS; baseline TSS–week-24 TSS); < 50% TSS responders are patients who achieved a < 50% improvement in modified MFSAF v2.0 TSS (baseline TSS–week-24 TSS).
Abbreviation: PGIC, Patient Global Impression of Change.
*Number of patients with a baseline and week-24 TSS and who completed the PGIC at week 24.

relative to baseline) occur within the first 4 weeks of treatment.[9] The nightly recording of symptoms by the patient and electronic data transfers contributed to a high degree of compliance by patients in obtaining symptom data. Overall, the baseline prevalence of symptoms and rapid, clinically meaningful improvements exhibited by ruxolitinib-treated patients are consistent with those from the phase II study, in which a paper-pencil version of the MFSAF was sensitive to detecting early and sustained symptom improvements with ruxolitinib treatment.[8] Meaningful reductions in symptom burden were observed for ruxolitinib doses ≥ 10 mg twice per day,

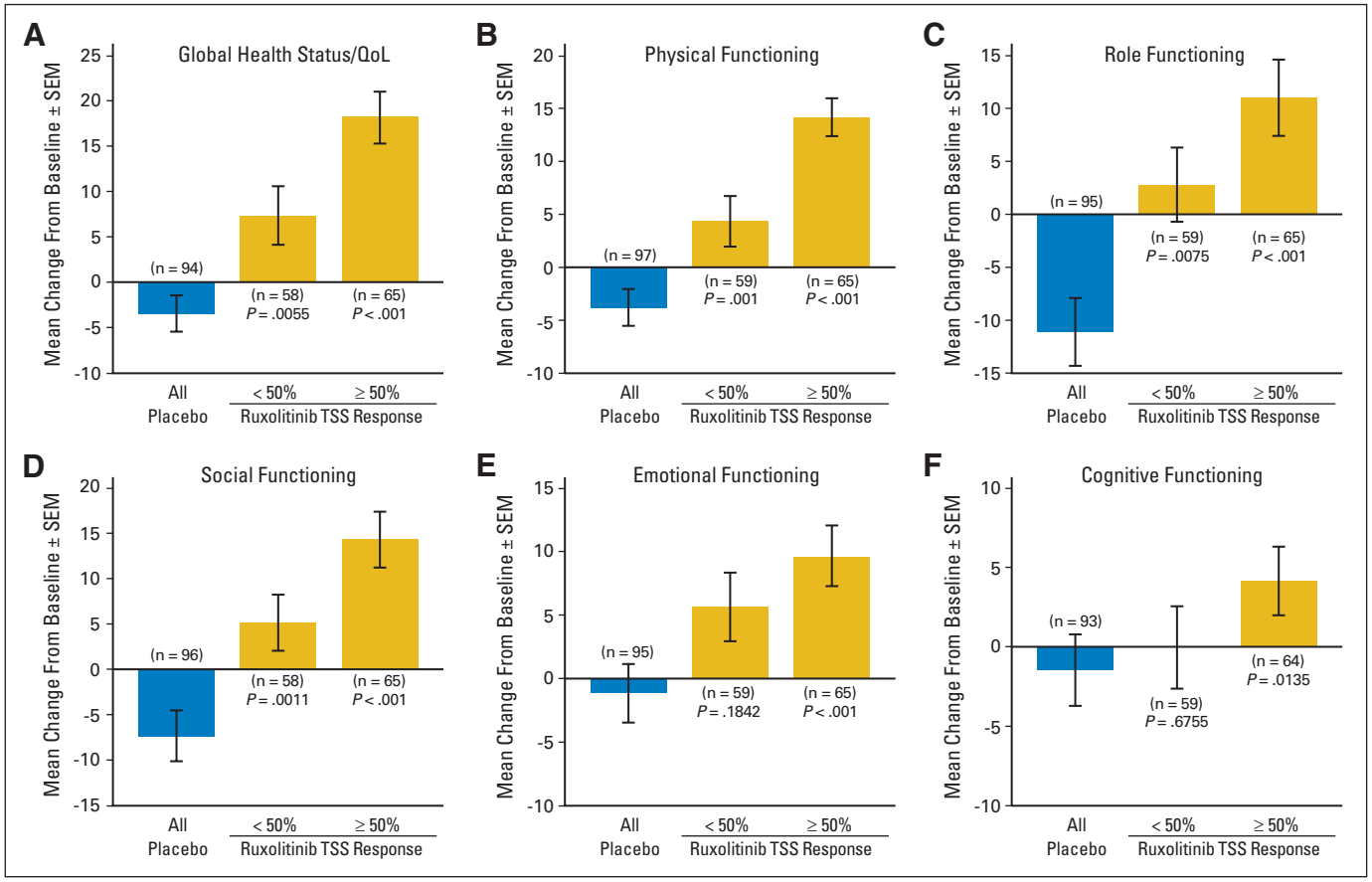


**Fig 4.** (A-F) Relationship between symptoms as assessed by the modified Myelofibrosis Symptom Assessment Form v2.0, with quality of life (QoL) as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) at baseline. Patients receiving ruxolitinib who were categorized as ≥ 50% Total Symptom Score (TSS) responders achieved significantly greater improvements in the EORTC QLQ-C30 subscales versus patients in the placebo group.

  

