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Markers of iron deficiency in patients with polycythemia vera receiving ruxolitinib or best available therapy

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ABSTRACT

Polycythemia vera (PV) is characterized by erythropoiesis and *JAK2*-activating mutations, with increased risks of morbidity and mortality. Most patients with PV are iron deficient, and treatment often includes hematocrit control with phlebotomy, which may exacerbate iron deficiency-associated complications. The phase 3 RESPONSE trial evaluated the JAK1/JAK2 inhibitor ruxolitinib (n = 110) versus best available therapy (BAT; n = 112) in patients with PV who were hydroxyurea-resistant/intolerant. Ruxolitinib was superior to BAT for hematocrit control, reduction in splenomegaly, and blood count normalization. This exploratory analysis, the first to evaluate iron status in a prospective study of patients with PV, investigated ruxolitinib effects on 7 serum iron markers and iron deficiency-related patient-reported outcomes (PRO). Among patients with evidence of baseline iron deficiency, ruxolitinib was associated with normalization of iron marker levels, compared with lesser improvement with BAT. Iron levels remained stable in ruxolitinib patients with normal iron levels at baseline. Regardless of baseline iron status, treatment with ruxolitinib was associated with improvements in concentration problems, cognitive function, dizziness, fatigue, headaches, and inactivity, although improvements were generally greater among patients with baseline iron deficiency. The improvements in iron deficiency markers and PROs observed with ruxolitinib are suggestive of clinical benefits that warrant further exploration.

1. Introduction

Polycythemia vera (PV) is a clonal hematologic malignancy that is distinguished from other myeloproliferative neoplasms by erythrocytosis and activating mutations in *Janus kinase 2 (JAK2)* [1]. Risks of morbidity [2] and mortality [3] are increased in patients with PV, at least in part from cardiovascular/thromboembolic events and iron deficiency. Most patients with PV have depleted bone marrow iron levels [4,5], and constitutive activation of JAK2 may further promote iron deficiency by dysregulating hepcidin, a hormone that controls the iron exporter ferroportin in a JAK2-dependent fashion [6]. Iron deficiency is associated with fatigue [7], cognitive impairment [7,8], headaches [9,10], and restless leg syndrome [11], and may be associated with increased risk of cardiovascular/thromboembolic events [12–15]. Unless contraindicated, patients with PV are often treated with aspirin [16] and phlebotomy to reduce the risk of cardiovascular-related morbidity or mortality [17], as supported by prospective, randomized clinical trial evidence and the European LeukemiaNet treatment guidelines [18]. However, frequent phlebotomies to control hematocrit may worsen iron deficiency [19]. Analyses exploring the impact of

Abbreviations: BAT, best available therapy; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; JAK2, Janus kinase 2; LLN, lower limit of normal; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; NHANES, National Health and Nutrition Examination Survey; PRO, patient-reported outcome; PV, polycythemia vera; TIBC, total iron-binding capacity; TSAT, transferrin iron saturation; ULN, upper limit of normal.

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contemporary treatment options for PV on iron deficiency markers are lacking from the biomedical literature.

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 [20] and by the European Medicines Agency for adult patients with PV who are resistant to or intolerant of hydroxyurea [21]. The phase 3 RESPONSE trial evaluated ruxolitinib versus best available therapy in patients with PV who were resistant to or intolerant of hydroxyurea. Best available therapy, chosen per investigator judgment, was hydroxyurea for 58.9% of patients, which reflected real-world clinical practice and underscored an unmet treatment need in this setting. The primary analysis has been published and demonstrated that ruxolitinib was more effective than best available therapy for the primary endpoint (a composite of hematocrit control without phlebotomy and ≥35% reduction from baseline in spleen volume at Week 32; ruxolitinib, 22.7%; best available therapy, 0.9%) and complete hematologic remission (ruxolitinib, 23.6%; best available therapy, 8.0%) [22,23]. In addition, RESPONSE trial data suggested that ruxolitinib was associated with greater improvements in PV-related symptom severity and quality of life compared with best available therapy [22,24]. Most patients, including those who did not achieve the primary endpoint, received clinical benefit and continued to receive ruxolitinib beyond the data cutoff for the primary analysis. In the phase 3b RESPONSE-2 trial, a ≥50% reduction from baseline in Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) total symptom score was achieved by 45.3% versus 22.7% of patients with PV and nonpalpable spleen in the ruxolitinib and best available therapy treatment groups, respectively [25]. Furthermore, in the phase 3b RELIEF trial, improvements, although nonsignificant, in cytokine-related symptoms were observed with ruxolitinib compared with hydroxyurea in patients with PV who were generally well-controlled with hydroxyurea but still reporting disease-associated symptoms [26]. The current unplanned exploratory analysis of RESPONSE trial data is the first of its kind to evaluate iron status in patients with PV who were followed in a prospective clinical trial. This analysis evaluated ruxolitinib versus best available therapy for changes in markers of iron deficiency and changes in patient-reported measures of symptom severity and quality of life that may be related to iron deficiency.

