Longitudinal Assessment of Transfusion Intensity in Patients With JAK Inhibitor–Naive or –Experienced Myelofibrosis Treated With Momelotinib

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Abstract

Binomial response/nonresponse endpoints may not fully characterize anemia-related benefits of myelofibrosis treatments. In these novel analyses of transfusion burden over time in patients with myelofibrosis from phase 2 and 3 trials, momelotinib was associated with a reduction in mean RBC transfusion burden in both JAK inhibitor–naive and –experienced populations. Across all trials, ≥77% of patients treated with momelotinib either maintained or experienced improved transfusion intensity compared with baseline, highlighting that momelotinib provides consistent anemia benefit for a majority of patients with myelofibrosis.

Purpose: Anemia is a cardinal feature of myelofibrosis often managed with red blood cell (RBC) transfusions, which may contribute to negative prognostic, quality-of-life, and healthcare-related economic impacts. The Janus kinase (JAK) 1/JAK2/activin A receptor type 1 inhibitor momelotinib was approved for the treatment of patients with myelofibrosis and anemia based on clinical trial evidence of anemia, spleen, and symptom benefits illustrated using binomial response/nonresponse endpoints. In the present post hoc, descriptive analyses, the impact of momelotinib on RBC transfusion burden over time was further characterized across JAK inhibitor–naive and –experienced patients. **Methods:** All RBC units transfused were collected during the baseline and 24-week treatment periods, initially in a single-arm phase 2 study as proof-of-concept analysis, and then versus comparators (ruxolitinib, best available therapy [BAT], and danazol) in the phase 3 SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM studies, respectively. **Results:** In the phase 2 study, mean transfusion requirement changed by −1.5 units/28 days, with 85% of patients (35/41) achieving numeric transfusion reduction. Across SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM, mean transfusion requirements decreased

Abbreviations: ACVR1, activin A receptor type 1; BAT, best available therapy; Hb, hemoglobin; ITT, intent to treat; JAK, Janus kinase; MF, myelofibrosis; NA, not available; PET-MF, post–essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis; QOL, quality of life, RBC, red blood cell; SD, standard deviation; TD, transfusion dependent; TI, transfusion independent; TI-R, transfusion independence response; TSS, Total Symptom Score.

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with momelotinib (−0.1, −0.36, and −0.86 units/28 days), while mean requirements with ruxolitinib, BAT, and danazol changed by +0.39, 0, and –0.28 units/28 days, respectively. Overall, 87% (185/213), 77% (79/103), and 85% (110/130) of patients had improved or stable transfusion intensities with momelotinib versus 54% (117/216), 62% (32/52), and 63% (41/65) with ruxolitinib, BAT, and danazol. **Conclusion:** These novel time-dependent transfusion burden analyses demonstrate that momelotinib is associated with anemia-related benefits in most patients and greater transfusion burden reduction versus comparators. **Trial registration:** ClinicalTrials.gov identifiers: NCT02515630, NCT01969838, NCT02101268, NCT04173494.

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Introduction

Anemia is a cardinal feature of myelofibrosis (MF), along with constitutional symptoms and splenomegaly.[1,2] An estimated 40% of patients are anemic at the time of diagnosis, including approximately 25% who are transfusion dependent (TD), and nearly all develop anemia during the course of the disease.[2] Anemia in MF represents a high medical need, as hemoglobin (Hb) levels of <100 g/L are a recognized independent negative prognostic factor for survival.[3] A 2023 study also suggested that cytopenias—primarily anemia—may be associated with poor symptom and spleen response in patients with MF treated with the Janus kinase (JAK) inhibitor ruxolitinib.[4] In addition, anemia has been associated with decreased quality of life (QOL), while response to anemia-targeted therapies has been correlated with improved QOL.[2,5]

Although red blood cell (RBC) transfusions are a commonly used approach for treating MF-related anemia, several studies have highlighted the detrimental impacts associated with transfusion requirement. Transfusion dependency has been linked to lower health-related QOL and worse survival, with TD patients having a risk of death >7 times greater than patients who are transfusion independent (TI).[6,7] In particular, modeling suggests a negative impact of RBC transfusion requirement during the initial stages of ruxolitinib treatment on overall survival, perhaps due in part to suboptimal dosing.[8] TD patients also have higher healthcare resource utilization than non-TD patients, including significantly higher rates of hospitalizations, emergency department visits, and outpatient visits, and have higher medical and pharmacy costs.[9] Taken together, these studies underscore the considerable burdens of anemia and transfusion dependence in MF, highlighting the importance of therapeutic options that are not myelosuppressive, may be taken at full dose, and can prevent or delay progression to transfusion dependency.

