SUPPLEMENTARY APPENDIX

Safety and efficacy of ruxolitinib in an open-label, multicenter, single-arm phase3b expanded-access study in patients with myelofibrosis: a snapshot of 1144 patients in the JUMP trial

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 doi:10.3324/haematol.2016.143677

Received: January 29, 2016.

Accepted: May 25, 2016.

Pre-published: May 31, 2016.

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Supplemental Methods

Eligibility criteria

Patients were required to have a peripheral blood blast count <10% and an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients were not required to have received prior therapy for MF.

Protocol-specified dosing regimen

All patients received ruxolitinib at a dose of 5-25 mg bid based on baseline platelet count until discontinuation criteria were met (ie, disease progression, unacceptable toxicity, death, discontinuation from the study for any other reason, physician decision, withdrawal of informed consent) or completed treatment per protocol (until 24 months after the last patient's first visit or until the drug became commercially available), whichever occurred first. Patients who completed treatment per protocol were considered to have discontinued treatment. The dose could be increased by 5 mg bid (5 mg/day for patients starting ruxolitinib at 5 mg bid) at week 4 (up to 25 mg bid) for inadequate efficacy if there were no treatment-related toxicities at the current dose level. Inadequate efficacy was defined as a <40% reduction from baseline in palpable spleen length. Dose decreases or interruptions were mandatory for safety reasons (eg, hematologic toxicities, such as declining platelet counts or absolute neutrophil count levels, and nonhematologic toxicities) and were made using a protocol-specified dosing regimen. For patients starting ruxolitinib at doses of 15 to 20 mg bid, the dose was decreased for platelet counts $<125\times10^9$/L and held for platelet counts $<50\times10^9$/L or absolute neutrophil count levels <500/μL.

Endpoints

PFS was defined as the time from the first dose to the date of progressive disease (by International Working Group for Myeloproliferative Neoplasms Research and Treatment criteria[15]) or death. AML-free survival was defined as the time from the first dose to the earliest date of either first bone marrow blasts ≥20% or first peripheral blood blasts ≥20% for ≥8 weeks or death. OS was defined as the time from the first study dose to the date of death, whatever the cause. The FACT-Lym TS and FACIT-Fatigue Scale were used to document patient-reported symptoms, including physical well-being, social/family well-being, emotional well-being, functional well-being, constitutional symptoms, and fatigue[16,17]

Statistical analysis

Changes in palpable spleen length were assessed in patients with baseline and postbaseline assessments at weeks 4, 8, 12, 24, 36, and 48. Patients who had a palpable but missing spleen length at baseline or at a postbaseline visit were excluded from the analysis for that visit. Best overall spleen response from baseline in palpable spleen length

at any time was recorded for each evaluable patient up to week 48 of treatment. Changes from baseline in mean scores were calculated based on the mean score for patients with an assessment at baseline and at week 4, 12, 24, or 48. The scale for the FACT-Lym TS is measured from 0 (worst) to 168 (best), with a range for the MID of 6.5 to 11.2 points.[18] The scale for the FACIT-Fatigue score is measured from 0 (worst) to 52 (best), with an MID of 3 points.[19] A response in the FACT-Lym TS or on the FACIT-Fatigue scale was defined as the upper limit of the MID (FACT-Lym TS, 11.2 points; FACIT-Fatigue score, 3 points). Survival assessments (PFS, AML-free survival, OS) were performed 28-37 days after patients discontinued from the study or completed treatment per protocol.

Supplemental Results

The dose of ruxolitinib did not differ substantially among patients with primary or secondary MF. Among patients with PMF (n=672), post-polycythemia MF (PPV-MF; n=278), and post-essential MF (PET-MF; n=190), 36.5%, 29.9%, and 24.2% had a starting dose of 15 mg bid, respectively, and 60.9%, 64.7%, and 72.6% had a starting dose of 20 mg bid, respectively. The median average daily dose was 30.0 mg/day (range, 10.0-49.6 mg/day) for patients with PMF, 29.8 mg/day (range, 10.0-48.8 mg/day) among patients with PPV-MF, and 31.2 mg/day (range, 7.1-49.6 mg/day) for patients with PET-MF. Median exposures were similar (PMF, 30.0 weeks [range, 7.7-50.5 weeks]; PPV-MF, 29.4 weeks [range, 7.9-48.8 weeks]; PET-MF, 31.1 weeks [range, 6.0-49.6 weeks]).

Efficacy by MF subtype

At week 24, 54.2%, 56.9%, and 59.2% of evaluable patients with PMF, PPV-MF, and PET-MF achieved a ≥50% reduction from baseline in palpable spleen length, respectively (**Supplemental Figure 1**); spleen response rates at week 48 were 57.3%, 65.5%, and 68.2%, respectively. At each assessment, after week 4, at least three-quarters of patients had a ≥25% reduction in palpable spleen length. Most patients with postbaseline assessments in each MF subgroup experienced a ≥50% reduction in spleen length at any time by week 48 (PMF, 66.9% [417/623]; PPV-MF, 70.7% [186/263]; PET-MF, 73.1% [122/167]). The median time to the first ≥50% reduction in palpable spleen length was shorter for patients with PET-MF (4.3 weeks [range, 2.6-51.3 weeks]) than for patients with PMF (7.1 weeks [range, 0.1-53.1 weeks]) or PPV-MF (7.9 weeks [range, 3.7-49.4 weeks]).

Clinically meaningful improvements in symptoms across MF subgroups were seen as early as 4 weeks after the start of treatment and were maintained over time, as evaluated by the FACT-Lym TS and FACIT-Fatigue scale. Approximately 40%-53% of patients with PMF, PPV-MF, or PET-MF achieved a response (ie, minimally important difference [MID]) at each time point in the FACT-Lym TS (**Supplemental Figure 3A-C**), and 41%-55% had a response on the FACIT-Fatigue scale (**Supplemental Figure 4A-C**).

