

ORIGINAL ARTICLE

Changes in quality of life and disease-related symptoms in patients with polycythemia vera receiving ruxolitinib or standard therapy

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Abstract

Objectives: Polycythemia vera (PV)-related symptoms may not be adequately controlled with conventional therapy. This current analysis of the RESPONSE trial evaluated the effects of ruxolitinib compared with standard therapy on quality of life (QoL) and symptoms in patients with PV who were hydroxyurea resistant/intolerant. **Methods:** In the previously reported primary analysis, ruxolitinib achieved the primary composite endpoint of hematocrit control and $\geq 35\%$ reduction in spleen volume at Week 32. The current analysis evaluated patient-reported outcomes using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), the Pruritus Symptom Impact Scale (PSIS), and the Patient Global Impression of Change (PGIC). **Results:** Compared with standard therapy, ruxolitinib was associated with greater improvements in global health status/QoL, functional subscales, and individual symptom scores of the EORTC QLQ-C30. At Week 32, more patients in the ruxolitinib arm (44%) achieved a ≥ 10 -point improvement in global health status/QoL vs. standard therapy (9%). Improvements in MPN-SAF symptom scores were consistent with improvements in EORTC QLQ-C30, PSIS, and PGIC scores. **Conclusions:** Ruxolitinib provides clinically relevant improvements in QoL and ameliorates symptom burden in patients with PV who are hydroxyurea resistant/intolerant.

Key words polycythemia vera; quality of life; signs and symptoms

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Patients with polycythemia vera (PV) may experience a reduced quality of life (QoL) compared with the general population (1–4). The level of impairment may be similar to that reported by patients with other myeloproliferative neoplasms (1, 3, 4). Negative effects on QoL in the PV setting

result in part from a broad symptom burden that may include fatigue, pruritus, and splenomegaly related discomfort (3, 5–9).

Management of PV aims to reduce the risk of thrombosis, minimize the risk of disease transformation, and reduce

symptom severity (10, 11). Phlebotomy to maintain hematocrit <45% (12) and aspirin (13) are recommended for all patients to reduce the risk of cardiovascular and thrombotic events. In addition, some patients may require cytoreductive therapy, often with hydroxyurea, to better control blood cell counts and reduce the risk of cardiovascular and thrombotic events (10, 14, 15). However, approximately 25% of patients with PV become intolerant of or resistant to hydroxyurea (16); patients who become resistant to hydroxyurea have a 5.6-fold greater risk of mortality compared with patients who respond to hydroxyurea (16). Furthermore, traditional treatment options, including hydroxyurea, interferon, phlebotomy, and aspirin, do not ameliorate PV-related symptoms in some patients (6, 17).

Details concerning the specific biochemical pathways associated with symptoms of PV have yet to be elucidated, but it is clear that overactive Janus-associated kinase (JAK) pathway signaling drives the PV disease state. The constitutively active *JAK2*^{V617F} mutation is present in nearly all patients with PV (18) and is associated with dysregulated hematopoiesis (19–23) and splenomegaly (19–21). Ruxolitinib is a potent JAK1/JAK2 inhibitor approved by the US Food and Drug Administration for patients with PV who have had an inadequate response to or are intolerant of hydroxyurea (24) and by the European Medicines Agency for adult patients with PV who are resistant to or intolerant of hydroxyurea (25). The ongoing phase 3 RESPONSE trial compared ruxolitinib with standard therapy in patients with PV who were resistant to or intolerant of hydroxyurea by modified European LeukemiaNet (ELN) criteria (26). RESPONSE met its primary endpoint, with ruxolitinib showing a significant benefit over standard therapy in hematocrit control without phlebotomy and a $\geq 35\%$ reduction in spleen volume from Baseline at Week 32 (26). The current analysis of the RESPONSE trial was conducted to further evaluate the effects of ruxolitinib compared with standard therapy on QoL- and symptom-related measures.