Momelotinib is a small-molecule JAK1/JAK2/activin A receptor type 1 (ACVR1) inhibitor initially approved in 2023 for the treatment of patients with MF and anemia.[10-12] Previously, a single-arm, phase 2, translational biology study showed that momelotinib reversed or reduced transfusion dependency in patients who were TD at baseline, which may be attributable to ACVR1-mediated regulation of hepcidin and iron homeostasis.[13] Momelotinib was further evaluated in 3 phase 3 trials, SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM, demonstrating anemia, spleen, and symptom benefits in JAK inhibitor–naive and –experienced patients with MF.[14-16] Across the phase 3 momelotinib trials, anemia benefit was assessed using a strict, prespecified endpoint definition of TI response: no RBC transfusions for ≥12 weeks immediately preceding the end of week 24, with all Hb levels of ≥80 g/L.[14-16] TI rates were consistently higher with momelotinib versus the comparator arms: SIMPLIFY-1 (momelotinib, 67%; ruxolitinib, 49%), SIMPLIFY-2 (momelotinib, 43%; best available therapy [BAT], 21%), and MOMENTUM (momelotinib, 30%; danazol, 20%).[14-16]

While the TI response rates from these phase 3 trials provided robust evidence of the anemia-related benefits of momelotinib in some patients, this binominal response/nonresponse endpoint may not fully characterize treatment-related changes in transfusion burden for patients with MF. For example, some patients might experience reductions in transfusions that do not meet the threshold for transfusion independence but could nevertheless be meaningful. Thus, analyses that quantify on-treatment changes in transfusion burden or capture cumulative transfusion burden may provide an additional perspective on the anemia-related benefits of a given treatment in patients with MF. The present analyses were undertaken to better characterize the relative anemia-related benefits associated with momelotinib by examining longitudinal changes in transfusion intensity using data from phase 2 and 3 trials.

Materials and Methods

Data Sources

Time-dependent transfusion burden was initially assessed in a phase 2 trial (NCT02515630) as proof-of-concept for this type of analysis.[13] Analyses were subsequently carried out using data from the phase 3 SIMPLIFY-1 (NCT01969838), SIMPLIFY-2 (NCT02101268), and MOMENTUM (NCT04173494) trials.[14-16]

The phase 2 trial was an open-label, translational biology study of momelotinib (200 mg once daily) in patients who were TD (≥4 RBC units in the 8 weeks prior to first dose) with intermediate- or high-risk MF.[13] Patients were treated for up to 24 weeks, with a primary endpoint of the rate of TI response by week 24 (defined as no RBC transfusions for any period ≥ 12 weeks on study).

SIMPLIFY-1 was a double-blind, double-dummy trial of patients with JAK inhibitor–naive MF randomized (1:1) to momelotinib or ruxolitinib.[15] SIMPLIFY-2 was an open-label trial of patients with JAK inhibitor–experienced MF randomized (2:1) to momelotinib

or BAT (88.5% on ruxolitinib).[16] In the double-blind, placebo-controlled MOMENTUM study, patients with symptomatic (Myelofibrosis Symptom Assessment Form Total Symptom Score ≥10), anemic (Hb <100 g/L), JAK inhibitor–experienced MF were randomized (2:1) to momelotinib or danazol.[14] In each of the phase 3 trials, patients received 24 weeks of treatment during the randomized treatment phase; patients who continued on the studies beyond 24 weeks received open-label momelotinib.[14-16] The primary endpoints were splenic response rate for SIMPLIFY-1 and SIMPLIFY-2, and Total Symptom Score response rate for MOMENTUM.[14-16] TI response, defined as no RBC transfusions for ≥12 weeks immediately preceding the end of week 24, with all Hb levels of ≥80 g/L, was a prespecified secondary endpoint in all 3 phase 3 trials.[14-16]

