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Effect of New or Worsening Anemia on Clinical Outcomes in Patients With Myelofibrosis Treated With Ruxolitinib: A Post Hoc Analysis of the COMFORT-I and -II Trials

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Introduction

- Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by cytopenias, splenomegaly, debilitating symptoms, and poor overall survival (OS)[1,2]
- Ruxolitinib (RUX) is a potent and selective Janus kinase (JAK)1/JAK2 inhibitor approved for the treatment of patients with intermediate- or high-risk MF[3]
- In the phase 3 COMFORT trials, RUX reduced spleen volume, improved MF-related symptoms, and prolonged OS compared with either placebo (COMFORT-I) or best available treatment (COMFORT-II)[4-8]
- However, RUX treatment was also associated with transient anemia[4,5]
- RUX-associated anemia usually occurred in the first 12 weeks of therapy and was managed with dose adjustments and/or red blood cell (RBC) transfusions[4,5]

Objective

- To assess the impact of new or worsening anemia induced by RUX on spleen volume response, symptom severity, and OS in patients with MF

Methods

Study Design and Patients

- In the COMFORT studies, patients were randomly assigned to receive RUX at a starting dose of 15 or 20 mg orally twice daily (depending on platelet count) or either matched placebo (COMFORT-I)[4] or best available treatment (COMFORT-II)[5]; patients initially assigned to placebo or best available treatment meeting protocol-defined worsening splenomegaly were permitted to cross over to RUX
  - This post hoc analysis of COMFORT-I and -II included patients from the RUX treatment arms
- Patients were stratified based on baseline anemia and transfusion status: nonanemic (hemoglobin [Hb] >100 g/L), anemic non–transfusion dependent (NTD; Hb <100 g/L, received <2 units RBC), and anemic transfusion dependent (TD; Hb <100 g/L, received ≥2 units RBC) over 8 (COMFORT-I) or 12 (COMFORT-II) weeks before first RUX dose

Assessments

- Percentage of patients with spleen volume reduction ≥35% from baseline (SVR35) based on pooled Week 24 and Week 48 data from COMFORT-I/II
- Symptom response as assessed by the MF-Symptom Assessment Form total symptom score (TSS response; ≥50% reduction from baseline [TSS50]; based on COMFORT-I data) or ≥6.5-point increase in Functional Assessment of Cancer Therapy–Lymphoma total score (FACT-Lym TS response; based on COMFORT-II data) at Week 24
- OS, defined as time from randomization to death due to any cause
- Outcomes were stratified by presence or absence of new or worsening anemia (Hb decrease ≥15 g/L or new transfusion requirement postbaseline until Week 12)

Statistical Analyses

- OS was assessed using the Kaplan-Meier method; *P* values for differences between patients with vs without new or worsening anemia postbaseline until Week 12 were generated using the stratified two-sided log-rank test
- *P* values for other assessments were generated using Fisher exact method

Results

Patients

- A total of 293 patients were included in the analysis, of which 162 patients developed new or worsening anemia at Week 12 and 131 did not (**Table 1**)
  - Patient demographics and baseline characteristics were generally similar between the 2 groups
  - At baseline, 54.3% of patients were nonanemic, 19.5% were anemic NTD, and 26.3% were anemic TD
  - Hemoglobin levels tended to be lower in the new or worsening anemia group (**Table 2**)

Treatment Exposure

- Patients both with and without new or worsening anemia received similar doses of RUX (**Figure 1**)

Spleen Volume Reduction

- Overall, 277 patients completed through Week 24; 154 (55.6%) were nonanemic at baseline, 55 (19.9%) were anemic NTD, and 68 (24.5%) were anemic TD
- Rates of SVR35 at Week 24 were similar between patients with and without new or worsening anemia for those who were nonanemic (48.8% vs 43.2%, respectively), anemic NTD (33.3% vs 23.1%), or anemic TD (41.4% vs 28.2%; **Figure 2**)
- Similar SVR35 rates were observed at Week 48

Symptom Response

- There was no significant difference in the percentage of patients with vs without new or worsening anemia who achieved TSS50 at Week 24 who were nonanemic (51.1% vs 42.9%), anemic NTD (42.1% vs 40.0%), or anemic TD (46.7% vs 54.2%; **Figure 3A**)
- Similarly, there was no significant difference in the percentage of patients achieving ≥6.5-point increase in FACT-Lym TS at Week 24 among those with vs without new or worsening anemia for patients who were nonanemic (48.6% vs 43.6%), anemic NTD (52.2% vs 50.0%), or anemic TD (28.6% vs 53.3%; **Figure 3B**)