Patients and methods

Study design

RESPONSE is a global, randomized, open-label, multicenter, phase 3 study. This study was conducted in compliance with Good Clinical Practice and according to the ethical principles of the Declaration of Helsinki. The study protocol and all amendments were approved by the Independent Ethics Committee or Institutional Review Board for each participating center. The study design has been described in a previous publication (26); briefly, eligible patients were randomized 1 : 1 to ruxolitinib 10 mg twice daily or single-agent standard therapy per treating physician discretion. Standard therapy options included hydroxyurea (at a tolerated dose if the investigator judged that the patient could derive some benefit from it); interferon/pegylated interferon; pipobroman; anagre-

lide; immunomodulators, such as lenalidomide or thalidomide; or observation without medication. Ruxolitinib dose modifications and changes in standard therapy were permitted for efficacy and safety reasons. Unless contraindicated, all patients received low-dose aspirin.

Patients

Eligible patients were ≥ 18 yr of age with a PV diagnosis, required phlebotomy for hematocrit control, had spleen volume ≥ 450 cm³ measured by magnetic resonance imaging or computed tomography, had no prior JAK-inhibitor treatment, and were resistant to or intolerant of hydroxyurea per modified ELN criteria (26, 27). In addition, patients were required to have hematocrit levels between 40% and 45% at randomization or within 14 d before day 1 (could be achieved by phlebotomy).

Patient-reported outcomes

Patient-reported outcomes were captured using four instruments: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (28), the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) (3, 26), the Pruritus Symptom Impact Scale (PSIS) (26), and the Patient Global Impression of Change (PGIC) (29).

Patient outcomes using the EORTC QLQ-C30 were captured every 4 wk between Baseline and Week 32 and at the patient's last visit. For each scale of the EORTC QLQ-C30, the raw score was standardized by linear transformation to a score of 0–100; higher scores on the global health status/QoL and functional subscales indicate better functioning, whereas higher scores on individual symptoms indicate worse symptom severity. Patients were also evaluated for a minimally important difference (MID; ≥ 10 -point improvement from Baseline) in the global health status/QoL at each time point.

Patient-reported symptoms were captured daily from 7 d before Baseline until the Week 32 visit using the MPN-SAF patient electronic diary. The MPN-SAF included 14 disease-related symptoms scored from 0 (absent) to 10 (worst imaginable) and was used to calculate a total symptom score (TSS; sum of 14 individual symptom scores) and three symptom cluster scores related to cytokines (TSS-C; sum of scores for tiredness, itching, muscle ache, night sweats, and sweats while awake), hyperviscosity (TSS-H; sum of scores for vision problems, dizziness, concentration problems, headache, numbness/tingling in hands/feet, ringing in ears, and skin redness), and splenomegaly (TSS-S; sum of scores for abdominal discomfort and early satiety) (26).

The 5-question PSIS survey evaluated pruritus severity and impact on daily life on a scale from 0 (not at all) to 10 (worst imaginable). The PSIS was completed at Baseline and every 4 wk from Week 4 through 32.

The PGIC measured patient opinion of treatment benefit on a scale that included ‘very much improved’, ‘much improved’, ‘minimally improved’, ‘no change’, ‘minimally worse’, ‘much worse’, and ‘very much worse’. The PGIC was completed every 4 wk from Week 4 through 32.

Subgroup analyses of the ruxolitinib arm were performed to evaluate the relationship of improvement in MPN-SAF TSS (<50% or ≥50%) with the least squares mean change from Baseline in EORTC QLQ-C30 at Week 32 and with PGIC scores at Week 32. For the relationship between MPN-SAF TSS response and EORTC QLQ-C30 scores, an analysis of covariance was used with the Baseline EORTC QLQ-C30 subscale as the covariate, the MPN-SAF TSS response as the main effect, and the standard therapy group as the reference level for comparisons. All other data in the current report were evaluated using descriptive statistical analyses.