2. Materials and methods

2.1. Study design and patients

Details about the RESPONSE trial (ClinicalTrials.gov, NCT01243944), study design, and patient population have been published previously [22]. Briefly, RESPONSE is an ongoing international, randomized, open-label, multicenter phase 3 clinical trial. The study design was approved by the institutional review board or central ethics committee at each participating institution and was conducted in accordance with the Declaration of Helsinki; all patients provided written informed consent.

Adult patients with a PV diagnosis, resistance to or intolerance of hydroxyurea, phlebotomy requirement for hematocrit control, and spleen volume ≥450 cm^3 were eligible for inclusion. Patients were randomized 1:1 to receive ruxolitinib 10 mg twice daily or single-agent best available therapy per treating physician judgment. Best available therapy options included hydroxyurea, interferon/pegylated interferon, pipobroman, anagrelide, immunomodulators (such as lenalidomide or thalidomide), or observation without medication. Crossover to ruxolitinib was permitted at Week 32 for patients who did not meet the primary endpoint or after Week 32 in case of phlebotomy eligibility or splenomegaly progression. Of note, hematocrit levels between 40% and 45% at randomization or within 14 days before Day 1 were also required and could be achieved with phlebotomy [22]. The current analysis included all randomized patients from RESPONSE, regardless of whether they achieved the primary endpoint.

2.2. Unplanned assessments and analyses

2.2.1. Markers of iron deficiency

Laboratory values for markers of iron deficiency included mean corpuscular volume (MCV), serum iron, ferritin, mean corpuscular hemoglobin concentration (MCHC), total iron-binding capacity (TIBC), and hepcidin. In addition, transferrin iron saturation (TSAT) was calculated as a percentage based on the ratio of serum iron and TIBC. A patient was defined as having iron deficiency if MCV, serum iron, ferritin, TSAT, or MCHC was below the lower limits of normal (LLN) or TIBC was above the upper limits of normal (ULN). The LLN and ULN for each marker of iron deficiency were defined by the individual study sites and ranged as follows: MCV LLN, 76–85 fL; MCV ULN, 92–102 fL; serum iron LLN, 7–14 μmol/L; serum iron ULN, 23–34 μmol/L; ferritin LLN, 16–67 pmol/L; ferritin ULN, 364–1067 pmol/L; TSAT LLN, 20%; TSAT ULN, 50%; MCHC LLN, 29–34 g/dL; MCHC ULN, 34–38 g/dL; TIBC LLN, 45–50 μmol/L; TIBC ULN, 70–76 μmol/L. Hepcidin LLN and ULN ranges were not established. In the ruxolitinib arm, these markers (excluding hepcidin) were evaluable at baseline and Weeks 16, 32, 48, 64, and 80. Data were evaluated at baseline and Weeks 16 and 32 among patients treated with best available therapy as the majority of these patients crossed over to ruxolitinib after Week 32 [22]. Hepcidin was evaluable at baseline and at Week 32 in both treatment arms.

The current unplanned exploratory analysis presents mean values for markers of iron deficiency in the ruxolitinib and best available therapy treatment arms, and within subgroups of each treatment arm stratified into 2 groups based on the presence or absence of iron deficiency at baseline.

2.2.2. Patient-reported outcomes

The current exploratory analysis evaluated changes in patient-reported outcomes (PROs) with a focus on outcomes and symptoms that may be most relevant for patients with iron deficiency. Changes from baseline at Week 32 in the ruxolitinib and best available therapy arms were evaluated among patients stratified into 2 groups based on the presence or absence of iron deficiency at baseline per MCV, ferritin, and TSAT levels.

The PROs were collected at baseline and Week 32 using the MPN-SAF (selected items: inactivity; dizziness, vertigo, or lightheadedness; headache problems; and concentration problems) [27] and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30; selected individual items: were you short of breath?, did you need to rest?, have you felt weak?; selected subscales: cognitive functioning and fatigue) [28]. Individual items on the MPN-SAF were reported on a scale from 0 (absent) to 10 (worst imaginable); reductions in MPN-SAF scores were associated with symptom improvement. Individual items on the EORTC QLQ-C30 were graded on a scale from 1 (not at all) to 4 (very much). Raw scores for cognitive functioning and fatigue subscales on the EORTC QLQ-C30 were standardized by linear transformation to a score of 0–100. Increases in cognitive function score were associated with better functioning; for all other EORTC QLQ-C30 measurements included in this analysis, score reductions were associated with better functioning.

