Impact of new or worsening anemia and thrombocytopenia on clinical outcomes in JAK inhibitor–naive myelofibrosis patients treated with ruxolitinib

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Spleen and symptom response rates may be lower with ruxolitinib in MF patients with cytopenias, supporting consideration of alternative therapies in these patients

Supplemental data

SCAN ME

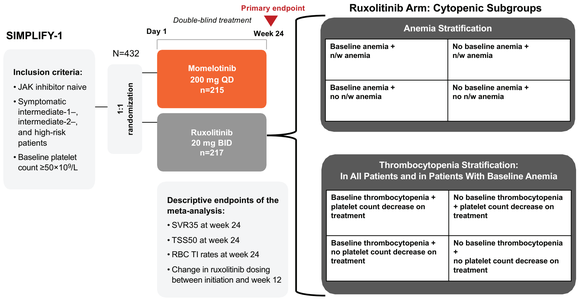
Introduction

- Myelofibrosis (MF) is characterized by splenomegaly, constitutional symptoms, and cytopenias[1]
  - Ruxolitinib, a Janus kinase (JAK) 1/JAK2 inhibitor, provides spleen and symptom benefits but is often associated with cytopenias; dose reductions may be necessary to manage new or worsening (n/w) anemia and/or platelet count decrease on treatment[2-4]
- A SIMPLIFY-1 subgroup analysis in patients with hemoglobin (Hb) <10 g/dL showed that lower starting doses of ruxolitinib in those with baseline platelet counts <200×10⁹/L were associated with lower rates of spleen volume reduction ≥35% (SVR35) at week 24[5]
  - SVR35 rates were 49% for patients with platelet counts >200×10⁹/L, 24% for those with platelet counts ≥100 to <200×10⁹/L, and 0% for those with platelet counts ≥50 to <100×10⁹/L[5]
  - This suggests that suboptimal ruxolitinib dosing may lead to reduced clinical benefit and highlights the importance of full-dose JAK inhibitor therapy for optimal spleen response
- The spleen and symptom response impacts of n/w anemia or platelet count decrease while on treatment with ruxolitinib are unclear
- This post hoc analysis of the phase 3 SIMPLIFY-1 trial evaluates the impacts of baseline and n/w anemia and thrombocytopenia on spleen response and symptom response in JAK inhibitor–naive patients with MF treated with ruxolitinib
  - In addition, concurrent ruxolitinib dose modifications occurring with n/w anemia and platelet count decrease on treatment are characterized

Methods

- SIMPLIFY-1 (NCT01969838) was a randomized, double-blind, phase 3 trial of JAK inhibitor–naive patients with MF (**Figure 1**)[8]
  - In this post hoc analysis, clinical outcomes were evaluated in patients in the ruxolitinib arm, stratified by the presence vs absence of baseline cytopenias and by the presence vs absence of n/w anemia or platelet count decrease on treatment
    - **Baseline anemia:** Hb <10 g/dL or transfusion dependence
    - **N/w anemia:** a decrease of ≥1.5 g/dL from baseline to an Hb level of <10 g/dL, or new transfusion requirement of ≥2 red blood cell (RBC) units transfused within 8 weeks at weeks 4, 8, or 12 following ruxolitinib initiation
    - **Baseline thrombocytopenia:** platelet counts <200×10⁹/L
    - **Platelet count decrease:** a decrease of >50×10⁹/L to a platelet count of <200×10⁹/L by week 12 following ruxolitinib initiation

Figure 1: **SIMPLIFY-1 Ruxolitinib Arm Cytopenic Subgroup Analyses: Study Design**



BID, twice daily; JAK, Janus kinase; QD, once daily; RBC, red blood cell; SVR35, spleen volume reduction ≥35%; TI, transfusion independence; TSS50, Total Symptom Score reduction ≥50%.

- Note that patients treated with momelotinib in the SIMPLIFY-1 trial were excluded from the present analyses, as improvements in anemia and transfusion burden are expected with momelotinib treatment
  - With momelotinib treatment, 69% of patients with baseline moderate anemia (Hb ≥8 to <10 g/dL) and 50% with baseline severe anemia (Hb <8 g/dL) achieved Hb >10 g/dL by week 24[6]
  - In baseline anemic patients, >80% had reduced or stable transfusion intensity during treatment with momelotinib[7]