Overall, there were 58 deaths (8.6%) among patients with PMF, 15 deaths (5.4%) among patients with PPV-MF, and 13 deaths (6.8%) among patients with PET-MF. The estimated OS probability at 48 weeks was similar for patients with primary or secondary MF (PMF, 0.9 [95% CI, 0.91-0.95]; PPV-MF, 1.0 [95% CI, 0.93-0.98]; PET-MF, 0.9 [95% CI, 0.90-0.97]).

Supplemental Table 1. Countries Participating in the JUMP Study With Corresponding Enrollment

Country	Patients, n (%)
Argentina	28 (2.4)
Austria	31 (2.7)
Belgium	53 (4.6)
Brazil	60 (5.2)
Canada	53 (4.6)
Colombia	9 (0.8)
Czech Republic	10 (0.9)
Germany	376 (32.9)
Greece	17 (1.5)
Hungary	19 (1.7)
Israel	20 (1.7)
Italy	276 (24.1)
Luxembourg	6 (0.5)
Poland	5 (0.4)
Portugal	18 (1.6)
Russian Federation	2 (0.2)
Saudi Arabia	4 (0.3)
Slovakia	1 (0.1)
South Africa	5 (0.4)
Spain	142 (12.4)
Thailand	9 (0.8)

Supplemental Table 2. Patient Disposition

n (%)	All Patients N=1144
Still on treatment	406 (35.5)
Treatment duration completed per protocol	383 (33.5)
Discontinued prior to treatment completion	355 (31.0)
Primary reasons for discontinuation	
Adverse event	158 (13.8)
Disease progression	81 (7.1)
Death	44 (3.8)
Consent withdrawal	43 (3.8)
Physician's decision	16 (1.4)
Protocol deviation	7 (0.6)
Loss to follow-up	3 (0.3)
Administrative problems	3 (0.3)

Supplemental Table 3. Adverse Events Leading to Discontinuations Regardless of Study Drug Relationship (in ≥2 patients)

Preferred Term	All Patients N=1144	
	All Grades, n (%)	Grade 3/4, n (%)
Thrombocytopenia	37 (3.2)	26 (2.3)
Anemia	30 (2.6)	20 (1.8)
Pyrexia	8 (0.7)	5 (0.4)
Cardiac failure	7 (0.6)	6 (0.5)
Leukocytosis	6 (0.5)	6 (0.5)
Pneumonia	6 (0.5)	5 (0.4)
Diarrhea	5 (0.4)	3 (0.3)
Respiratory failure	5 (0.4)	5 (0.4)
Acute myeloid leukemia	4 (0.4)	4 (0.4)
Dyspnea	4 (0.4)	3 (0.3)
Leukopenia	4 (0.4)	3 (0.3)
Platelet count decreased	4 (0.4)	3 (0.3)
Septic shock	4 (0.4)	4 (0.4)
Neutropenia	3 (0.3)	3 (0.3)
Ascites	3 (0.3)	1 (0.1)
Asthenia	3 (0.3)	3 (0.3)
Fatigue	3 (0.3)	1 (0.1)
Hemoglobin decreased	3 (0.3)	2 (0.2)
Renal failure acute	3 (0.3)	3 (0.3)
Pain in extremity	3 (0.3)	1 (0.1)
Coagulopathy	2 (0.2)	2 (0.2)
Cardiac arrest	2 (0.2)	2 (0.2)
General physical health deterioration	2 (0.2)	1 (0.1)
Sudden death	2 (0.2)	2 (0.2)
Sepsis	2 (0.2)	2 (0.2)
Fall	2 (0.2)	1 (0.1)

General physical condition abnormal	2 (0.2)	2 (0.2)
Neutrophil count decreased	2 (0.2)	2 (0.2)
Platelet count increased	2 (0.2)	2 (0.2)
Weight increased	2 (0.2)	0
Musculoskeletal chest pain	2 (0.2)	0
Lung neoplasm malignant	2 (0.2)	2 (0.2)
Cerebral hemorrhage	2 (0.2)	1 (0.1)
Headache	2 (0.2)	1 (0.1)
Paresthesia	2 (0.2)	1 (0.1)
Acute respiratory distress syndrome	2 (0.2)	2 (0.2)

Supplemental Table 4. Infections Regardless of Study Drug Relationship (in ≥1% patients)

	All Patients N=1144	
Preferred Term	**All Grades, n (%)**	**Grade 3/4, n (%)**
Nasopharyngitis	72 (6.3)	0
Urinary tract infection	69 (6.0)	13 (1.1)
Pneumonia	61 (5.3)	41 (3.6)
Bronchitis	48 (4.2)	1 (0.1)
Herpes zoster	41 (3.6)	1 (0.1)
Influenza	34 (3.0)	1 (0.1)
Upper respiratory tract infection	33 (2.9)	1 (0.1)
Cystitis	28 (2.5)	2 (0.2)
Gastroenteritis	21 (1.8)	6 (0.5)
Respiratory tract infection	20 (1.8)	4 (0.4)
Oral herpes	18 (1.6)	0

Supplemental Table 5. Baseline Characteristics of Patients With Intermediate-1–Risk MF

	N=163
Age, median (range), years	62.0 (25.0-79.0)
≥65 years, n (%)	49 (30.1)
Male, n (%)	88 (54.0)
Time since initial diagnosis, median (range), months[a]	17.9 (0.2-276.0)
MF subtype, n (%)	
PMF	88 (54.0)
PPV-MF	47 (28.8)
PET-MF	28 (17.2)
Hemoglobin level, median (range), g/L[a]	115.5 (59.0-177.0)
<100 g/L, n (%)	35 (21.5)
Platelet count, median (range), $\times 10^9$/L[a]	276.0 (75.0-915.0)
<100×10^9/L, n (%)	13 (8.0)
100 to <200×10^9/L, n (%)	43 (26.4)
≥200×10^9/L, n (%)	106 (65.0)
Prior transfusions, n (%)	16 (9.8)
Peripheral blasts ≥1%, n (%)[b]	21 (15.0)
Palpable spleen length, median (range), cm[c]	12.0 (4.0-45.0)