All evaluations in the current analysis were exploratory and were summarized using descriptive statistics.

Table 1
Percentage of Patients With Abnormal Markers Suggestive of Iron Deficiency at Baseline.

Marker,[a] n (%)	Ruxolitinib (n = 110)	Best Available Therapy (n = 112)	Total (N = 222)
MCV below LLN	74 (67.3)	63 (56.3)	137 (61.7)
Serum iron below LLN	91 (82.7)	90 (80.4)	181 (81.5)
Ferritin below LLN	68 (61.8)	73 (65.2)	141 (63.5)
TSAT below LLN	98 (89.1)	99 (88.4)	197 (88.7)
MCHC below LLN	77 (70.0)	77 (68.8)	154 (69.4)
TIBC above ULN	29 (26.4)	25 (22.3)	54 (24.3)

LLN, lower limit of normal; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; TIBC, total iron-binding capacity; TSAT, transferrin iron saturation; ULN, upper limit of normal.

[a] Abnormal values suggestive of iron deficiency for each marker were defined by the individual study sites (see Methods text for details).

3. Results

3.1. Patient characteristics

Patient demographics and baseline characteristics for the RESPONSE trial have been reported previously [22]. Briefly, patients randomized to ruxolitinib or best available therapy were predominately male (60.0% vs 71.4%, respectively), with similar median ages (60 vs 62 years) and median times since PV diagnosis (8.2 vs 9.3 years). The majority of patients received ≥1 phlebotomy during the 24 weeks before screening (100% in the ruxolitinib arm vs 98.2% in the best available therapy arm).

For the majority of patients, baseline laboratory values were suggestive of iron deficiency for all markers of iron deficiency, with the exception of TIBC (Table 1). Treatment with concomitant iron supplementation (iron bivalent, oral preparations) was infrequent, occurring in <10% of patients in each treatment arm. Even among patients with evidence of iron deficiency, ≤12.2% in the ruxolitinib arm and ≤12.0% in the best available therapy arm received an iron bivalent oral supplement at baseline, depending on the marker (Table 2).

3.2. Markers of iron deficiency

Among patients with baseline laboratory values consistent with iron deficiency, treatment with ruxolitinib was associated with rapid and consistent improvements in marker levels over time (ie, increases in MCV, serum iron, ferritin, TSAT, and MCHC and decreases in TIBC), reaching normal ranges as early as Week 16 that remained stable through Week 80 (Fig. 1), whereas treatment with best available therapy was associated with lesser improvements in all iron indices.

Among patients treated with ruxolitinib who had normal iron status at baseline, marker levels remained within normal ranges through Week 80 (Fig 1).

Mean (SD) hepcidin levels in the ruxolitinib arm changed from 623.9 (1475.4) pg/mL at baseline (n = 96) to 4577.5 (2747.0) pg/mL at Week 32 (n = 85). In the best available therapy arm, mean (SD) hepcidin levels changed from 827.7 (1818.3) pg/mL at baseline (n = 84) to 1299.3 (2239.7) pg/mL at Week 32 (n = 76).

3.3. Patient-reported outcomes

Patients who received ruxolitinib experienced greater improvements from baseline at Week 32 in MPN-SAF symptom severity scores and EORTC QLQ-C30 individual and subscale scores compared with those who received best available therapy, regardless of iron deficiency status at baseline (Figs. 2 and 3). For the majority of these patient-reported outcomes, improvements were more pronounced among patients with evidence of iron deficiency at baseline compared with those who had normal iron levels.

4. Discussion

This exploratory analysis of patients with PV who were intolerant of or resistant to hydroxyurea from the RESPONSE trial is the first comprehensive evaluation of iron status in a prospective study of patients with PV. The results suggest that treatment with ruxolitinib is associated with greater control of iron indices compared with best available therapy. In patients with marker levels indicative of iron deficiency at baseline, treatment with ruxolitinib, but not best available therapy, was associated with rapid normalization of iron-related laboratory values. Among patients with normal values at baseline, levels remained stable during treatment with ruxolitinib. Of particular note is the normalization of hepcidin levels with ruxolitinib treatment. Hepcidin is a hormone that controls iron homeostasis by regulating iron uptake through JAK2-dependent interactions [6] with the iron transporter ferroportin [29]. The changes from baseline in hepcidin levels observed among ruxolitinib-treated patients in the current analysis were suggestive of normalized iron homeostasis.