Results

Anemia Subgroups

Patients

- The analysis was based on the safety population of 216 patients who received ≥1 dose of treatment (**Table 1**)
  - At baseline, 103 patients were anemic, and 84 (81.6%) developed worsening anemia within 12 weeks of starting ruxolitinib
  - Among the 113 nonanemic patients, 23 (20.4%) developed new anemia
- Baseline characteristics for these subgroups are described elsewhere[7] and may be found behind the QR code

Spleen Outcomes

- In both baseline anemic and baseline nonanemic subgroups, n/w anemia was associated with numerically lower SVR35 rates vs no n/w anemia (**Figure 2**)

Symptom Outcomes

- In both baseline anemic and baseline nonanemic subgroups, n/w anemia was associated with numerically lower TSS50 rates than no n/w anemia (**Figure 3**)

Ruxolitinib Dose Changes

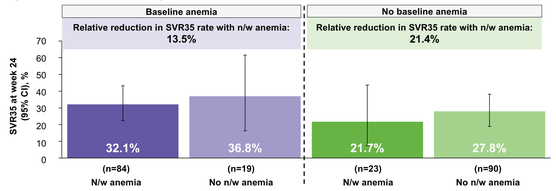
- Regardless of baseline anemia status, baseline ruxolitinib doses were similar between n/w anemia and no n/w anemia (mean starting doses, 32.1 vs 34.6 mg daily)
- In both baseline anemic and nonanemic subgroups, numerically greater ruxolitinib dose reductions were observed in patients who experienced n/w anemia during the first 12 weeks (**Table 2**)

Table 1: **Anemia Subgroups**

	N/w anemia, n (%)	No n/w anemia, n (%)	Total, n[a]
Baseline thrombocytopenia	84 (81.6)	19 (18.4)	103
No baseline thrombocytopenia	23 (20.4)	90 (79.6)	113
Overall	107 (49.5)	109 (50.5)	216

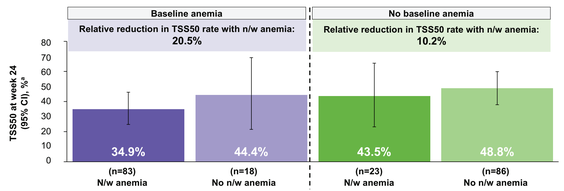
n/w, new or worsening.
[a] *Percentages based on baseline anemia status ("Total" column) as denominator.*

Figure 2: **Anemia Subgroups Spleen Response**



n/w, new or worsening; SVR35, spleen volume reduction ≥35%.

Figure 3: **Anemia Subgroups Symptom Response**



n/w, new or worsening; TSS, Total Symptom Score; TSS50, Total Symptom Score reduction ≥50%.
[a] *TSS50 evaluable in patients with nonmissing, nonzero baseline TSS values.*

Table 2: **Anemia Subgroups Ruxolitinib Dosing Change**

	Baseline anemia (n=103)		No baseline anemia (n=112)	
	N/w anemia (n=84)	No n/w anemia (n=19)	N/w anemia (n=23)	No n/w anemia (n=89)
Ruxolitinib dose at index, mean (SD), mg	30.8 (10.55)	33.7 (11.16)	37.0 (4.70)	34.8 (8.93)
Average ruxolitinib dose over the first 12 weeks, mean (SD), mg	27.1 (11.04)	32.0 (12.81)	31.7 (9.40)	31.0 (10.13)
Change in dose between index and 12 weeks, mean (SD), mg	**−3.7** (5.45)	**−1.7** (6.51)	**−5.2** (6.68)	**−3.9** (6.05)

n/w, new or worsening.

Thrombocytopenia Subgroups

Patients

- At baseline, 86 patients had thrombocytopenia, with 82 (95.3%) having further platelet count decrease within 12 weeks of starting ruxolitinib (**Tables 3 and 4**)
- Among the 130 patients with no baseline thrombocytopenia, 85 (65.4%) had platelet count decrease on treatment
- Because the proportion of patients who did not have platelet count decrease on treatment was low, outcomes were only evaluated based on the presence or absence of baseline thrombocytopenia

Spleen Outcomes

- Patients with baseline thrombocytopenia had numerically lower SVR35 rates than patients without baseline thrombocytopenia (**Figure 4**)

Symptom Outcomes

- Patients with baseline thrombocytopenia had numerically lower TSS50 rates than patients without baseline thrombocytopenia (**Figure 5**)

