Clinical Effectiveness and Safety of Momelotinib Compared With Continued Ruxolitinib or Best Available Therapy in Patients With Myelofibrosis Who Required Red Blood Cell Transfusions: Subgroup Analysis of the Phase 3 SIMPLIFY-2 Study

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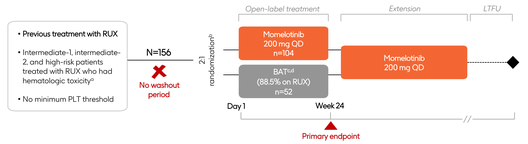
Introduction

- Anemia remains a significant challenge in the management of myelofibrosis (MF), with approximately one-third of patients having anemia at diagnosis and nearly all patients becoming anemic over time[1,2]
- Janus kinase (JAK) inhibitors are the backbone of the MF treatment landscape due to their efficacy in managing symptoms and reducing splenomegaly; however, JAK inhibitors such as ruxolitinib (RUX) and fedratinib do not alleviate, and may even exacerbate, anemia[3-6]
  - Dose reductions often used to manage RUX-related anemia may limit clinical benefit[7]
- Treatments for anemia include erythropoiesis-stimulating agents (ESAs), often in combination with RUX or fedratinib, and androgens such as danazol[1,7]
  - However, these adjunct treatments have demonstrated limited efficacy, durability, and tolerability
- Red blood cell (RBC) transfusions are the mainstay of anemia management in MF, but transfusion dependency is associated with diminished quality of life and is a negative prognostic factor for survival[7]
- Momelotinib, a JAK1/JAK2/activin A receptor type 1 inhibitor recently approved by the US Food and Drug Administration for the treatment of patients with MF and anemia,[4] has demonstrated clinically meaningful and durable improvements in anemia, splenomegaly, and symptoms in patients with MF across 3 phase 3 trials[8-10]
- In order to evaluate outcomes in patients who switched to momelotinib vs those who continued best available therapy (BAT)/RUX, we present a descriptive subgroup analysis of patients enrolled in SIMPLIFY-2 (NCT02101268) who were considered transfusion dependent (TD) or transfusion requiring (TR) at baseline[9]

Methods

- SIMPLIFY-2 was an international, multicenter, open-label, phase 3 clinical trial investigating the efficacy and safety of momelotinib vs BAT/RUX in patients with MF who had hematologic toxicities while receiving RUX (**Figure 1**)
- A total of 156 patients were randomized 2:1 to receive open-label momelotinib or BAT, which was RUX in 88.5% of patients; treatment washout from prior RUX was not permitted before study enrollment
- The primary endpoint was spleen volume reduction ≥35% (SVR35)
  - Key secondary endpoints included Total Symptom Score (TSS) response rate (≥50% reduction [TSS50]) and transfusion independence response (no RBC transfusions for ≥12 weeks immediately before the end of week 24, with all hemoglobin [Hb] levels ≥8 g/dL)
- This post hoc, descriptive analysis evaluated patients treated with either momelotinib or BAT/RUX who were considered non–transfusion independent (TI), defined as either TD or TR, at baseline
  - TI: absence of RBC transfusions and no Hb level of <8 g/dL in the previous 12 weeks
  - TD: ≥4 units of RBC transfusions or Hb level of <8 g/dL in the previous 8 weeks
  - TR: receipt of transfusions but no satisfaction of TD criteria

Figure 1. **SIMPLIFY-2 Study Design**



Primary endpoint
- SVR35 from baseline to week 24 (superiority)

Secondary endpoints (tested sequentially)
- MPN-SAF TSS response rate from baseline to week 24
- RBC transfusion rate
- RBC transfusion independence rate at week 24 (terminal 12-week criteria)[e]
- RBC transfusion dependence rate at week 24