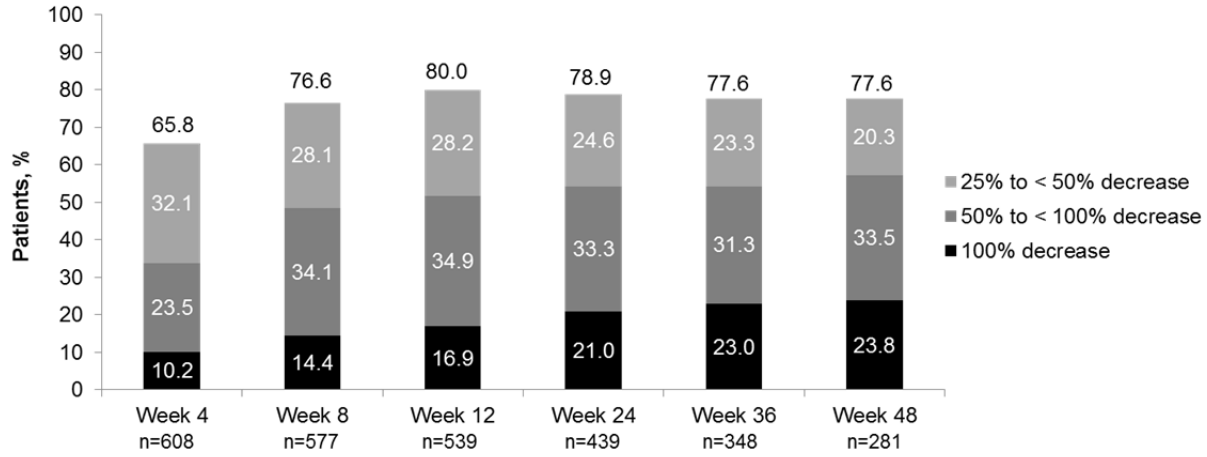
[a] n=162; [b] n=140; [c] n=161.

Supplemental Table 6. Adverse Events Regardless of Study Drug Relationship in Patients With Intermediate-1–Risk MF (in ≥5% of Patients)

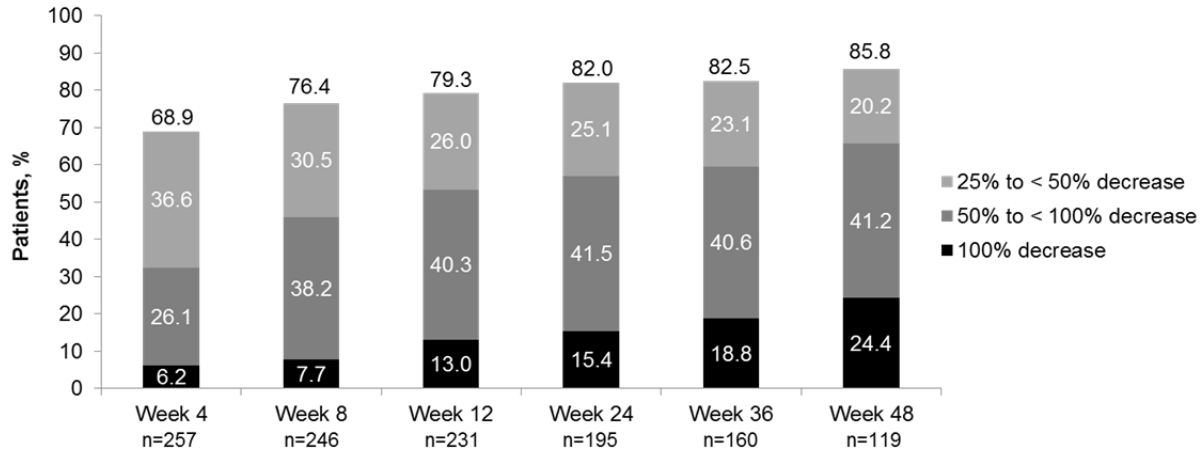
Preferred Term[a]	All Patients N=163	
	All Grades, n (%)	Grade 3/4, n (%)
Hematologic AEs		
Anemia	88 (54.0)	40 (24.5)
Thrombocytopenia	66 (40.5)	18 (11.0)
Neutropenia	9 (5.5)	5 (3.1)
Nonhematologic AEs		
Asthenia	24 (14.7)	4 (2.5)
Pyrexia	19 (11.7)	3 (1.8)
Herpes zoster	13 (8.0)	1 (0.6)
Weight increased	11 (6.7)	2 (1.2)
Bronchitis	10 (6.1)	1 (0.6)
Constipation	10 (6.1)	0
Alanine aminotransferase increased	9 (5.5)	0
Cough	9 (5.5)	0
Fatigue	9 (5.5)	0
Headache	9 (5.5)	0
Nausea	9 (5.5)	0
Peripheral edema	9 (5.5)	0

[a] AEs occurring within 28 days are included.

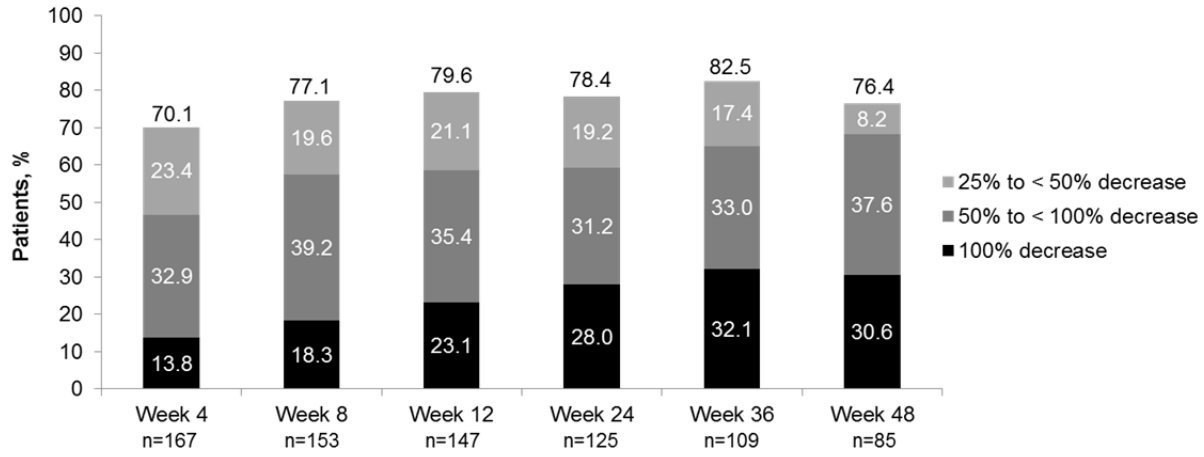
Supplemental Figure 1A. Patients With Primary Myelofibrosis With a ≥25% Decrease From Baseline in Palpable Spleen Length