Results

Patients

Patients were randomized to ruxolitinib ($n = 110$) or standard therapy ($n = 112$); patient enrollment, demographics,

and disposition have been reported previously (26). Briefly, median age (ruxolitinib, 62.0 yr; standard therapy, 60.0 yr), median time since PV diagnosis (8.2 and 9.3 yr, respectively), mean $JAK2^{V617F}$ allele burden (76.2% and 75.0%), and median spleen volume (1195 and 1322 cm³) were similar between treatment arms. The ruxolitinib and standard therapy arms included more male patients (60.0% and 71.4%, respectively) than female patients.

Baseline EORTC QLQ-C30 functional subscale and individual symptom scores in the ruxolitinib arm were similar to those of the standard therapy arm and to those reported by patients with other hematologic malignancies (Table 1). Individual symptom severity scores measured with the MPN-SAF at Baseline were generally similar to scores previously reported by patients with myeloproliferative neoplasms, although some symptom scores (e.g., tiredness, abdominal discomfort) were somewhat higher (i.e., worse) in the RESPONSE study patients compared with previous studies in a broader population of patients with PV (Table S1).

Efficacy

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30: Treatment

Table 1 Mean Baseline EORTC QLQ-C30 scores in RESPONSE and previously reported for patients with other hematologic malignancies

EORTC QLQ-C30	PV (RESPONSE) ¹					
	Ruxolitinib ($n = 110^2$)	Standard therapy ($n = 112^2$)	MF ³ ($n = 147$)	MF ⁴ ($n = 96$)	CML ⁵ ($n = 73$)	Myeloma ⁶ ($n = 944$)
Global health status/QoL	59.9	61.6	52.9	59.9	70.2	55.7
Functional subscales						
Social	81.7	81.3	66.1	74.9	84.3	63.2
Physical	79.8	81.9	67.2	74.9	78.0	67.7
Role	77.8	77.2	63.2	68.8	78.1	60.1
Cognitive	77.6	78.3	80.1	77.0	86.1	78.1
Emotional	76.3	76.2	75.5	76.5	78.8	71.3
Individual symptoms						
Fatigue	37.9	38.9	54.1	41.0	29.8	48.7
Insomnia	26.6	36.5	39.1	33.7	26.9	28.9
Pain	24.7	25.1	29.9	22.6	10.1	47.1
Dyspnea	21.2	21.4	37.0	29.8	15.5	26.0
Financial difficulties	16.5	14.1	NA	17.5	18.3	16.1
Constipation	12.8	12.4	NA	16.8	9.6	23.2
Appetite loss	12.3	16.0	33.3	15.1	13.7	23.2
Diarrhea	12.2	10.8	NA	21.1	7.3	9.6
Nausea and vomiting	5.3	4.8	NA	6.3	5.0	10.5

CML, chronic myelocytic leukemia; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL, quality of life; MF, myelofibrosis; NA, not available; PV, polycythemia vera.

¹RESPONSE Baseline values.

²Number of randomized patients; the number of patients with Baseline data varied between EORTC QLQ-C30 components.

³Mesa *et al.* (32).

⁴Scherber *et al.* (3).

⁵Homewood *et al.* (30).

⁶Scott *et al.* (31).

with ruxolitinib was associated with greater benefit in QoL measures compared with standard therapy as indicated by EORTC QLQ-C30 subscale scores. Patients who received ruxolitinib experienced improvements from Baseline at Week 32 in EORTC QLQ-C30 global health status/QoL and all functional subscales, whereas patients who received standard therapy experienced worsening of these measurements, with the exception of the emotional functioning subscale (26). Patients in the ruxolitinib arm also experienced improvements in all individual symptoms measured by the EORTC QLQ-C30, including fatigue, insomnia, pain, appetite loss, dyspnea, financial difficulties, diarrhea, constipation, and nausea and vomiting (Fig. 1). In comparison, individual symptom scores were less improved or

worse for patients in the standard therapy arm. A greater proportion of patients in the ruxolitinib arm compared with the standard therapy arm achieved a minimally important difference (MID; ≥ 10 -point improvement from Baseline) in global health status/QoL from Baseline at each postbaseline study visit through Week 32 (Fig. 2). By Week 32, 46 patients (44%) in the ruxolitinib arm achieved an MID, whereas only ten patients (9%) did so in the standard therapy arm.