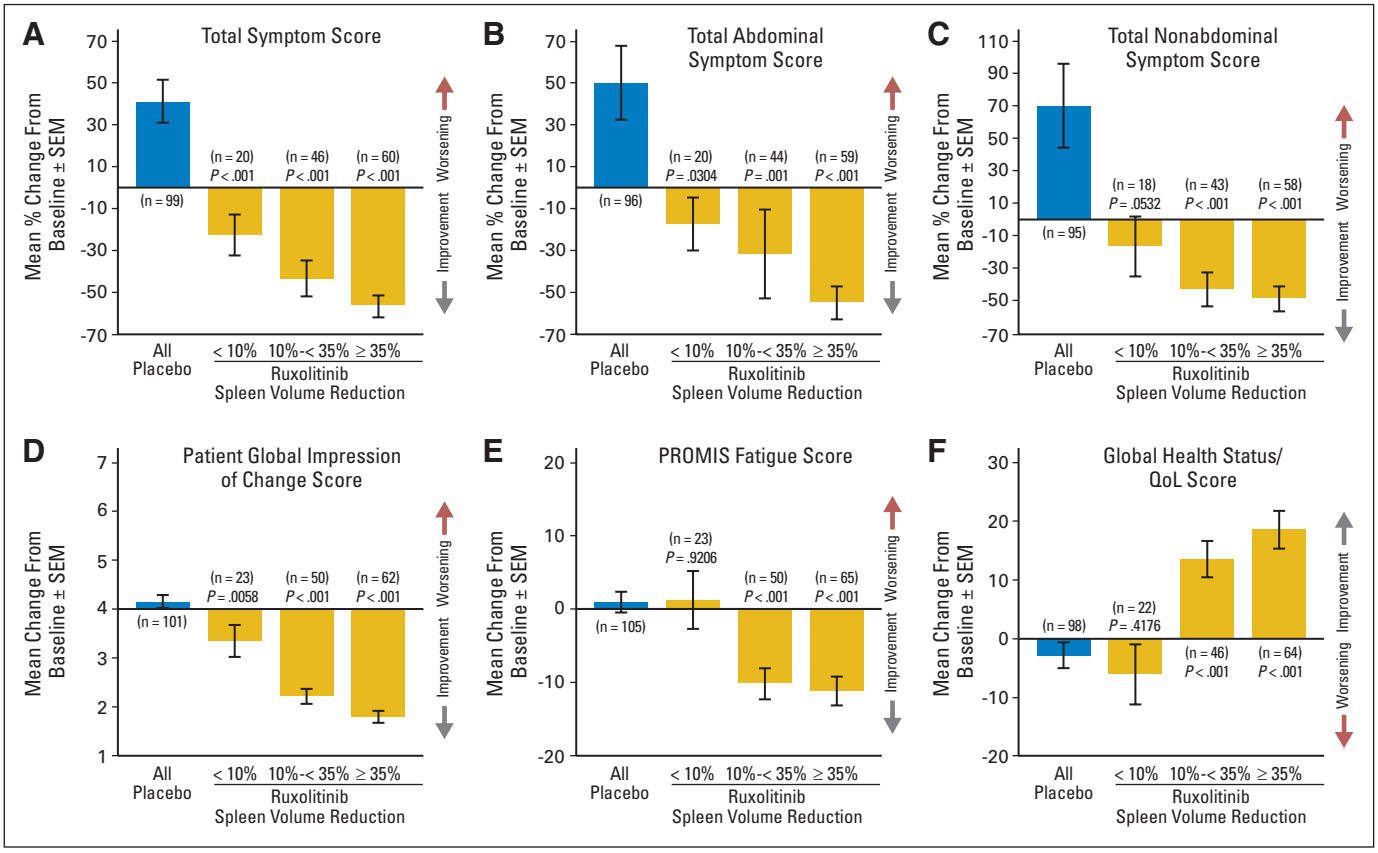


**Fig 5.** (A-F) Relationship between spleen volume reduction with ruxolitinib and patient-reported outcomes (PROs). Ruxolitinib-treated patients who achieved a ≥ 35% reduction in spleen volume experienced the greatest improvements in all PROs, whereas patients receiving placebo reported worsening of symptoms on these measures. However, patients given ruxolitinib who had ≥ 10% reduction in spleen volume also achieved significant improvements in all PROs. (D) Change from baseline in patient perception of their disease (baseline = score of 4 [no change]). PROMIS, Patient Reported Outcomes Measurement Information System; QoL, quality of life.

while placebo-treated patients reported symptom worsening. Notably, ruxolitinib-treated patients also demonstrated improvement in fatigue (a common symptom in patients with myelofibrosis) relative to baseline and to patients in the placebo group on two PRO instruments.

The modified MFSAF v2.0 was also shown to correlate well with other established PRO assessment tools, including the PGIC and the EORTC QLQ-C30, further supporting use of the MFSAF in patients with myelofibrosis. At baseline, many of the scores for EORTC QLQ-C30 subscales, such as the Global Health Status/QoL, were much lower than those of the general population[15,16] and were consistent with scores for other populations with advanced cancer[15] as well as for another patient population with myelofibrosis.[16] Moreover, the changes in the EORTC QLQ-C30 subscale scores with treatment mirrored trends in the MFSAF, with ruxolitinib ≥ 50% TSS responders showing the most improvement. Even ruxolitinib less than 50% TSS responders demonstrated significant improvements compared with those in the placebo group in EORTC QLQ-C30 subscale scores except for the Emotional Functioning and Cognitive Functioning domains; scores for these two domains were similar between the COMFORT-I population and general population at baseline.[16]