Overall Survival

- Among patients without anemia at baseline, median OS was not reached (not estimable [NE]) in patients with or without new or worsening anemia (*P*=0.68; **Figure 4A**)
- Among patients with anemia at baseline, there was no significant difference between groups; however, a trend toward longer OS was seen in patients with vs without new or worsening anemia (median [95% CI], 50.0 [37.6, 55.8] vs 38.4 [29.7, 51.4] months; *P*=0.26; **Figure 4B**)
  - Between-group OS differences were not significant for both anemic NTD (median [95% CI], 51.3 [43.1, NE] vs 34.4 [19.4, NE] months; *P*=0.51) and anemic TD patients (median [95% CI], 39.5 [30.5, 55.8] vs 38.4 [29.5, 51.4] months; *P*=0.69; **Figure 4C**)
  - However, data interpretation was limited by small patient number (anemic NTD, n=43 and n=14 for patients with and without new or worsening anemia, respectively; anemic TD, n=35 and n=42)

Table 1. Patient Demographics and Baseline Characteristics*

Variable	New/worsening anemia up to Week 12 (n=162)	No new/worsening anemia up to Week 12 (n=131)	Total (N=293)
Age, median (range), y	67.0 (36–83)	66.0 (35–91)	66.0 (35–91)
≤65 y, n (%)	69 (42.6)	65 (49.6)	134 (45.7)
>65 y, n (%)	93 (57.4)	66 (50.4)	159 (54.3)
Male, n (%)	74 (45.7)	83 (63.4)	157 (53.6)
BMI, mean (SD), kg/m^2	24.0 (3.1)	25.6 (5.5)	24.7 (4.4)
Hb, mean (SD), g/L	106.0 (16.5)	112.6 (25.5)	108.9 (21.2)
Baseline anemia status, n (%)			
Nonanemic	84 (51.9)	75 (57.3)	159 (54.3)
Anemic NTD	43 (26.5)	14 (10.7)	57 (19.5)
Anemic TD	35 (21.6)	42 (32.1)	77 (26.3)

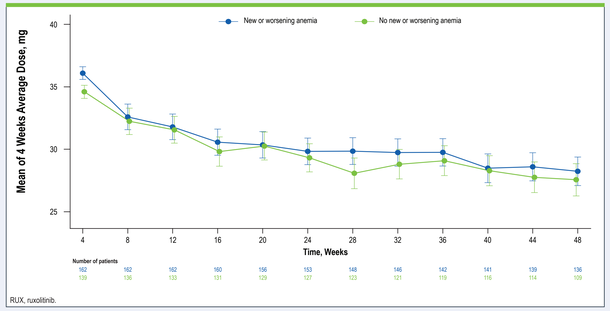
BMI, body mass index; Hb, hemoglobin; NTD, anemic non–transfusion dependent; TD, anemic transfusion dependent.
* Among intent-to-treat population who completed ≥12 weeks of study treatment.

Table 2. Baseline Hemoglobin in Patients With vs Without New or Worsening Anemia*

Hb, mean (SD), g/L	Nonanemic (n=159)	Anemic NTD (n=57)	Anemia TD† (n=77)	Total (N=293)
New/worsening anemia	117.2 (12.9)	88.2 (7.4)	100.9 (9.0)	106.0 (16.5)
No new/worsening anemia	130.2 (18.2)	93.9 (3.9)	87.6 (11.6)	112.6 (25.5)

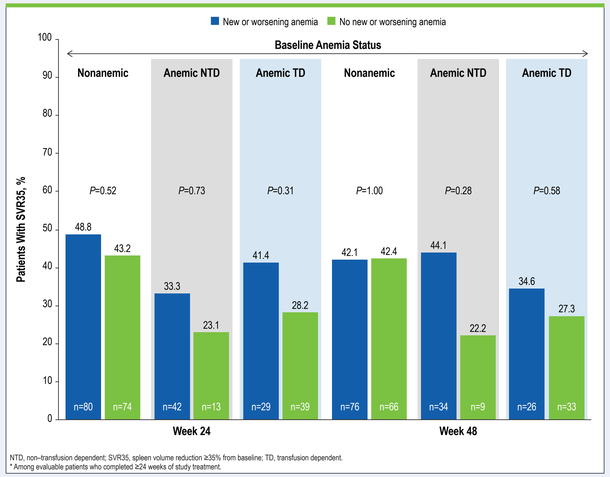
* Among intent-to-treat population who completed ≥12 weeks of study treatment.
† Some patients received transfusions during the screening period before baseline values were recorded, resulting in higher Hb values.