Outcomes

All RBC units transfused and Hb levels associated with transfusions were collected during the 24-week study period and during the baseline period (56 days prior to enrollment for the phase 2 study, 84 days prior to enrollment for SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM) before the initiation of momelotinib or comparator, if applicable. Time-dependent transfusion burden (number of RBC units administered per 28 days) was tracked for each patient, with corresponding mean baseline- and treatment-period (approximately 168 days for most patients) intensities per patient. Descriptive summary measures for the total study patient population, including mean change in RBC transfusion intensity from baseline, were also calculated and visualized via cumulative distribution function curves of baseline- and treatment-period intensities, illustrating the percentage of patients (y-axis) with less than or equal to each number of RBC transfusion units per 28 days on the x-axis.

To further visualize changes to RBC transfusion burden during treatment, patients were arrayed in ordinal bins jointly based on their baseline- and treatment-period intensities of RBC units per 28 days: exactly zero units, >0 to 1 unit, >1 to 2 units, >2 to 3 units, >3 to 4 units, and >4 units. For the phase 3 analyses, patients who received <14 days of study treatment were excluded.

Results

Phase 2 Study

Baseline patient characteristics are summarized in Table 1. At baseline, all patients with known transfusion status (40/41) were TD, and 71% had Hb levels of ≥80 g/L, with a mean Hb of 83 g/L; 88% (36/41) were JAK inhibitor naive (Table 1). The mean RBC transfusion requirement was 3.2 units per 28 days during the baseline period before momelotinib treatment (range, 1.5-6.0 units per 28 days), decreasing to 1.7 units per 28 days during the treatment period (range, 0-6 units per 28 days), for a mean change of −1.5 (SD, standard deviation [SD], 1.3) units per 28 days (Table 2, Supplemental Table 1). Improvement (ie, reduction) in RBC transfusion burden for the entire treatment period was also evident in the leftward shift of the cumulative distribution function curve (Figure 2A) versus the baseline-period curve, reflecting an overall lower distribution of transfusion intensities on treatment. The median transfusion intensity at baseline was 3.0 units/28 days, improving to 1.6 units/28 days during the treatment period (Supplemental Table 1; also shown with a dotted line at 50% in Figure 2A).

A numeric reduction in treatment- versus baseline-period RBC transfusion intensities was observed in 35 of 41 patients (85%) treated with momelotinib (Table 2, Figure 1; as noted by increase in lighter shading during the treatment period). No patients were transfusion free (ie, had transfusion intensities of 0) during the baseline period; achieving transfusion-free status for the entire treatment period correlated well with the prespecified primary endpoint of TI, with 78% (7/9) of transfusion-free patients also counted as TI responders. When patients with similar baseline-period transfusion intensities were grouped using ordinal bins, the majority (63% [26/41]) had improved RBC transfusion intensities during the treatment period (depicted with the lightest shading in Figure 2B), including the 9 patients who became transfusion free for the entire treatment period; transfusion intensities remained stable during the treatment period from baseline in another 27% (11/41; medium shading in Figure 2B).

SIMPLIFY-1

In SIMPLIFY-1 (JAK inhibitor–naive patients), most patients were TI at baseline; only 25% of patients (53/215) in the momelotinib arm and 24% (52/217) in the ruxolitinib arm were TD. At baseline, 87% and 90% in the momelotinib and ruxolitinib arms, respectively, had Hb levels of ≥80 g/L; respective mean Hb levels were 106 and 107 g/L (Table 1).