Finally, improvements in symptom burden and perceived change in condition, fatigue, and QoL in ruxolitinib-treated patients were not dependent on reaching the protocol-defined threshold of spleen response (≥ 35% reduction in spleen volume at week 24). Even patients with spleen volume reductions ≥ 10% who received ruxolitinib had significant improvements in symptom burden and perceived change in condition, fatigue, and QoL. A similar finding was observed in the phase II study.[8]

In conclusion, changes in the modified MFSAF v2.0 with ruxolitinib therapy were clinically meaningful. In addition, the modified MFSAF v2.0 correlated well with established PRO measures. Although there was a trend for greater improvements in PROs with greater spleen volume reductions with ruxolitinib, even patients with modest changes in spleen size or symptom scores demonstrated improvements in symptom burden and QoL, whereas patients receiving placebo continued to worsen by these same measures. These data support the use of the MFSAF in clinical studies of treatments for myelofibrosis.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure*

*categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*
**Employment or Leadership Position:** Thomas Hare, Incyte (C); Susan Erickson-Viitanen, Incyte (C); William Sun, Incyte (C); Victor Sandor, Incyte (C); Richard S. Levy, Incyte (C) **Consultant or Advisory Role:** Jason Gotlib, Incyte (C); Vikas Gupta, Incyte (C), Novartis (C), sanofi-aventis (C), YM BioSciences (C); John V. Catalano, Incyte (C), Novartis (C); Alan L. Shields, Incyte (C); Carole B. Miller, Incyte (C), Novartis (C); Moshe Talpaz, Novartis (C), sanofi-aventis (C); Elliott F. Winton, Incyte (C) **Stock Ownership:** Thomas Hare, Incyte; Susan Erickson-Viitanen, Incyte; William Sun, Incyte; Victor Sandor, Incyte; Richard S. Levy, Incyte **Honoraria:** Jason Gotlib, Incyte; Vikas Gupta, Incyte, Novartis; John V. Catalano, Incyte, Novartis; Michael W. Deininger, Incyte; Carole B. Miller, Incyte, Novartis; Moshe Talpaz, Novartis; Elliott F. Winton, Incyte **Research Funding:** Ruben A. Mesa, Incyte; Jason Gotlib, Incyte; Vikas Gupta, Incyte, Novartis; Moshe Talpaz, Incyte, Novartis, sanofi-aventis; Elliott F. Winton, Incyte; Hagop M. Kantarjian, Incyte; Srdan Verstovsek, Incyte **Expert Testimony:** None **Other Remuneration:** Vikas Gupta, Incyte, Novartis