Ruxolitinib Dosing Changes

- Patients with platelet count decrease on treatment had numerically lower mean ruxolitinib doses at baseline and numerically greater ruxolitinib dose reductions from baseline to week 12 compared with patients who did not have platelet count decrease (**Table 5**)
- By week 24, 57 patients (66.3%) with baseline thrombocytopenia were receiving doses of ≤20 mg daily vs only 16 (12.3%) without baseline thrombocytopenia, reflecting worsening thrombocytopenia on treatment
- However, 37 patients (43.0%) with baseline thrombocytopenia were TI (no transfusions and no Hb <8 g/dL in the 12 weeks immediately preceding week 24) vs 70 (53.8%) without baseline thrombocytopenia, suggesting these reduced doses were of limited efficacy in preventing progressive anemia

Table 3: **Thrombocytopenia Subgroups**

	Platelet count decrease on treatment, n (%)	No platelet count decrease on treatment, n (%)	Total, n[a]
Baseline thrombocytopenia	82 (95.3)	4 (4.7)	86
No baseline thrombocytopenia	85 (65.4)	45 (34.6)	130
Overall	167 (77.3)	49 (22.7)	216

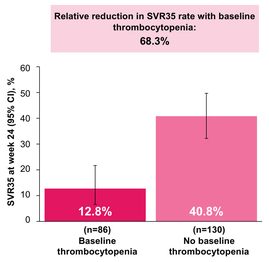
[a] *Percentages based on baseline thrombocytopenia status ("Total" column) as denominator.*

Table 4: **Thrombocytopenia Subgroups Baseline Characteristics[a]**

	Baseline thrombocytopenia (n=86)	No baseline thrombocytopenia (n=130)
Age, median (range), years	66.0 (35-79)	66.0 (25-86)
≥65 years, n (%)	48 (55.8)	74 (56.9)
Male, n (%)	48 (55.8)	71 (54.6)
Time since MF diagnosis, median (range), years	1.9 (0-20)	1.0 (0-24)
IPSS, n (%)		
Int-1	11 (12.8)	31 (23.8)
Int-2	27 (31.4)	40 (30.8)
High	48 (55.8)	59 (45.4)
Palpation spleen length, median (range), cm	12.0 (5-28)	10.0 (5-31)
>5 cm, n (%)	80 (93.0)	122 (93.8)
Hb, median (range), g/dL	9.8 (6-19)	10.5 (6-17)
RBC transfusion status, n (%)[b]		
TI	50 (58.1)	101 (77.7)
TD	31 (36.0)	21 (16.2)
TR	5 (5.8)	8 (6.2)
PLT count, median (range), ×10⁹/L	132.0 (52-199)	362.5 (203-2865)
Baseline ruxolitinib dose, median (range), mg/day	30.0 (10-30)	40.0 (20-40)

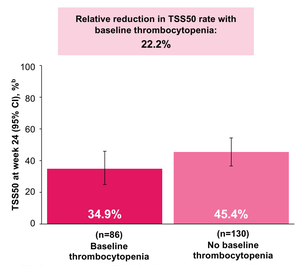
Hb, hemoglobin; int, intermediate; IPSS, International Prognostic Scoring System; MF, myelofibrosis; PLT, platelet; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independent; TR, transfusion requiring.
[a] *Because the proportion of patients who did not have platelet count decrease on treatment was low, baseline characteristics are only stratified by the presence or absence of baseline thrombocytopenia.* [b] *TI: no RBC transfusions and no Hb <8 g/dL in the 12 weeks before randomization. TD: ≥4 RBC units transfused or Hb <8 g/dL in the 8 weeks before randomization. TR: not meeting criteria for TI or TD.*

Figure 4: **Thrombocytopenia Subgroups Spleen Response[a]**



SVR35, spleen volume reduction ≥35%.
[a] *As only 4 patients with baseline thrombocytopenia did not have further platelet count decrease on treatment, relative reduction in SVR35 based on platelet count decrease on treatment could not be calculated in the baseline thrombocytopenia subgroup.*

Figure 5: **Thrombocytopenia Subgroups Symptom Response[a]**



TSS, Total Symptom Score; TSS50, Total Symptom Score reduction ≥50%.
[a] *As only 4 patients with baseline thrombocytopenia did not have further platelet count decrease on treatment. TSS50 based on platelet count decrease on treatment could not be calculated in the baseline thrombocytopenia subgroup.* [b] *TSS50 evaluable in patients with nonmissing, nonzero baseline TSS values.*