Mean transfusion intensity was low during the baseline period in both arms (0.5 [range, 0-6.7] units per 28 days for momelotinib versus 0.5 [range, 0-5.3] units per 28 days for ruxolitinib) (Supplemental Table 1). However, while mean transfusion intensity decreased further during the treatment period with momelotinib (0.4 [range, 0-7.8] units per 28 days), it nearly doubled with ruxolitinib (0.9 [range, 0-7.0] units per 28 days) (Supplemental Table 1). Overall, mean RBC transfusion burdens per 28 days changed by −0.10 units (SD, 0.7) in the momelotinib arm and +0.39 units (SD, 1.0) in the ruxolitinib arm during the treatment period from baseline (Table 2). RBC transfusion burden improvement for the entire treatment period with momelotinib is seen in the leftward shift of the cumulative distribution function when comparing the baseline- versus treatment-period curves (Figure 3A). By contrast, patients treated with ruxolitinib showed increased transfusion burden during the treatment period versus baseline, as evident in the rightward shift of the cumulative distribution function (Figure 3A).

During the baseline period, 70% (150/213) of evaluable patients in the momelotinib arm and 75% (163/216) of evaluable patients in the ruxolitinib arm were transfusion free (Table 1). Using ordinal bins, a higher proportion of these patients who were transfusion free during the baseline period in the momelotinib arm (95% [142/150]) versus the ruxolitinib arm (57% [93/163]) maintained this status for the entire treatment period (Figure 3B). Another 29% (18/63) versus 13% (7/53), respectively, with some transfusion burden during the baseline period, became transfusion free for the entire treatment period (Figure 3B). Overall, 19% (41/213) and 68% (144/213) of patients in the momelotinib arm had improved and stable RBC transfusion intensities, respectively, during the treat-

Table 1 Key Transfusion-Related Baseline Characteristics of Patients From the Phase 2 Study, SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM

	Phase 2 study	SIMPLIFY-1		SIMPLIFY-2		MOMENTUM	
	Momelotinib (n = 41)	Momelotinib (n = 215)	Ruxolitinib (n = 217)	Momelotinib (n = 104)	BAT (n = 52)	Momelotinib (n = 130)	Danazol (n = 65)
JAK inhibitor naive	36 (88)	215 (100)	217 (100)	0	0	0	0
TSS, mean (SD)	20.7 (14.7)	19.4 (13.2)	17.9 (11.5)	18.5 (13.0)	20.5 (16.0)	28.0 (13.8)	25.7 (12.8)
Hb level, mean (SD), g/L	83 (10)	106 (21)	107 (24)	94 (19)	95 (16)	81 (11)	79 (8)
Hb level ≥80 g/L, n (%)	29 (71)	187 (87)	195 (90)	77 (74)	46 (89)	67 (52)	33 (51)
Transfusion independent, n (%)	0	147 (68)	152 (70)	32 (31)	19 (37)	17 (13)	10 (15)
Transfusion dependent, n (%)[a]	40 (97.6)[b]	53 (25)	52 (24)	58 (56)	27 (52)	63 (48)	34 (52)
Transfusion intensity, units/28 days, n (%)							
0	0	150 (70)[c]	163 (75)[c]	37 (36)[d]	19 (37)	26 (20)	11 (17)
>0 to 3	22 (54)	57 (27)[c]	42 (19)[c]	47 (46)[d]	27 (52)	78 (60)	36 (55)
>3	19 (46)	6 (3)[c]	11 (5)[c]	19 (18)[d]	6 (12)	26 (20)	18 (28)

Abbreviations: BAT = best available therapy; Hb = hemoglobin; JAK = Janus kinase; SD = standard deviation; TSS = Total Symptom Score.