The burden of frequent phlebotomies and iron deficiency in a contemporary population of patients with PV has not been described. However, studies in broader patient populations suggest that iron deficiency may lead to a range of complications related to patient energy levels [7,11], cognitive function [7,8], and cardiovascular health [12–14]. In agreement with ruxolitinib-associated normalization of iron indices identified here, patients in the ruxolitinib arm, regardless of iron status at baseline, reported improvements in PV-related symptoms with the MPN-SAF and EORTC QLQ-C30 questionnaires. In addition, previous RESPONSE data indicated that the thromboembolic event rate in the 80-week analysis was lower among patients in the ruxolitinib arm (1.8 per 100 patient-years of exposure) compared with those treated with best available therapy (8.2 per 100 patient-years of exposure) [23]. However, RESPONSE was not powered to analyze patient-reported outcomes or thromboembolic event rates statistically, and further research will be required to determine the relationship between phlebotomies and iron deficiency with PV-related symptoms and other patient outcomes.

The treatment goals for patients with PV are to reduce the risk of cardiovascular/thromboembolic events, minimize the risk of disease transformation, and manage symptoms [18]. The role of iron deficiency within this paradigm is not clearly defined by current clinical evidence. On the one hand, iron deficiency may cause dysregulation of hematopoiesis [30], and therefore contribute to disease control in patients with PV. In agreement with this concept, few patients in either treatment arm of this analysis were receiving iron supplementation at baseline. This parallels current PV treatment practices [31] and the RESPONSE study protocol, which did not include recommendations for the treatment of iron deficiency. Iron supplementation has been associated with increased erythropoiesis in cancer patients with chemotherapy-induced anemia [30], which is counterproductive in the PV setting. However,

Table 2
Concomitant Iron Supplementation[a] at Baseline.

Marker, n/N[b] (%)	Ruxolitinib (n = 110)		Best Available Therapy (n = 112)	
	Suggestive of Iron Deficiency	Suggestive of Normal Iron	Suggestive of Iron Deficiency	Suggestive of Normal Iron
Iron bivalent, oral preparation supplement				
MCV	9/74 (12.2)	1/36 (2.8)	6/63 (9.5)	1/48 (2.1)
Serum Iron	8/91 (8.8)	2/19 (10.5)	7/90 (7.8)	0/18 (0)
Ferritin	5/68 (7.4)	5/42 (11.9)	5/73 (6.8)	2/36 (5.6)
TSAT	8/98 (8.2)	1/10 (10.0)	7/99 (7.1)	0/9 (0)
MCHC	7/77 (9.1)	2/28 (7.1)	6/77 (7.8)	1/29 (3.4)
TIBC	2/29 (6.9)	7/79 (8.9)	3/25 (12.0)	4/83 (4.8)
Other iron supplement				
MCV	1/74 (1.4)	0/36 (0)	1/63 (1.6)	0/48 (0)
Serum Iron	1/91 (1.1)	0/19 (0)	0/90 (0)	1/18 (5.6)
Ferritin	1/68 (1.5)	0/42 (0)	1/73 (1.4)	0/36 (0)
TSAT	1/98 (1.0)	0/10 (0)	1/99 (1.0)	0/9 (0)
MCHC	1/77 (1.3)	0/28 (0)	0/77 (0)	1/29 (3.4)
TIBC	1/29 (3.4)	0/79 (0)	1/25 (4.0)	0/83 (0)
Iron in other combinations				
MCV	2/74 (2.7)	0/36 (0)	0/63 (0)	0/48 (0)
Serum Iron	2/91 (2.2)	0/19 (0)	0/90 (0)	0/18 (0)
Ferritin	1/68 (1.5)	1/42 (2.4)	0/73 (0)	0/36 (0)
TSAT	2/98 (2.0)	0/10 (0)	0/99 (0)	0/9 (0)
MCHC	2/77 (2.6)	0/28 (0)	0/77 (0)	0/29 (0)
TIBC	1/29 (3.4)	1/79 (1.3)	0/25 (0)	0/83 (0)

MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; TIBC, total iron-binding capacity; TSAT, transferrin iron saturation.
[a] All iron supplements were oral; no intravenous iron supplements were administered.
[b] N is the number of patients with or without evidence of iron deficiency at baseline, as defined by each marker.

on the other hand, the iron-deficient state is associated with a range of complications [7,8,11–14]. An ideal treatment option for patients with PV would provide disease control in the absence of iron deficiency-related complications. Maintaining hematocrit levels <45% with phlebotomy is associated with reduced risk of cardiovascular/thrombotic events [17]. Although phlebotomies may worsen the iron-deficient state, even patients with complications related to iron deficiency may continue to be treated with phlebotomies given the importance of reducing the risks of cardiovascular/thromboembolic events and resulting mortality. Several traditional medical treatment options provide clinical benefit for patients with PV, including hydroxyurea [32] and interferon-α [33], but the effects of these treatments on complications related to iron deficiency are unclear. Furthermore, some patients with low-risk PV may continue receiving phlebotomies because of lack of access to cytoreductive treatments. The current analysis, combined with previous RESPONSE trial results [22], suggests that ruxolitinib may provide an opportunity to manage PV without dysregulation of iron homeostasis.