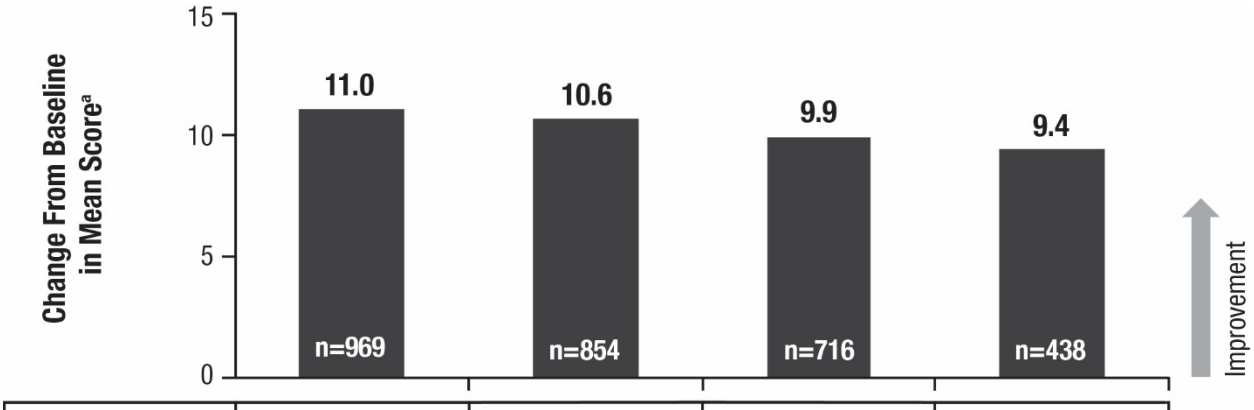
Supplemental Figure 1B. Patients With Post–Polycythemia Vera Myelofibrosis With a ≥25% Decrease From Baseline in Palpable Spleen Length



Supplemental Figure 1C. Patients With Post–Essential Thrombocythemia Myelofibrosis With a ≥25% Decrease From Baseline in Palpable Spleen Length



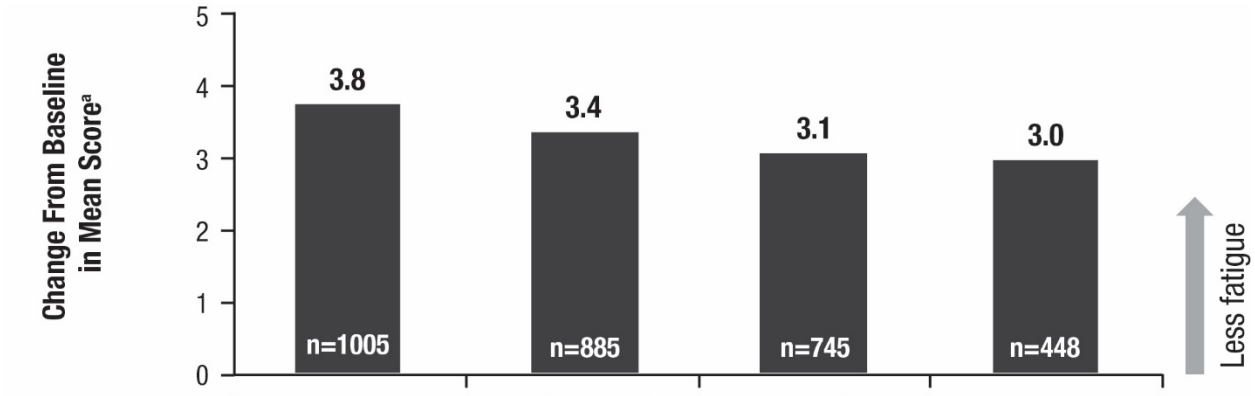
Supplemental Figure 2A. Mean Change From Baseline in FACT-Lymphoma Total Score



Mean scores	Week 4	Week 12	Week 24	Week 48
Baseline=113.4	124.5	124.6	124.2	122.7

Scale=0 (worst) to 168 (best).
Range of values for minimally important difference =6.5 to 11.2 points.[18]