Myeloproliferative Neoplasm Symptom Assessment Form: The mean MPN-SAF TSS and TSS symptom cluster scores improved over time in the ruxolitinib arm (Figure S1); in comparison, standard therapy was associated with less improvement or worsening. Consistent with these mean

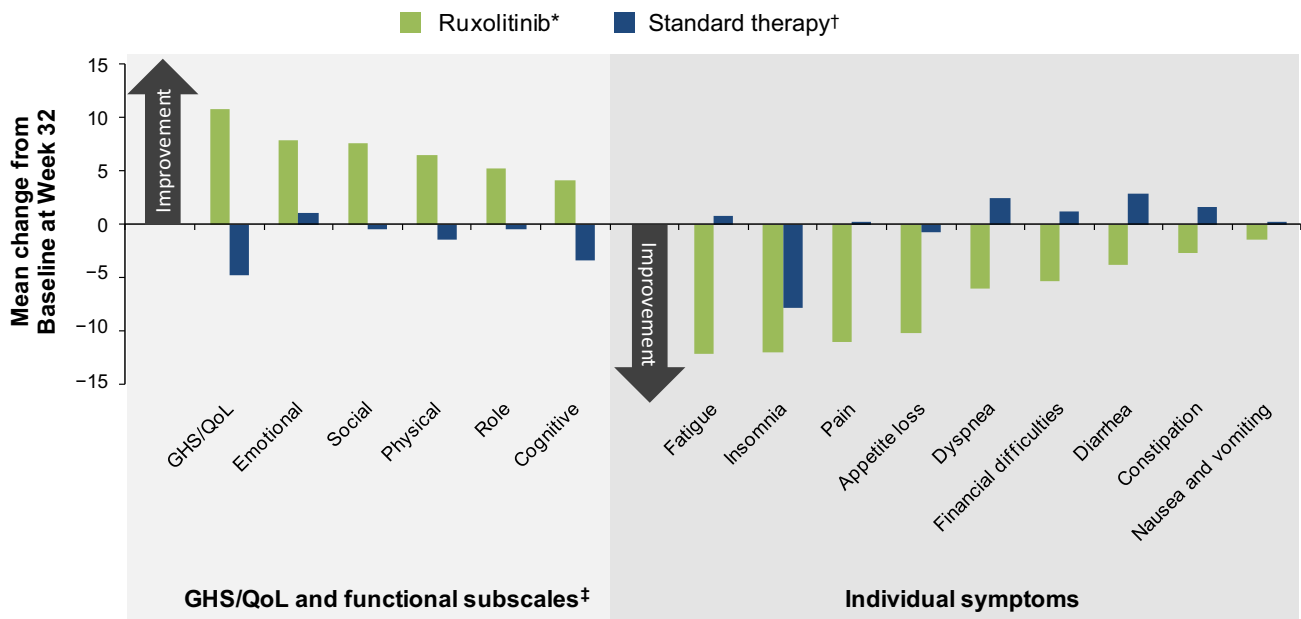


Figure 1 Mean change from Baseline in EORTC QLQ-C30 scores at Week 32. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; GHS = global health status; QoL = quality of life. *Number of patients in the ruxolitinib arm with data available at Baseline and Week 32 ranged from 86 to 90. [†]Number of patients in the standard therapy arm with data available at Baseline and Week 32 ranged from 80 to 84. [‡]GHS/QoL and functional subscale data were adapted from Vannucchi et al. (26).