Most patients in the RESPONSE trial had iron-related laboratory values that were abnormal and suggestive of iron deficiency. In contrast, prevalence of iron deficiency in the US general population, based on National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2000, is much lower (men, 2%–3%; women, 6%–16%, depending on age group; defined as an abnormal value for ≥2 of the following indicators: serum ferritin, transferrin saturation, and free erythrocyte protoporphyrin) [34]. Iron deficiency levels in the RESPONSE patient population were in agreement with a prospective study of patients with PV (N = 173) that identified a subset with low serum ferritin levels [35]. However, because large observational and prospective trials in PV—including ECLAP and CYTO-PV—have not reported the prevalence of iron deficiency [16,17,32,36,37], it remains unclear if iron levels in the RESPONSE trial were representative of the general PV patient population.

Patients with PV should be educated on and routinely evaluated for the signs and symptoms of iron deficiency. In addition, physicians should be aware that iron deficiency-related signs and symptoms may occur in the absence of anemia in some patients [9,10,38].

The full mechanism by which ruxolitinib may affect iron homeostasis in patients with PV remains unclear. Treatment with ruxolitinib is associated with hematocrit control and reduced phlebotomy requirement [22], thereby diminishing the amount of iron extracted from the body. Similarly, ruxolitinib reduces enlarged spleen size [22], which may reduce the amount of red blood cells and iron sequestered in the spleen [39]. As a JAK1/JAK2 inhibitor, ruxolitinib inhibits cytokine signaling and may have anti-inflammatory activity [22,40], which may inhibit hepcidin and promote increases in serum iron levels [6,41]. Sample sizes in the current analysis were insufficient for a subgroup analysis stratified by phlebotomy treatment to evaluate whether ruxolitinib modifies iron deficiency independent of phlebotomy requirement.

Key strengths of this analysis include the use of data from a multicenter, randomized, controlled trial. To address the lack of consensus on iron deficiency diagnostic criteria, which may vary based on marker preference or patient condition [42–44], we employed 7 markers for iron deficiency in this analysis. Limitations of note include the exploratory nature of the analysis, which was not powered for statistical comparisons. Iron marker thresholds for iron deficiency were defined locally at each study site rather than by a standardized definition. As a result, patient populations with versus without iron deficiency may have varied among sites. In addition, iron levels were based on serum iron markers rather than measurements of bone marrow iron stores. Although this study assessed serum ferritin levels, which is a good surrogate for bone marrow iron stores in most patients [45], future study designs may benefit from the assessment of iron levels in bone marrow biopsies. It remains unclear whether ruxolitinib-related effects on the patient-reported outcomes resulted from an improvement in iron status, achievement of hematocrit control with reduced or absent phlebotomy requirement, or a combination of the two. Few patients in the ruxolitinib group had a phlebotomy (20% between Weeks 8 and 32) [22], precluding the use of a phlebotomy-based subgroup analysis to address this question. Furthermore, ruxolitinib was associated with improvements in nearly all individual