Supplemental Figure 2B. Mean Change From Baseline in FACIT-Fatigue Scale

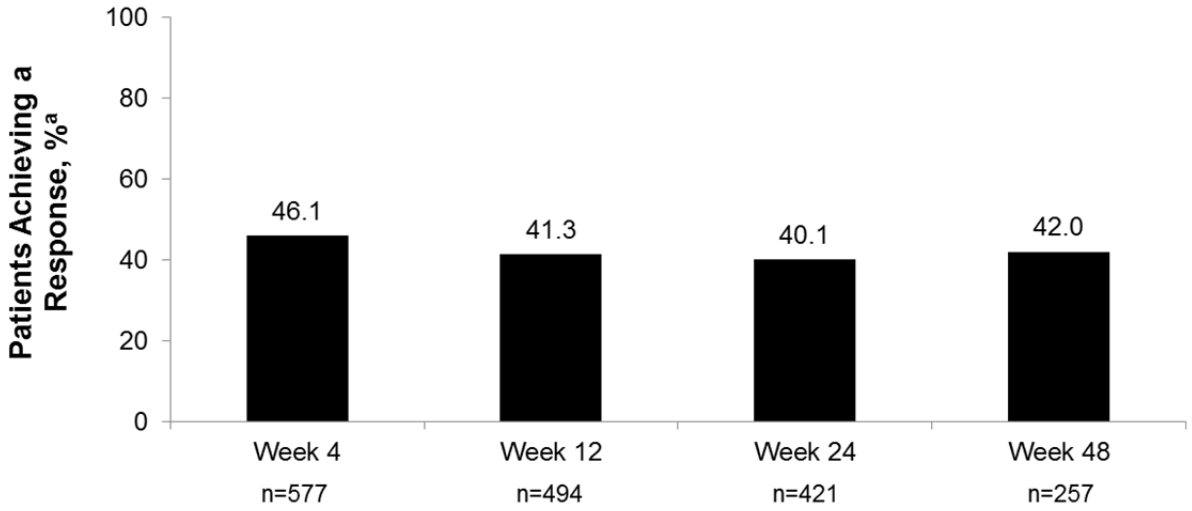


Mean scores	Week 4	Week 12	Week 24	Week 48
Baseline=32.6	36.4	36.3	36.4	36.8

Scale=0 (worst) to 52 (best).
Minimally important difference =3 points.[16]

[a] Calculated based on the mean score for patients with an assessment baseline and week x.

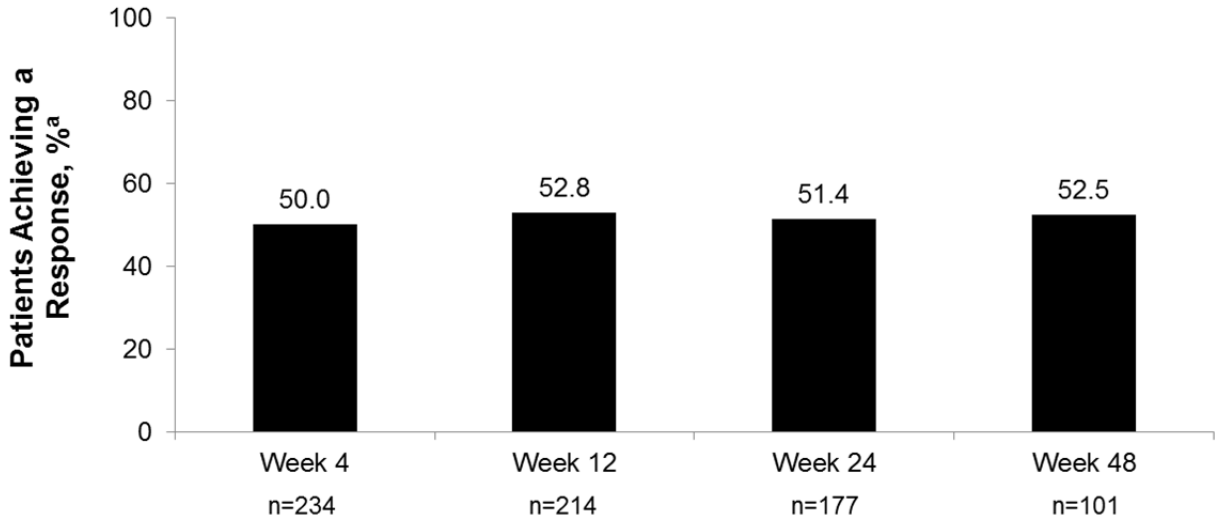
Supplemental Figure 3A. Proportion of Patients With Primary Myelofibrosis Achieving a Response in the FACT-Lymphoma Total Score



FACT, Functional Assessment of Cancer Therapy.

[a] Response was defined as the upper limit of the minimally important difference (FACT-Lym total score, 11.2 points).

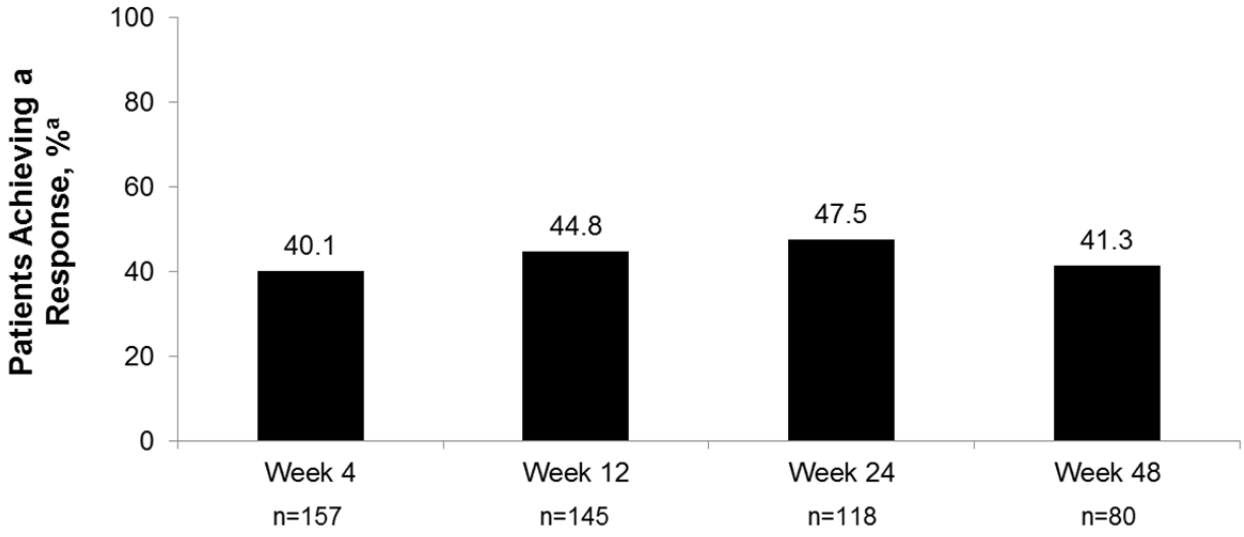
Supplemental Figure 3B. Proportion of Patients With Post–Polycythemia Vera Myelofibrosis Achieving a Response in the FACT-Lymphoma Total Score



FACT, Functional Assessment of Cancer Therapy.