## AUTHOR CONTRIBUTIONS

**Conception and design:** Ruben A. Mesa, Vikas Gupta, Susan Erickson-Viitanen, William Sun, Richard S. Levy, Srdan Verstovsek
**Provision of study materials or patients:** Ruben A. Mesa, Jason Gotlib, Vikas Gupta, John V. Catalano, Michael W. Deininger, Alan L. Shields, Carole B. Miller, Richard T. Silver, Moshe Talpaz, Elliott F. Winton, Jimmie H. Harvey, Hagop M. Kantarjian, Srdan Verstovsek
**Collection and assembly of data:** Ruben A. Mesa, Jason Gotlib, Vikas Gupta, John V. Catalano, Michael W. Deininger, Alan L. Shields, Carole B. Miller, Richard T. Silver, Moshe Talpaz, Elliott F. Winton, Jimmie H. Harvey, Thomas Hare, Victor Sandor, Hagop M. Kantarjian, Srdan Verstovsek
**Data analysis and interpretation:** Ruben A. Mesa, Vikas Gupta, John V. Catalano, Alan L. Shields, Richard T. Silver, Elliott F. Winton, Jimmie H. Harvey, Susan Erickson-Viitanen, William Sun, Victor Sandor, Hagop M. Kantarjian
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

## REFERENCES


**1.** Tefferi A: Myelofibrosis with myeloid metaplasia. N Engl J Med 342:1255-1265, 2000

**2.** Mesa RA, Niblack J, Wadleigh M, et al: The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): An international Internet-based survey of 1179 MPD patients. Cancer 109: 68-76, 2007

**3.** Cervantes F, Dupriez B, Pereira A, et al: New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 113:2895-2901, 2009

**4.** Kralovics R, Passamonti F, Buser AS, et al: A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 352:1779-1790, 2005

**5.** Tefferi A: Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. Leukemia 24:1128-1138, 2010

**6.** Vainchenker W, Dusa A, Constantinescu SN: JAKs in pathology: Role of Janus kinases in hematopoietic malignancies and immunodeficiencies. Semin Cell Dev Biol 19:385-393, 2008

**7.** Mesa RA, Schwager S, Radia D, et al: The Myelofibrosis Symptom Assessment Form (MFSAF): An evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. Leuk Res 33:1199-1203, 2009

**8.** Mesa RA, Kantarjian H, Tefferi A, et al: Evaluating the serial use of the Myelofibrosis Symptom Assessment Form for measuring symptomatic improvement: Performance in 87 myelofibrosis patients on a JAK1 and JAK2 inhibitor (INCB018424) clinical trial. Cancer 117:4869-4877, 2011

**9.** Verstovsek S, Mesa RA, Gotlib J, et al: A double-blind placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 366:799-807, 2012

**10.** Tefferi A, Vardiman JW: Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia 22:14-22, 2008

**11.** Cella D, Hahn EA, Dineen K: Meaningful change in cancer-specific quality of life scores: Differences between improvement and worsening. Qual Life Res 11:207-221, 2002

**12.** Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993

**13.** Garcia SF, Cella D, Clauser SB, et al: Standardizing patient-reported outcomes assessment in cancer clinical trials: A patient-reported outcomes measurement information system initiative. J Clin Oncol 25:5106-5112, 2007

**14.** Verstovsek S, Kantarjian H, Mesa RA, et al: Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med 363:1117-1127, 2010

**15.** Scott NW, Fayers PM, Aaronson NK, et al: EORTC QLQ-C30 Reference Values, 2008. http://groups.eortc.be/qol/sites/default/files/img/newsletter/reference_values_manual2008.pdf

**16.** Scherber R, Dueck AC, Johansson P, et al: The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): International prospective validation and reliability trial in 402 patients. Blood 118:401-408, 2011



## *Support*

Supported by Incyte.


  