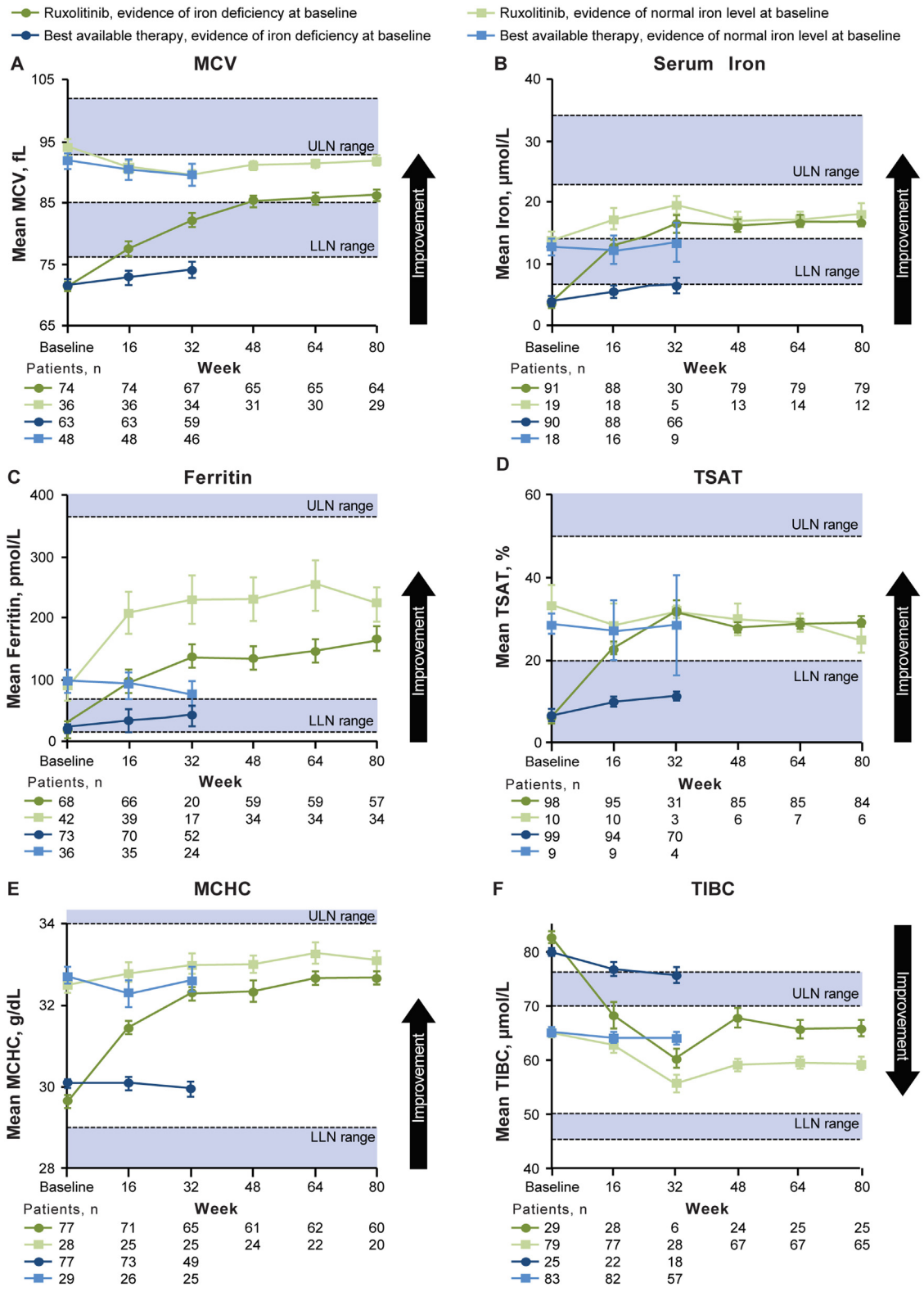

Fig. 1. Levels of Markers of Iron Deficiency Over Time. LLN, lower limit of normal; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; TIBC, total iron-binding capacity; TSAT, transferrin iron saturation; ULN, upper limit of normal.

symptoms in the primary analysis, regardless of a plausible association with iron deficiency, creating the potential for a positive bias in the analysis. The improvements in marker levels and symptoms with ruxolitinib may occur sooner than one would expect based solely on a reduction in phlebotomy requirement. However, an appropriately designed prospective study would be required to test this hypothesis. An additional question that remains unanswered is whether ruxolitinib-associated normalization of iron levels is based