[a] Response was defined as the upper limit of the minimally important difference (FACT-Lym total score, 11.2 points).

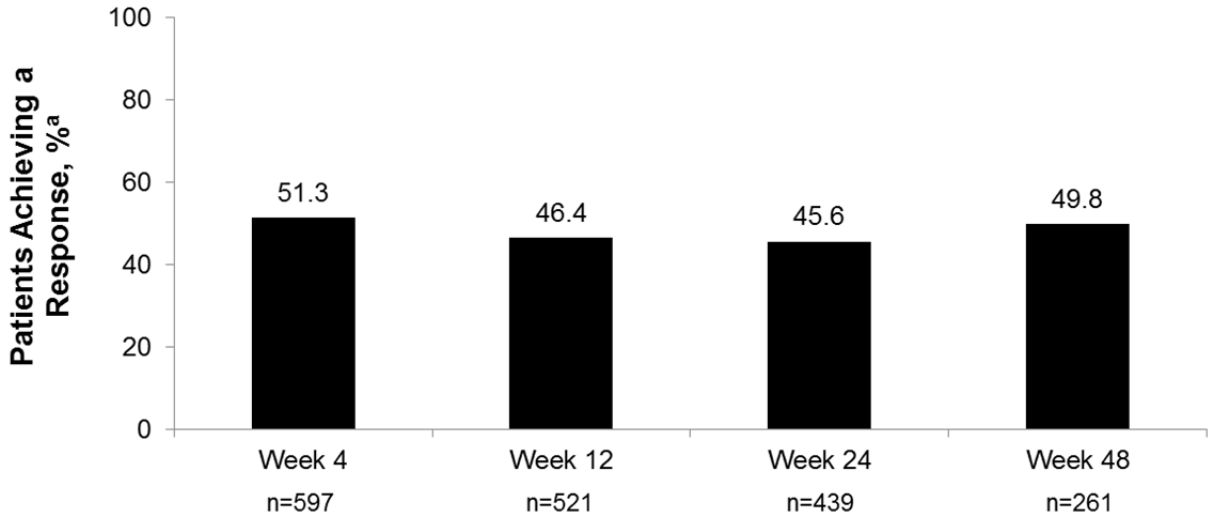
Supplemental Figure 3C. Proportion of Patients With Post–Essential Thrombocythemia Myelofibrosis Achieving a Response in the FACT-Lymphoma Total Score



FACT, Functional Assessment of Cancer Therapy.

[a] Response was defined as the upper limit of the minimally important difference (FACT-Lym total score, 11.2 points).

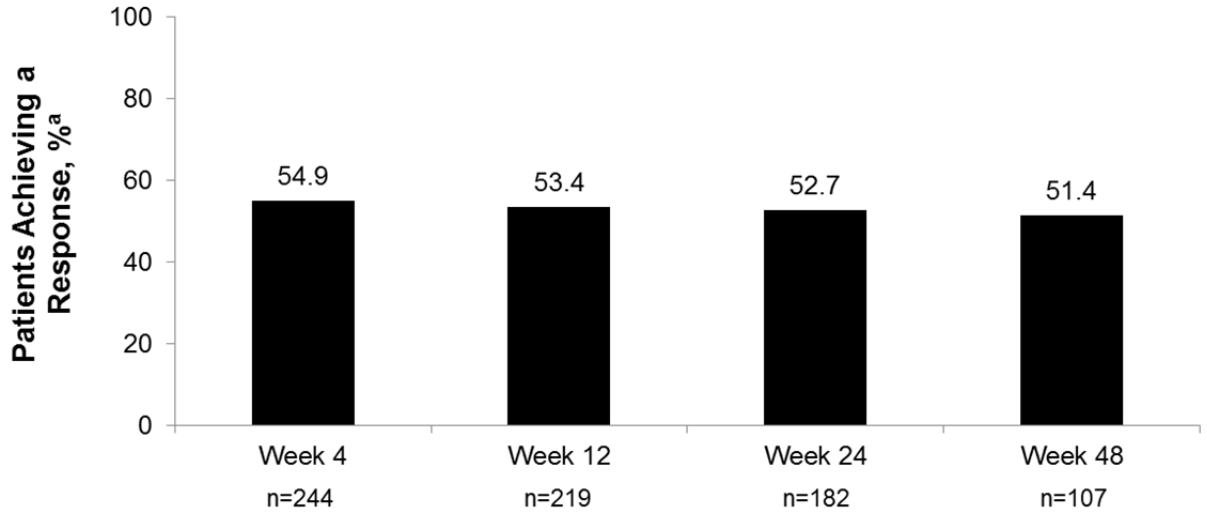
Supplemental Figure 4A. Proportion of Patients With Primary Myelofibrosis Achieving a Response in the FACIT-Fatigue Scale



FACIT, Functional Assessment of Chronic Illness Therapy.

[a] Response was defined as the upper limit of the minimally important difference (FACIT-Fatigue score, 3 points).