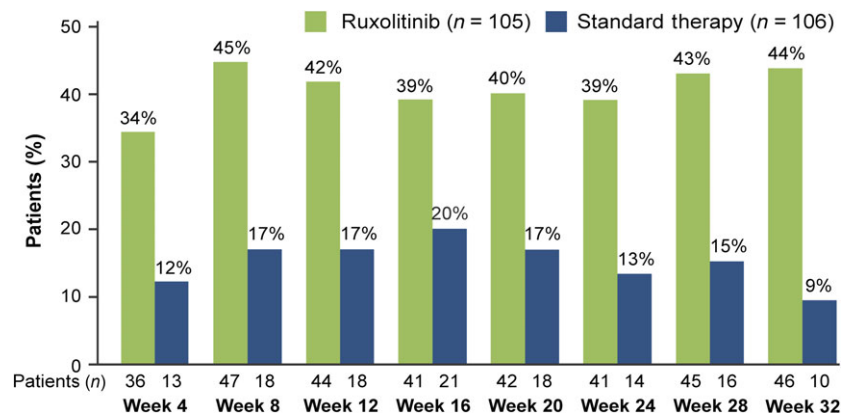


Figure 2 Proportion of patients achieving an MID (≥ 10 -point improvement) in EORTC QLQ-C30 global health status/QoL over time. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; MID = minimally important difference; QoL = quality of life.

changes in MPN-SAF scores, a greater proportion of patients in the ruxolitinib arm compared with the standard therapy arm achieved $\geq 50\%$ improvement in MPN-SAF TSS, TSS-C, TSS-H, and TSS-S scores at Week 32, regardless of whether standard therapy was hydroxyurea or a non-hydroxyurea option (Fig. 3). Furthermore, a greater proportion of patients in the ruxolitinib arm achieved $\geq 50\%$ improvement from Baseline in individual MPN-SAF symptom scores at Week 32 compared with standard therapy (Figure S2).

Pruritus Symptom Impact Scale: Ruxolitinib treatment was associated with improvements in all five components of the PSIS that were rapid (i.e., achieved as early as Week 4) and durable (Figure S3). Treatment with standard therapy led to worsening or minimal improvements in all PSIS components.

Patient Global Impression of Change: Ruxolitinib-associated improvements in PGIC were rapid and durable, with 46% of patients reporting that their condition was ‘much’ or ‘very much’ improved at Week 4 compared with 11% in the standard therapy arm (Figure S4). Compared with the ruxolitinib arm, fewer patients treated with standard therapy reported that their condition was ‘much’ or ‘very much’ improved at every study time point between Weeks 4 and 32.

Consistency of Results Between Patient-Reported Outcomes: Patients in the ruxolitinib arm who achieved $\geq 50\%$ improvement from Baseline at Week 32 in MPN-SAF TSS scores had greater improvements in EORTC QLQ-C30 QoL and functional subscale scores compared with patients in the ruxolitinib arm with $< 50\%$ improvement (Fig. 4). Mean changes in all EORTC QLQ-C30 QoL and functional subscale scores were significantly better in the ruxolitinib patient subgroup among patients with $\geq 50\%$ improvement in MPN-SAF TSS compared with the standard therapy arm. Mean change in global health status/QoL was also significantly better in the ruxolitinib patient subgroup among patients with $< 50\%$ improvement in MPN-SAF TSS compared with the standard therapy arm; non-significant improvements in EORTC QLQ-C30 functional subscale

scores were observed in this ruxolitinib subgroup compared with standard therapy (Fig. 4). Similarly, greater proportions of ruxolitinib-treated patients in the $\geq 50\%$ improvement subgroup and the $< 50\%$ improvement subgroup reported that their condition was ‘much’ or ‘very much’ improved at Week 32 on the PGIC compared with the standard therapy arm (Table 2).

Discussion

In this analysis of RESPONSE data, ruxolitinib was more effective than traditional treatment options for ameliorating symptom burden and improving QoL in patients with PV who are resistant to or intolerant of hydroxyurea. Patients from the RESPONSE trial had Baseline symptom severity and QoL impairments that were comparable to those experienced by patients with other cancers, including breast cancer, lung cancer, recurrent/metastatic cancer, and other hematologic malignancies (3, 30–32), which further emphasizes the unmet treatment needs in this PV patient population.