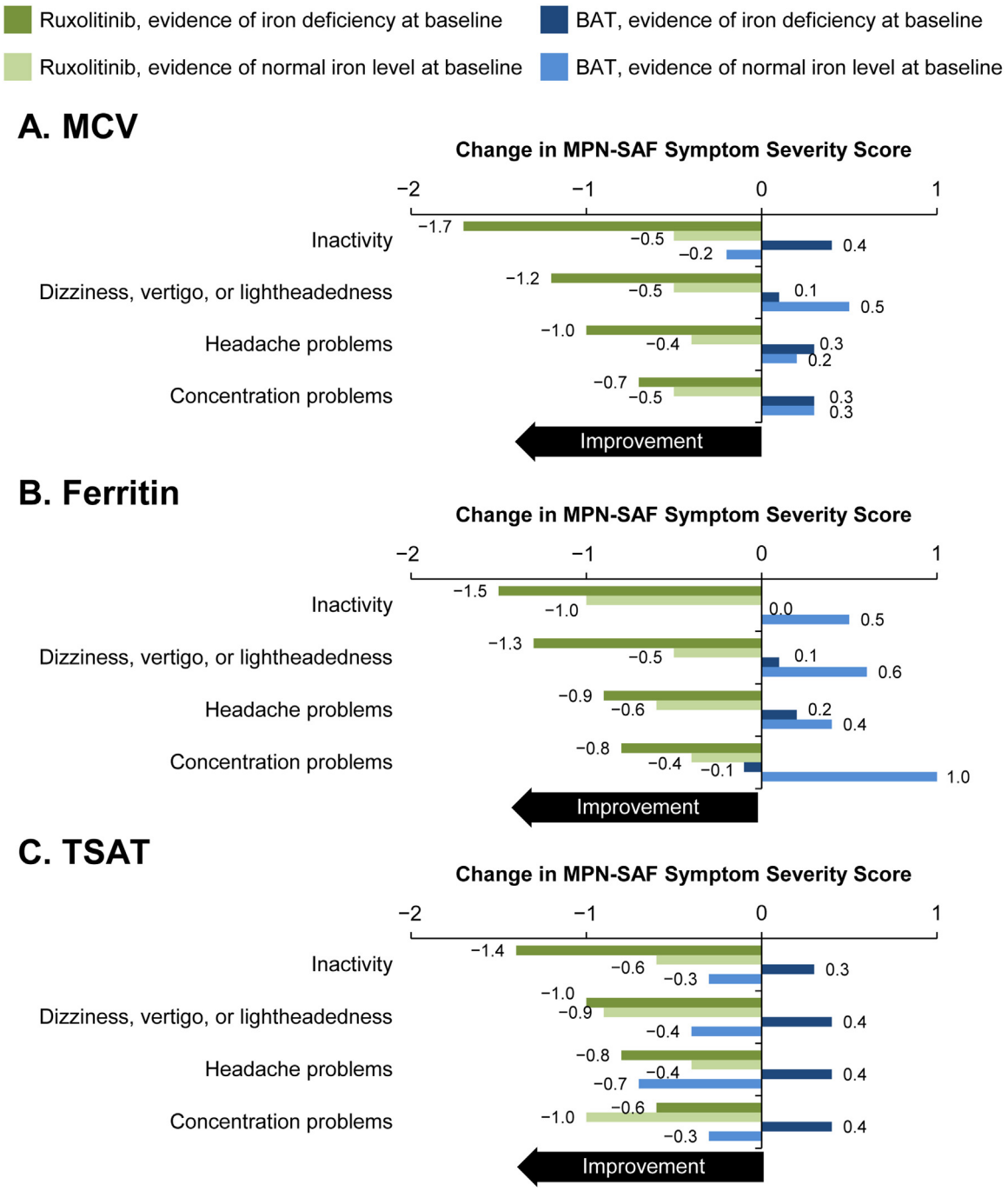

Fig. 2. Change From Baseline at Week 32 in MPN-SAF Symptom Severity Scores in Patients Stratified by Baseline Iron Status. Iron status was determined based on serum levels of (A) MCV, (B) ferritin, and (C) TSAT. BAT, best available therapy; MCV, mean corpuscular volume; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSAT, transferrin saturation.

on a reduction in phlebotomy requirement or another mechanism. Finally, the RESPONSE patient population was limited to those who were resistant to or intolerant of hydroxyurea; additional studies will be required to determine the effect of ruxolitinib on iron deficiency in other patient populations.

5. Conclusion

In conclusion, ruxolitinib treatment of patients with PV was associated with rapid and sustained improvements in iron indices, compared with lesser improvements with best available therapy. Regardless of iron indices at baseline, ruxolitinib treatment was associated with improvements in patient-reported outcomes on the MPN-SAF and EORTC QLQ-C30. The rapid improvements in markers of iron deficiency with ruxolitinib treatment observed in this analysis are suggestive of a clinical effect that warrants further exploration.

Conflict of interest statement

SV received institutional research funding from Incyte Corporation. CNH received honoraria from Novartis Pharmaceuticals Corporation, CTI, Sanofi, and Baxter; served on speakers bureaus for Novartis Pharmaceuticals Corporation, CTI, Sanofi, Baxter, and