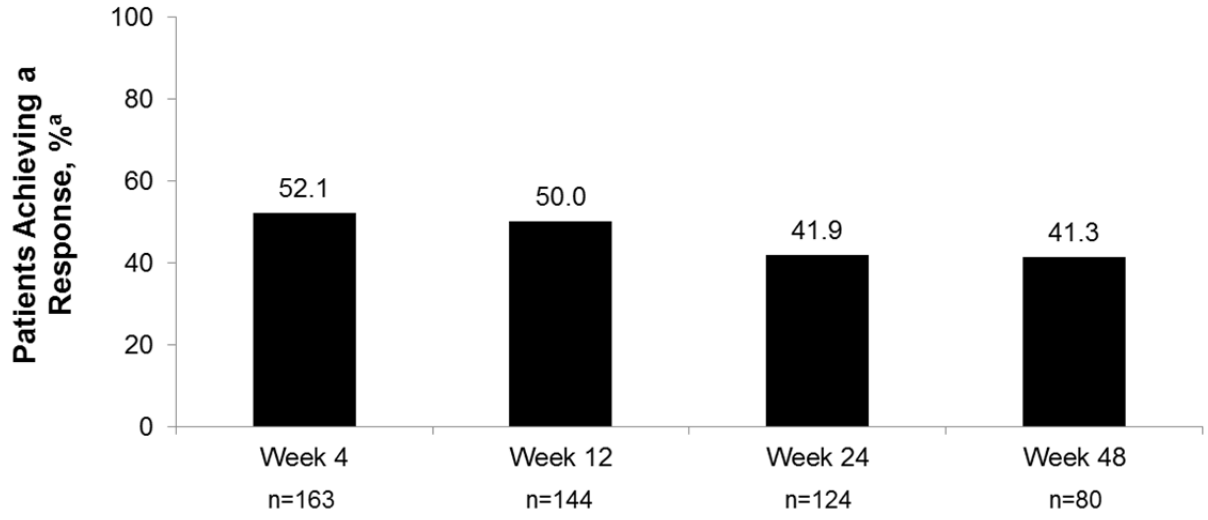
Supplemental Figure 4B. Proportion of Patients With Post–Polycythemia Vera Myelofibrosis Achieving a Response in the FACIT-Fatigue Scale



FACIT, Functional Assessment of Chronic Illness Therapy.

[a] Response was defined as the upper limit of the minimally important difference (FACIT-Fatigue score, 3 points).

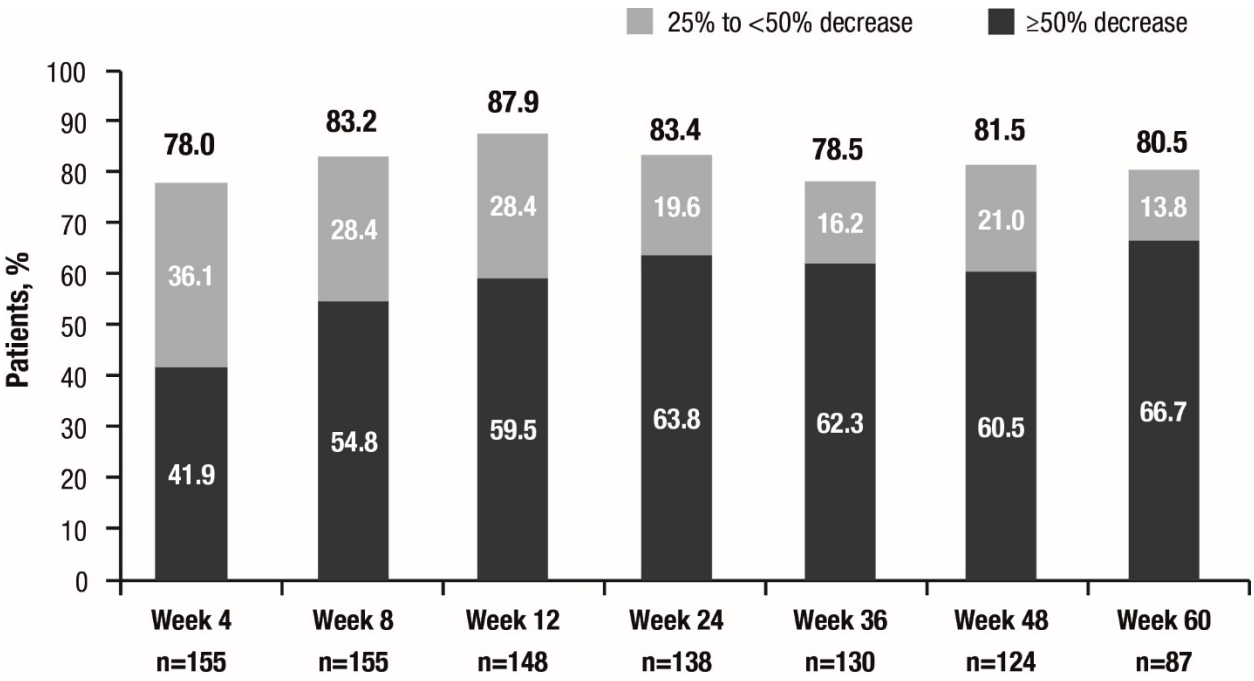
Supplemental Figure 4C. Proportion of Patients With Post–Essential Thrombocythemia Myelofibrosis Achieving a Response in the FACIT-Fatigue Scale



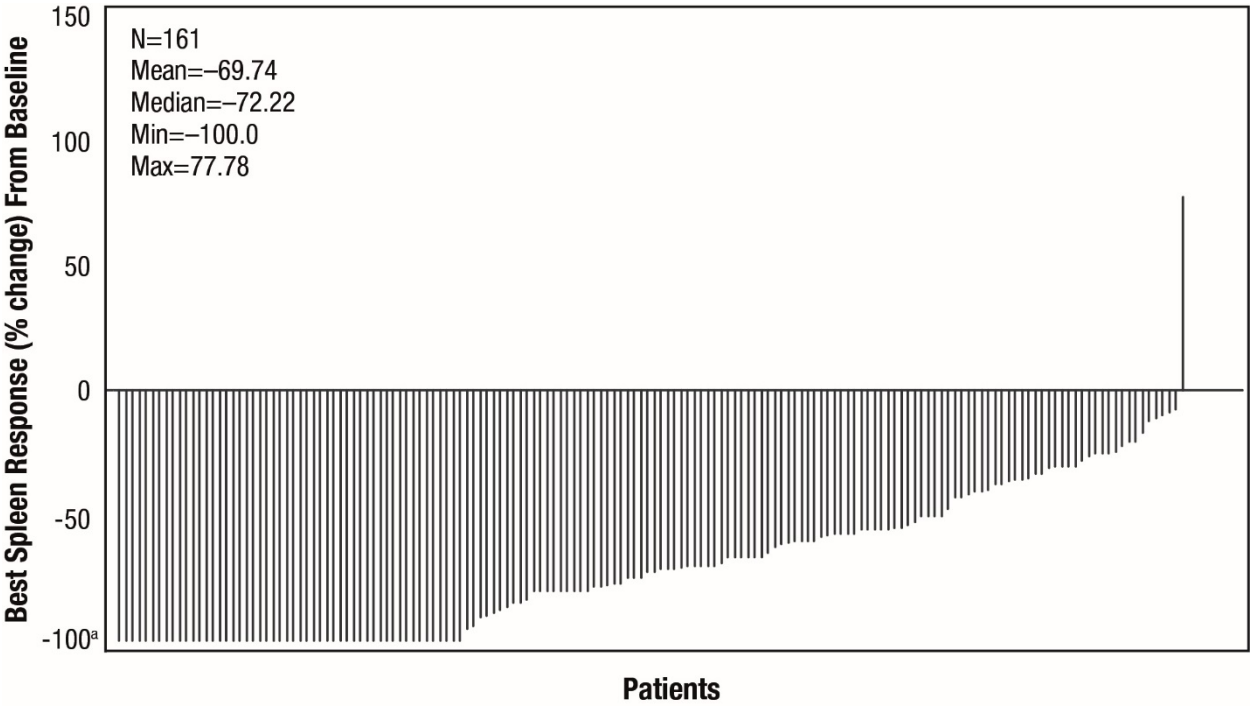
FACIT, Functional Assessment of Chronic Illness Therapy.