It is unclear why ruxolitinib improves patient symptoms and QoL better than traditional treatment options, but it is rational to hypothesize that this finding stems from the targeted mechanism of action of ruxolitinib as a potent inhibitor of JAK1 and JAK2 (33). To date, ruxolitinib is the only approved treatment option for patients with PV that targets the JAK/signal transducer and activator of transcription (STAT) pathway. Nearly all patients with PV have somatic activating mutations in *JAK2* (18), which drives excessive and dysregulated hematopoiesis (34) and indirectly promotes symptoms related to hyperviscosity (35) and splenomegaly (36). In addition, patients with PV have been reported to have elevated inflammatory cytokine levels (37), which signal through JAK1 and/or JAK2 (38), suggesting an important role for the immune system in PV-related symptoms. Indeed, allele burden of the most common activating mutation in PV (*JAK2*^{V617F}) has been positively correlated with serum levels of C-reactive protein, a marker for systemic inflammation (39). Treatment with ruxolitinib is unique com-

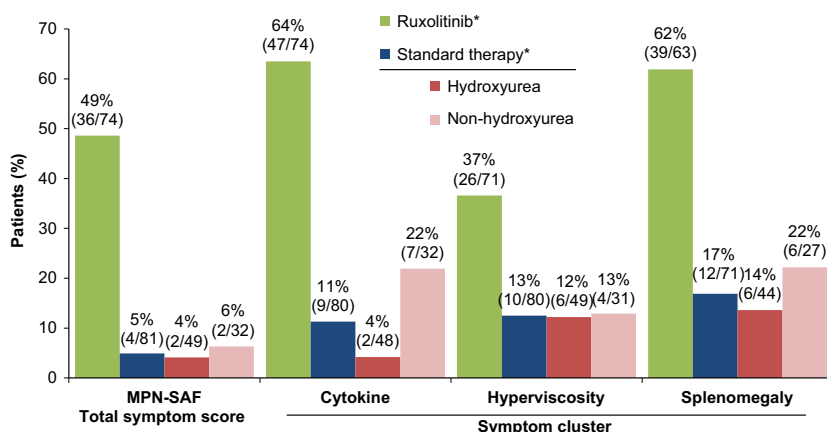


Figure 3 Proportion of patients with $\geq 50\%$ improvement from Baseline in MPN-SAF total symptom score at Week 32. Patients with scores at Baseline and Week 32 were included. MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form. *The ruxolitinib and overall standard therapy arm data were adapted from Vannucchi *et al.* (26).