Figure 1. Average Dose of RUX in Patients With vs Without New or Worsening Anemia



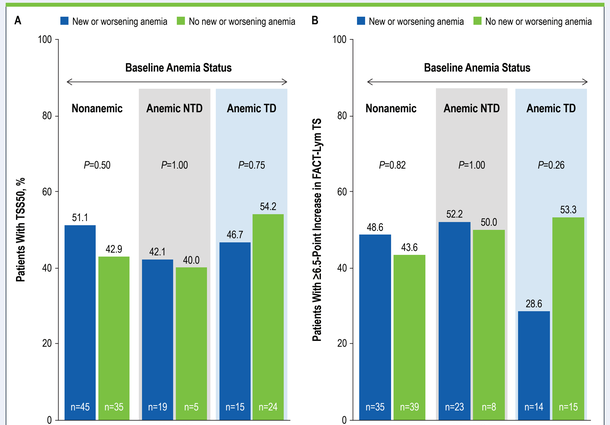
RUX, ruxolitinib.

Figure 2. Percentage of Patients Achieving SVR35 at Weeks 24 and 48 by Baseline Anemia and Transfusion Status and New or Worsening Anemia*



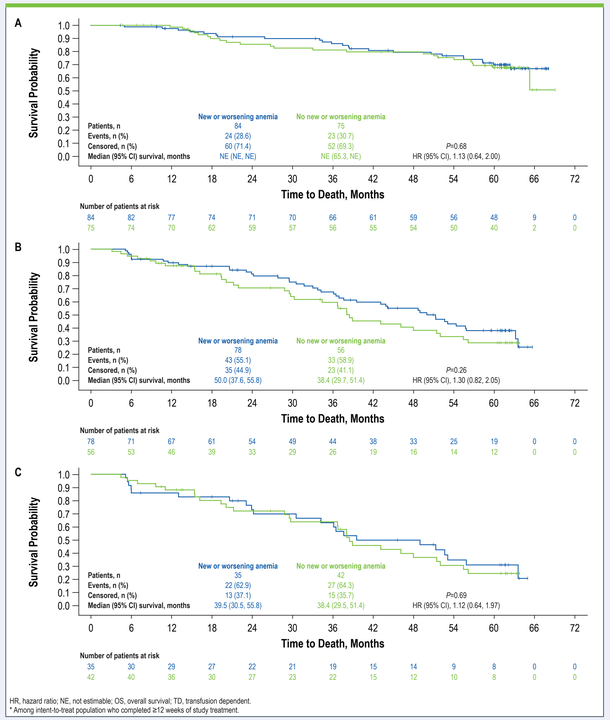
NTD, non–transfusion dependent; SVR35, spleen volume reduction ≥35% from baseline; TD, transfusion dependent.
* Among evaluable patients who completed ≥24 weeks of study treatment.

Figure 3. Percentage of Patients Achieving (A) TSS50 and (B) ≥6.5-Point Increase in FACT-Lym TS at Week 24 by Baseline Anemia and Transfusion Status and New or Worsening Anemia*



FACT-Lym TS, Functional Assessment of Cancer Therapy–Lymphoma total score; NTD, non–transfusion dependent; TD, transfusion dependent; TSS, total symptom score; TSS50, TSS reduction ≥50% from baseline.
* Among evaluable patients who completed ≥24 weeks of study treatment.

Figure 4. OS of Patients With vs Without New or Worsening Anemia Who Were (A) Nonanemic, (B) Anemic (Overall), and (C) Anemic TD at Baseline Up to Week 12*



HR, hazard ratio; NE, not estimable; OS, overall survival; TD, transfusion dependent.
* Among intent-to-treat population who completed ≥12 weeks of study treatment.

Conclusions

- **The onset of new or worsening anemia postbaseline did not diminish clinical benefit of RUX treatment vs that observed in patients without new or worsening anemia**
- **In patients with MF, RUX was associated with a reduction in spleen volume and a reduction in symptoms associated with MF regardless of baseline anemia and transfusion status**

References

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