[a] Response was defined as the upper limit of the minimally important difference (FACIT-Fatigue score, 3 points).

Supplemental Figure 5A. Patients With Intermediate-1–Risk MF With a ≥25% or ≥50% Decrease From Baseline in Palpable Spleen Length

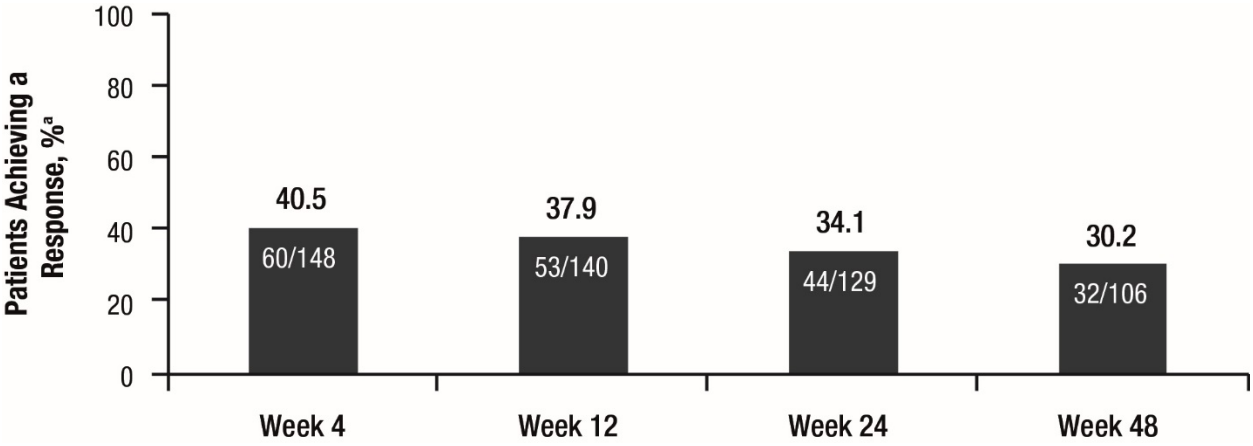


Supplemental Figure 5B. Best Percent Change From Baseline in Palpable Spleen Length at Any Time by Week 72 in Patients With Intermediate-1–Risk MF



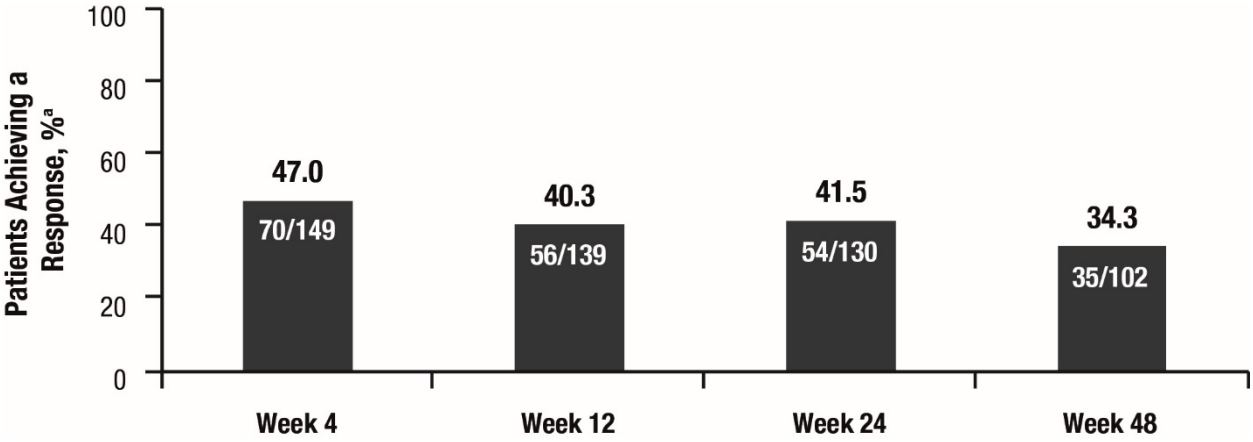
[a] Note: −100% change was defined as nonpalpable.

Supplemental Figure 6A. Proportion of Patients With Intermediate-1–Risk MF Achieving a Response in the FACT-Lymphoma Total Score



[a] Response was defined as the upper limit of the minimally important difference (FACT-Lymphoma total score, 11.2 points).

Supplemental Figure 6B. Proportion of Patients With Intermediate-1–Risk MF Achieving a Response in the FACIT-Fatigue Scale



[a] Response was defined as the upper limit of the minimally important difference (FACIT-Fatigue scale, 3 points).