[a] Criteria for hematologic toxicity were requirement of RBC transfusion while on RUX treatment or dose adjustment of RUX to <20 mg twice daily at start of or during RUX treatment and ≥1 of the following while on RUX treatment: grade ≥3 thrombocytopenia, anemia, or hematoma (bleed). [b] Treatment assignment was stratified by transfusion dependence (yes or no; defined as ≥4 units of RBCs or Hb level of <8 g/dL in the 8 weeks before random assignment, excluding patients associated with clinically overt bleeding) and baseline TSS (<18 or ≥18). [c] Most patients in the BAT arm were anticipated to receive non-RUX agents (eg, hydroxyurea, corticosteroids) or subtherapeutic doses of RUX. However, many patients were maintained on RUX, including some at therapeutic doses, despite toxicities. Thus, although the intent of the study was to show the superiority of momelotinib over therapies other than RUX, the majority of patients in the BAT arm remained on RUX. [d] In the BAT arm, 88.5% received RUX, 23% received hydroxyurea, and 12% received corticosteroids; 27% of patients were treated with RUX plus additional therapies, most commonly hydroxyurea and corticosteroids. [e] No transfusions or Hb levels <8 g/dL in the last 12 weeks before week 24.

Results

- In SIMPLIFY-2, 72 of 104 patients (69%) in the momelotinib arm and 33 of 52 patients (63%) in the BAT/RUX arm were non-TI at baseline, and baseline characteristics were balanced between both patient groups (**Table 1**)
  - Mean duration of prior treatment with RUX was 64.6 and 59.5 weeks in non-TI patients in the momelotinib and BAT/RUX arms, respectively
- All patients randomized to the momelotinib arm received a starting dose of 200 mg daily, and in the BAT arm, 29 of 33 patients (88%) were treated with RUX, alone or in combination, with 17 of those 29 patients (59%) receiving a baseline dose of ≤10 mg twice daily

Table 1. **Baseline Characteristics in the Baseline Non-TI Subgroup**

	Momelotinib group (n=72)	BAT/RUX group (n=33)
Age, median, years	69.0	70.0
Sex, n (%)		
Male	55 (76)	16 (48)
Female	17 (24)	17 (52)
DIPSS risk category, n (%)		
Intermediate-1	6 (8.3)	8 (24.2)
Intermediate-2	48 (66.7)	17 (51.5)
High	18 (25.0)	8 (24.2)
Total Symptom Score, mean (SD)	17.5 (11.7)	21.0 (16.3)
ECOG performance status		
0	23 (31.9)	11 (33.3)
1	44 (61.1)	16 (48.5)
2	5 (6.9)	6 (18.2)
Duration of prior RUX treatment, mean (SD), weeks	64.6 (61.8)	59.5 (56.6)
***JAK2* V617F mutation,[a] n (%)**		
Positive	47 (65.3)	23 (69.7)
Negative	23 (31.9)	7 (21.2)
Hemoglobin, mean (SD), g/dL	8.6 (1.3)	8.7 (1.0)
Transfusion dependent, n (%)		
Yes	58 (80.6)	27 (81.8)
No	14 (19.4)	6 (18.2)
Platelet count, mean (SD), ×10⁹/L	190.8 (159.0)	119.4 (93.0)
Absolute neutrophil count, mean (SD), ×10³ cells /μL	10.3 (15.0)	6.0 (7.3)

[a] In the momelotinib arm, 70 of 72 patients were previously assessed for the JAK2 V617F mutation and in the BAT/RUX arm, 30 of 33 patients were previously assessed.

- Anemia supportive therapies, administered alone or in combination with RUX, in the BAT/RUX arm are listed in **Table 2**
  - The most common were ESAs, which were administered to 5 patients; 4 of these patients also received RUX
    - At baseline, 3 of these patients were TI (Hb levels, 9.8, 10.3, and 9.6 g/dL), 1 was TR (Hb level, 8.5 g/dL), and 1 was TD (Hb level, 7.6 g/dL)

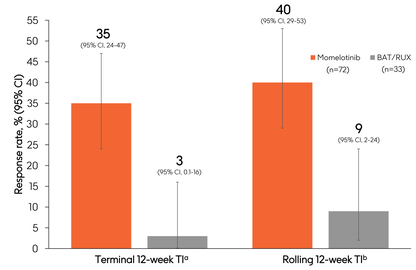
Table 2. **Summary of RUX and/or Anemia Supportive Agent Administration in the BAT/RUX Arm of the Baseline Non-TI Subgroup**