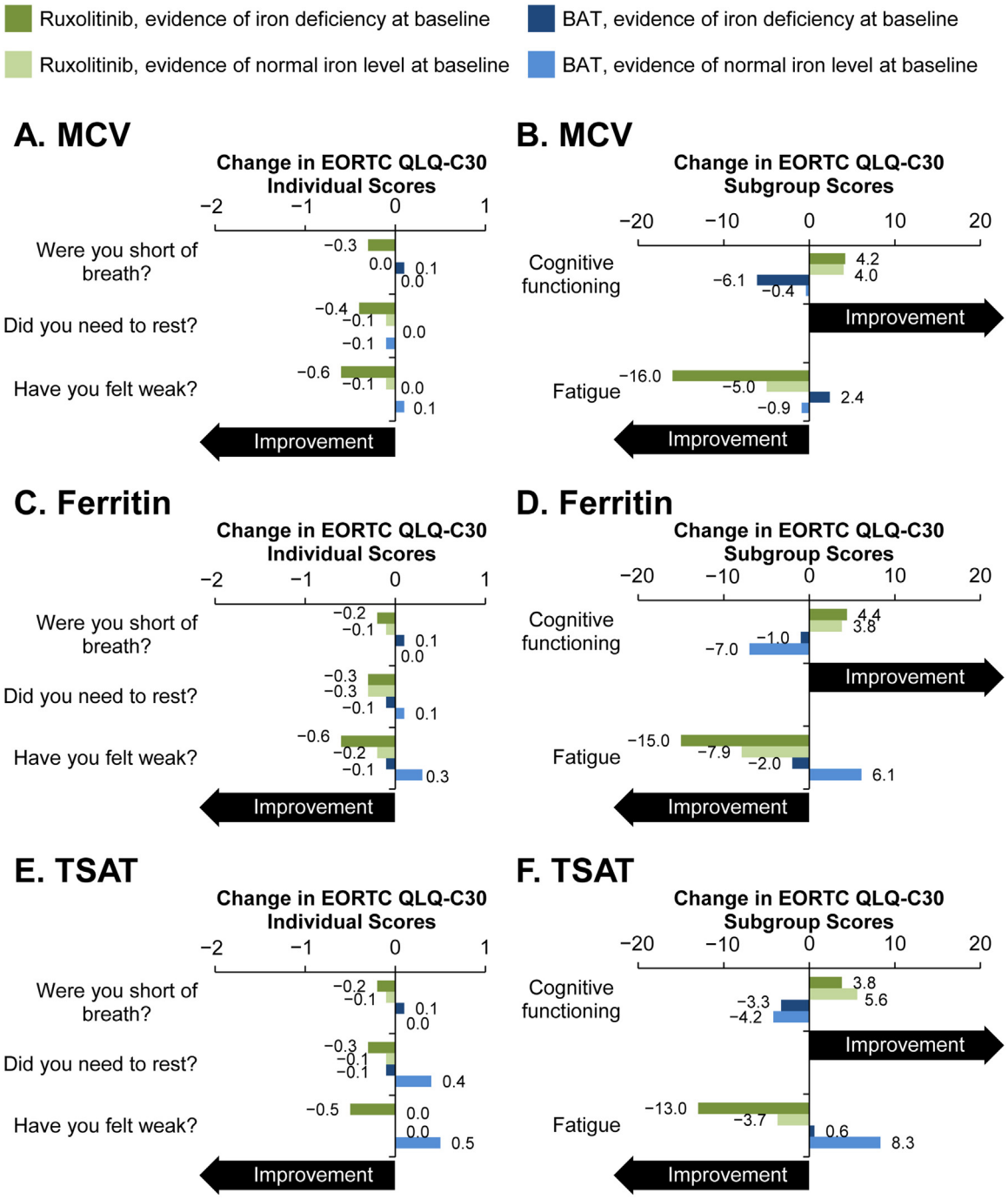

Fig. 3. Change From Baseline at Week 32 in EORTC QLQ-C30 Scores in Patients Stratified by Baseline Iron Status. Iron status was determined based on serum levels of (A, B) MCV, (C, D) ferritin, and (E, F) TSAT. BAT, best available therapy; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; MCV, mean corpuscular volume; TSAT, transferrin saturation.

Shire; received institutional research funding from Novartis Pharmaceuticals Corporation, CTI, Sanofi, Celgene, and Gilead Sciences; and had travel expenses paid for by Novartis Pharmaceuticals Corporation. J–JK served as a consultant for Incyte Corporation, Novartis Pharmaceuticals Corporation, and Shire and received institutional research funding from Novartis Pharmaceuticals Corporation and AOP Orphan. CM received institutional research funding, honoraria, and served as a consultant to Incyte Corporation and Novartis Pharmaceuticals Corporation. ABN and DCP are employees of and stockholders in Incyte Corporation. DH is an employee of and stockholder in Novartis Pharmaceuticals Corporation. AMV received institutional research funding and served as a consultant for Novartis Pharmaceuticals Corporation and served on speakers bureaus for Novartis Pharmaceuticals Corporation and Shire. Writing assistance for this manuscript was funded by Incyte Corporation.

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