Conclusion

- Patients with n/w anemia demonstrated numerically lower SVR35 and TSS50 rates compared with those without n/w anemia, in both the baseline anemic and baseline nonanemic cohorts
- Patients with baseline thrombocytopenia also demonstrated numerically lower SVR35 and TSS50 rates compared with those without baseline thrombocytopenia
- Reduced spleen and symptom response rates observed in patients with anemia or thrombocytopenia may be attributable to dose-limiting toxicities, necessitating ruxolitinib dose reductions
- These findings have implications for real-world practice, as managing ruxolitinib dose to balance spleen and symptom benefits vs worsening cytopenias is challenging

Table 5: **Thrombocytopenia Subgroups Ruxolitinib Dosing Change**

	Baseline thrombocytopenia (n=86)		No baseline thrombocytopenia (n=130)	
	Platelet count decrease on treatment (n=82)	No platelet count decrease on treatment (n=4)	Platelet count decrease on treatment (n=85)	No platelet count decrease on treatment (n=45)
Ruxolitinib dose at index, mean (SD), mg	23.7 (8.82)	27.5 (5)	39.6 (2.43)	40 (0)
Average ruxolitinib dose over the first 12 weeks, mean (SD), mg	16.6 (7.51)	30 (0)	33.1 (9.31)	39.1 (6.76)
Change in dose between index and 12 weeks, mean (SD), mg	**−7.2** (7.75)	**0**	**−6.5** (9.8)	**−0.9** (6.76)

Patients With Baseline Anemia and Baseline Thrombocytopenia (see QR code)

- In the baseline anemic cohort (n=94), 47 patients (50.0%) also had baseline thrombocytopenia, and 72 (76.6%) had platelet count decrease within 12 weeks of starting treatment with ruxolitinib; outcomes are stratified by baseline cytopenias
- Patients with both baseline anemia and baseline thrombocytopenia had numerically lower SVR35 but numerically higher TSS50 rates compared with baseline anemic patients without baseline thrombocytopenia
- Among patients with baseline anemia, those who had baseline thrombocytopenia had numerically lower starting mean ruxolitinib doses and numerically greater dose reduction over the first 12 weeks compared with those without baseline thrombocytopenia; by week 24, 63.8% of patients with baseline thrombocytopenia and anemia were receiving doses of ≤20 mg daily vs 12.8% without baseline thrombocytopenia
  - 21.3% of patients with baseline thrombocytopenia and anemia were TI at week 24 vs 31.9% without baseline thrombocytopenia

Discussion

New or Worsening Anemia

- Despite similar baseline ruxolitinib doses, numerically greater dose reductions by week 12 were observed in patients with n/w anemia, potentially contributing to less favorable spleen and symptom outcomes
  - The generally small dose reductions across subgroups may reflect the short 12-week duration of assessment; longer-term dosing data at 24 weeks would provide further context to the sustainability of ruxolitinib dosing in the presence of n/w anemia
  - These results were also incorporated in a meta-analysis of n/w anemia to assess SVR35 and ruxolitinib dose modifications[9]

Platelet Count Decrease on Treatment

- Numerically greater ruxolitinib dose reductions by week 12 were observed in patients with platelet count decrease over this same time period; despite dose reductions, ruxolitinib doses remained >20 mg daily in most subgroups, potentially contributing to the lack of clear differences in outcomes
- While baseline thrombocytopenia differentiated outcomes, the definition of "platelet count decrease" applied in this analysis may not have been sufficient to determine the effect of on-treatment decreases in platelet count on outcomes, as few patients failed to meet this definition; additional research is needed to fully characterize the effects of n/w thrombocytopenia in patients with MF treated with ruxolitinib
  - The assessment duration of 12 weeks may be too short to observe clear differentiation in outcomes
- Results were consistent with a previous SIMPLIFY-1 subgroup analysis[5]: Lower ruxolitinib doses in patients with baseline platelet counts <200×10⁹/L were associated with numerically lower SVR35 rates

Baseline Anemic Patients With Thrombocytopenia

- Results in patients with both baseline anemia and thrombocytopenia were consistent with the overall population in showing numerically lower SVR35 rates compared with anemic patients without thrombocytopenia
- However, patients with both baseline anemia and thrombocytopenia had higher TSS50 rates than those with anemia alone
  - This may reflect a ceiling effect for symptom burden in this patient subgroup, as anemia is associated with increased likelihood of high symptom burden, including fatigue[10]

Abbreviations

BID, twice daily; Hb, hemoglobin; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; n/w, new or worsening; PLT, platelet; QD, once daily; RBC, red blood cell; SVR35, spleen volume reduction ≥35%; TD, transfusion dependent; TI, transfusion independent; TR, transfusion requiring; TSS, Total Symptom Score; TSS50, Total Symptom Score reduction ≥50%.

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