	BAT/RUX non-TI (n=33)[a]
RUX only	15 (45%)
Danazol only[b]	1 (3%)
RUX + danazol	1 (3%)
Prednisolone only[b]	1 (3%)
RUX + prednisolone	1 (3%)
ESA only	1 (3%)
RUX + ESA	4 (12%)
Lenalidomide only[c]	0
RUX + lenalidomide[c]	0

[a] Of the 29 patients who received RUX in the BAT/RUX arm who were non-TI at baseline, the remaining 8 patients not presented in this table received RUX plus another therapy not directed at anemia supportive care. [b] One patient received both danazol and prednisolone. [c] No patients in this subgroup received lenalidomide but it is included in the table for completeness.

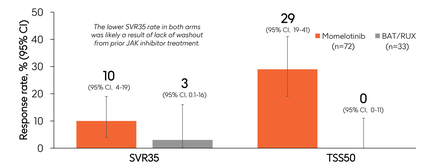
- In baseline non-TI patients, without prior JAK inhibitor washout, treatment with momelotinib was associated with higher transfusion independence, SVR, and TSS response rates compared with BAT/RUX (**Figures 2 and 3**)
  - Many responders with momelotinib achieved 2 or all 3 endpoints (16 of 36 responders [44%]); there were no dual or triple responses in the BAT/RUX arm
  - 35% of patients achieved a transfusion independence response with momelotinib at week 24 per the predefined terminal 12-week definition; 40% achieved a response by week 24 per the rolling 12-week definition (no transfusions or hemoglobin levels <8 g/dL during any 12-week period through week 24) (**Figure 2**)
- Of the 5 patients in the BAT/RUX arm who received ESAs with or without RUX, 3 patients achieved a single response (1 for each endpoint: TSS50, SVR35, and transfusion independence)
  - The patient who achieved TSS50 at week 24 did not receive RUX
  - Both the SVR35 and TI responders at week 24 received RUX + ESA
- No patients who received other anemia supportive therapies achieved transfusion independence (terminal 12-week definition) at week 24

Figure 2. **Week 24 TI Responses in the Baseline Non-TI Subgroup**



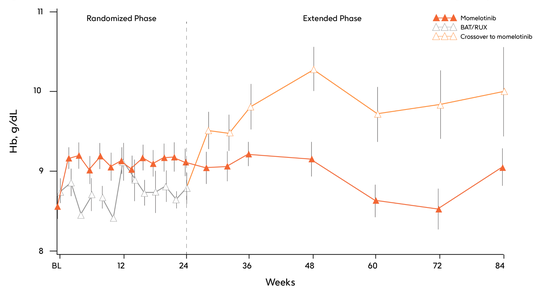
TI defined as no transfusions or Hb levels <8 g/dL [a]in the last 12 weeks before week 24 or [b]during any 12-week period through week 24.

Figure 3. **Week 24 Spleen and Symptom Responses in the Baseline Non-TI Subgroup**



- Similar to the overall intent-to-treat (ITT) population,[9] baseline non-TI patients treated with momelotinib had higher mean Hb levels over time than those treated with BAT/RUX, including improvements in the BAT/RUX arm after crossover (**Figure 4**)
  - However, the median rate of RBC transfusion through week 24 was lower in the momelotinib arm than in the BAT/RUX arm, at 1.2 vs 1.8 units/month

Figure 4. **Mean Hb Levels Over Time in the Baseline Non-TI Subgroup**



Conclusion

- Among patients with MF who required RBC transfusions at baseline, treatment with momelotinib demonstrated an ability to deliver higher SVR, transfusion independence, and TSS response rates compared with BAT/RUX
  - With momelotinib, 25 patients in this baseline non-TI subgroup (35%) became TI (terminal 12-week criteria) at week 24 vs only 1 patient (3%) with BAT/RUX
  - Durability of transfusion independence with momelotinib is suggested by the similar TI response rates per terminal and rolling 12-week criteria (35% and 40%, respectively)
- Mean Hb levels in this subgroup improved rapidly with momelotinib and remained higher than in those treated with BAT/RUX through week 24, despite the momelotinib arm having a lower median transfusion rate than the BAT/RUX arm during that period
- Safety results in this subgroup were consistent with those previously reported for the ITT population
- **Collectively, these data suggest that in patients who need RBC transfusions, outcomes—notably anemia benefits, including week 24 transfusion independence rate, median transfusion rate through week 24, and mean Hb levels over time—are improved by switching to momelotinib rather than continuing RUX and using ESAs or other supportive therapies to manage anemia**