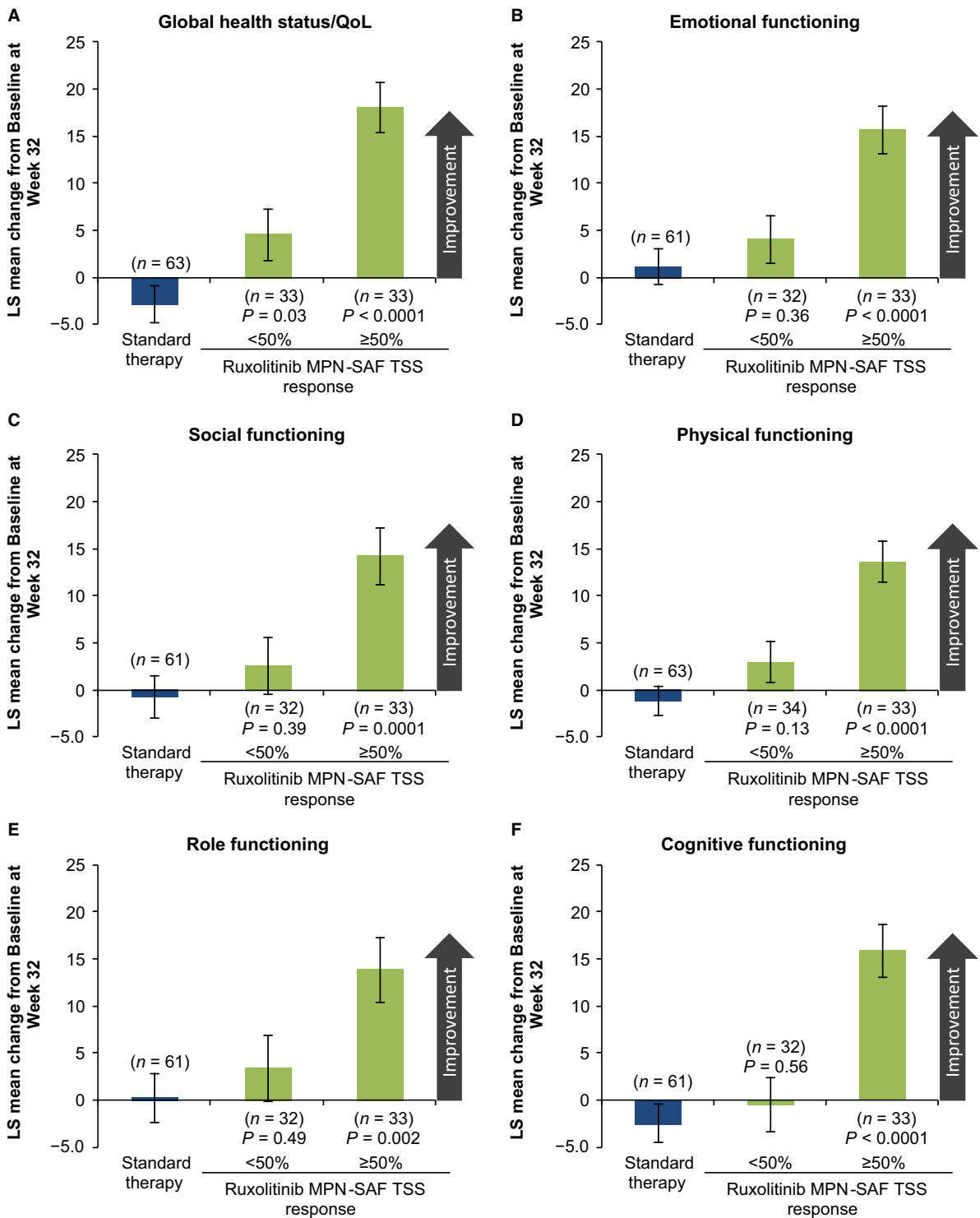


Figure 4 LS mean change from Baseline in EORTC QLQ-C30 QoL and functional subscale scores at Week 32 by MPN-SAF TSS response. EORTC QLQ-C30 QoL and functional subscales included global health status/QoL (A), emotional functioning (B), social functioning (C), physical functioning (D), role functioning (E), and cognitive functioning (F). Nearly all patients who received standard therapy had <50% improvement or worsening in MPN-SAF TSS at Week 32; therefore, results for the total standard therapy arm are shown. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; LS = least squares; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; QoL = quality of life. Includes patients with Baseline and Week 32 MPN-SAF TSS who completed the EORTC QLQ-C30 at Week 32. ≥50% TSS responders includes patients who achieved a ≥50% improvement in MPN-SAF TSS; <50% TSS responders includes patients who achieved a <50% improvement in MPN-SAF TSS. Error bars represent standard error of the mean.

Table 2 Relationship between PGIC at Week 32 and MPN-SAF TSS response¹

PGIC scale, n (%)	Ruxolitinib (n = 71) MPN-SAF TSS response		Standard therapy (n = 81) MPN-SAF TSS response		Total sample (N = 152) MPN-SAF TSS response	
	≥50% (n = 36)	<50% (n = 35)	≥50% (n = 4)	<50% (n = 77)	≥50% (n = 40)	<50% (n = 112)
Very much improved	21 (58.3)	9 (25.7)	0	4 (5.2)	21 (52.5)	13 (11.6)
Much improved	13 (36.1)	16 (45.7)	0	7 (9.1)	13 (32.5)	23 (20.5)
Minimally improved	1 (2.8)	7 (20.0)	2 (50.0)	17 (22.1)	3 (7.5)	24 (21.4)
No change	0	3 (8.6)	2 (50.0)	33 (42.9)	2 (5.0)	36 (32.1)
Minimally worse	1 (2.8)	0	0	14 (18.2)	1 (2.5)	14 (12.5)
Much worse	0	0	0	2 (2.6)	0	2 (1.8)

PGIC, Patient Global Impression of Change; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score.