- Safety outcomes were consistent with those previously reported for the ITT population[9] (**Tables 3 and 4**)

Table 3. **Overall Summary of TEAEs in the Baseline Non-TI Subgroup**

n (%)	Momelotinib (n=72)	BAT/RUX (n=33)
Any-grade TEAE	71 (98.6)	30 (90.9)
Grade ≥3 TEAE	45 (62.5)	14 (42.4)
Treatment-related AE	52 (72.2)	11 (33.3)
Grade ≥3 treatment-related AE	22 (30.6)	6 (18.2)
Serious TEAE	27 (37.5)	8 (24.2)
Treatment-related serious AE	9 (12.5)	1 (3.0)
TEAE leading to discontinuation[a]	17 (23.6)	1 (3.0)
TEAE leading to dose reduction/interruption	9 (12.5)	6 (18.2)
TEAE leading to death	5 (6.9)	3 (9.1)

[a] Discontinuation of BAT was inconsistently reported because changes in therapy or intentional absence of therapy were permissible options for this treatment group.

Table 4. **TEAEs Observed in ≥10% of Patients in the Momelotinib Arm During the Randomized Treatment Phase in the Baseline Non-TI Subgroup**

n (%)	Momelotinib (n=72)	BAT/RUX (n=33)
Diarrhea	23 (31.9)	5 (15.2)
Asthenia	15 (20.8)	7 (21.2)
Pyrexia	14 (19.4)	4 (12.1)
Anemia	13 (18.1)	5 (15.2)
Nausea	12 (16.7)	1 (3.0)
Abdominal pain	11 (15.3)	3 (9.1)
Cough	11 (15.3)	3 (9.1)
Dizziness	11 (15.3)	2 (6.1)
Thrombocytopenia	11 (15.3)	4 (12.1)
Dyspnea	10 (13.9)	4 (12.1)
Headache	10 (13.9)	1 (3.0)
Peripheral edema	10 (13.9)	4 (12.1)
Pruritus	10 (13.9)	2 (6.1)
Fatigue	9 (12.5)	6 (18.2)
Urinary tract infection	9 (12.5)	4 (12.1)
Arthralgia	8 (11.1)	2 (6.1)
Dyspepsia	8 (11.1)	0
Peripheral sensory neuropathy	8 (11.1)	0
Weight decreased	8 (11.1)	2 (6.1)
Neutropenia	7 (9.7)	0

Abbreviations

AE, adverse event; BAT, best available therapy; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ITT, intent to treat; JAK, Janus kinase; LTFU, long-term follow-up; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; PLT, platelet; QD, once daily; RBC, red blood cell; RUX, ruxolitinib; SVR, spleen volume reduction; SVR35, spleen volume reduction ≥35%; TD, transfusion dependent; TEAE, treatment-emergent adverse event; TI, transfusion independent; TI-R, transfusion independence response; TR, transfusion requiring; TSS, Total Symptom Score; TSS50, Total Symptom Score reduction ≥50%.

References

1. Naymagon L, Mascarenhas J. *Hemasphere.* 2017;1:e1.
2. Tefferi A, et al. *Mayo Clin Proc.* 2012;87:25-33.
3. Vonja (pacritinib). Prescribing information. CTI BioPharma Corp; 2022.
4. Ojjaara (momelotinib) Prescribing information. GSK; 2023.
5. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; 2021.
6. Inrebic (fedratinib). Prescribing information. Bristol Myers Squibb; 2022.
7. Chifotides HT, et al. *J Hematol Oncol.* 2022;15:1-17.
8. Mesa RA, et al. *J Clin Oncol.* 2017;35:3844-3850.
9. Harrison CN, et al. *Lancet Haematol.* 2018;5:e73-e81.
10. Verstovsek S, et al. *Lancet.* 2023;401:269-280.

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