¹Includes patients with a Baseline and Week 32 MPN-SAF TSS who completed the PGIC at Week 32. ≥50% TSS responders include patients who achieved a ≥50% improvement in MPN-SAF TSS; <50% TSS responders include patients who achieved a <50% improvement in MPN-SAF TSS.

pared with traditional treatment options and may alleviate symptoms by targeting the JAK/STAT signaling pathway.

An important strength of the RESPONSE trial is its real-world applicability. Treatment choices in the standard therapy arm were made at the discretion of investigators, and included hydroxyurea, interferon, anagrelide, pipobroman, immunomodulators, and observation without medication. A subgroup of patients in the standard therapy arm who were resistant to hydroxyurea per ELN criteria at Baseline continued to receive hydroxyurea as their primary treatment. This scenario is representative of management strategies that have been used by many physicians in an effort to achieve some clinical benefit with limited treatment options, even if that response is suboptimal. The ELN criteria for hydroxyurea resistance/intolerance are important for defining patient populations in clinical trials, but may not be useful in real-world clinical practice. In addition, patients with PV may also experience intolerable hydroxyurea-related side effects (16). The RESPONSE patient population included roughly equal proportions of patients who were hydroxyurea resistant or intolerant (26), and, importantly, the study yielded reliable and consistent data. MPN-SAF data were collected daily by patients to limit recall bias, and as a result, consistency between patient-reported outcome instruments was high. Finally, RESPONSE is the only randomized controlled trial to date that has evaluated the effect of treatment on symptom burden and QoL in a large population of patients with PV.

Limitations of this analysis should be considered. First, RESPONSE was designed as an open-label trial, which precludes the elimination of patient treatment bias from having a potential influence on patient-reported outcomes. Second, some of the patient-reported outcomes analyzed here were exploratory endpoints and were therefore not powered for statistical comparisons between treatment arms. Finally, the eligibility criteria, which selected patients who required phlebotomy for hematocrit control, had splenomegaly, and were resistant to or intolerant of hydroxyurea, enriched for

patients with problematic and/or advanced PV. Although this provided an opportunity to evaluate ruxolitinib-associated benefits in patients with the greatest unmet clinical needs, further studies will be required to fully evaluate the clinical benefits of ruxolitinib in other PV settings.

In conclusion, traditional treatment options for patients with PV who are resistant to or intolerant of hydroxyurea do not fully address patient needs related to symptom severity and QoL impairments. The findings of this analysis support the JAK1/JAK2 inhibitor ruxolitinib as an effective treatment option for ameliorating symptom burden in patients with PV who are resistant to or intolerant of hydroxyurea.

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Conflict of interest and sources of funding

RM received research funding from Incyte Corporation, CTI, Gilead, Genentech, Eli Lilly, Promedior, NS Pharma, Sanofi, and Celgene and has served as a consultant for Novartis and ARIAD. SV received funding for research and compensation for serving on advisory boards for Incyte Corporation. J-JK, SD, CNH, and AMV received honoraria and research funding and served on advisory boards for Novartis Pharmaceuticals. TM served on advisory boards for Novartis Pharmaceuticals. MMJ and SP are employees and stockholders of Incyte Corporation. JL, IC, and DH are employees and stockholders of Novartis Pharmaceuticals. MG, FPas, FPan, and PZ have no conflict of interests to disclose. Funding for the study was provided by Incyte Corporation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Mean MPN-SAF symptom scores in RESPONSE and previously reported for patients with myeloproliferative neoplasms.

Figure S1. Change over time in MPN-SAF TSS and symptom cluster scores.

Figure S2. Proportion of patients with $\geq 50\%$ improvement from Baseline at Week 32 in individual MPN-SAF symptom scores.

Figure S3. Mean percentage change from Baseline in Pruritus Symptom Impact Scale scores.

Figure S4. Proportion of patients who reported being ‘much’ or ‘very much’ improved on the Patient Global Impression of Change.