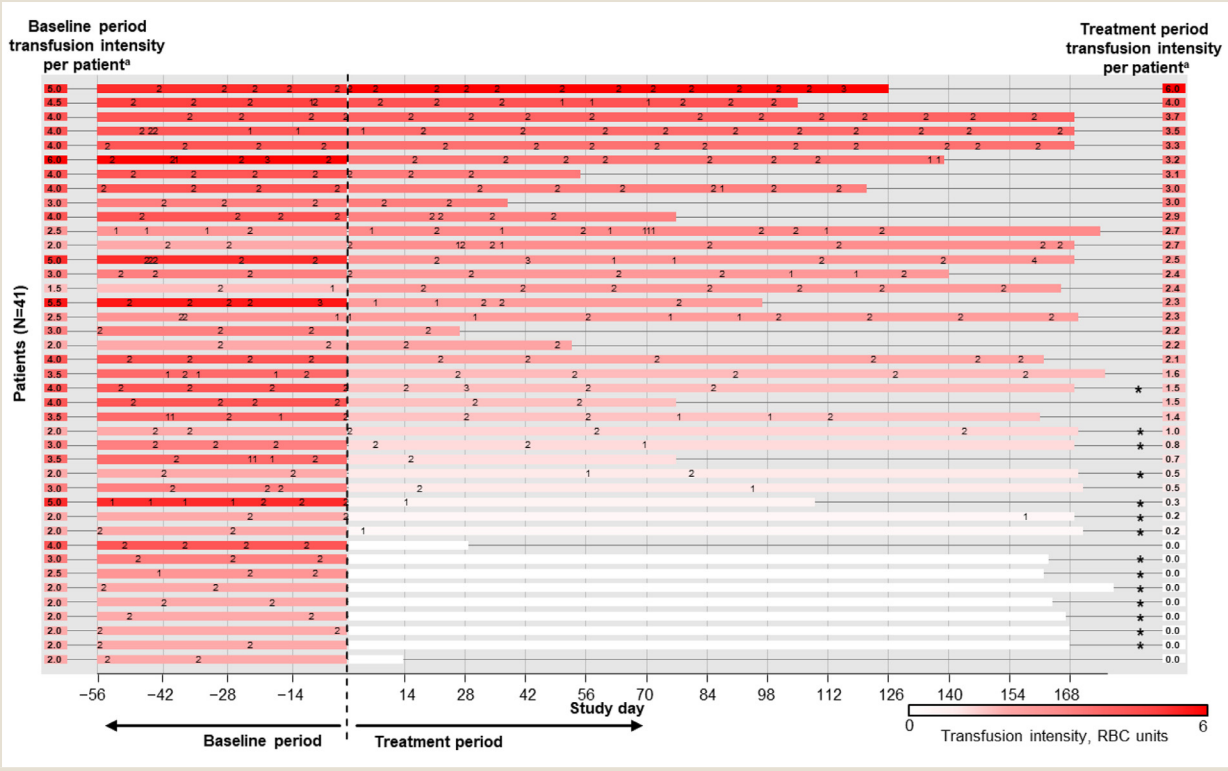
[a] Transfusion dependent was defined as ≥4 RBC units in the prior 8 weeks in the phase 2 study, ≥4 RBC units or Hb of <80 g/L in the prior 8 weeks in SIMPLIFY-1 and SIMPLIFY-2, and ≥4 RBC units in the prior 8 weeks, each in response to Hb of ≤95 g/L on the transfusion record, in MOMENTUM.

[b] One patient enrolled without a confirmed transfusion history and was categorized as a nonresponder at week 24.

[c] Two patients in the momelotinib arm and 1 patient in the ruxolitinib arm were not evaluable for transfusion intensity (evaluable populations, n = 213 and n = 216, respectively).

[d] One patient in the momelotinib arm was not evaluable for transfusion intensity (evaluable population, n = 103).

Figure 1 RBC transfusions per patient throughout the baseline and treatment periods in the phase 2 study. Patients are sorted from highest to lowest treatment-period RBC transfusion intensity. Numerals along each bar indicate the number of RBC units transfused on each day on which a transfusion occurred.
RBC = red blood cell; TI-R = transfusion independence response.
*Indicates patients who met the primary endpoint TI-R, defined as 0 RBC units transfused for any period ≥12 weeks on study.
[a]RBC transfusion unit intensity for the baseline period (56 days; left of dashed line) and treatment period (up to 168 days for most patients, indicated by length of bars; right of dashed line). Shading indicates intensity over the entire baseline or treatment period, from the minimum of 0 to the maximum of 6 RBC units transfused per 28 days.



ment versus baseline periods, compared with only 11% (23/216) and 44% (94/216) in the ruxolitinib arm; in contrast, more patients had worsened (ie, increased) RBC transfusion intensities during the treatment versus baseline periods in the ruxolitinib arm (46% [99/216]) compared with the momelotinib arm (13% [28/213]) (Table 2).

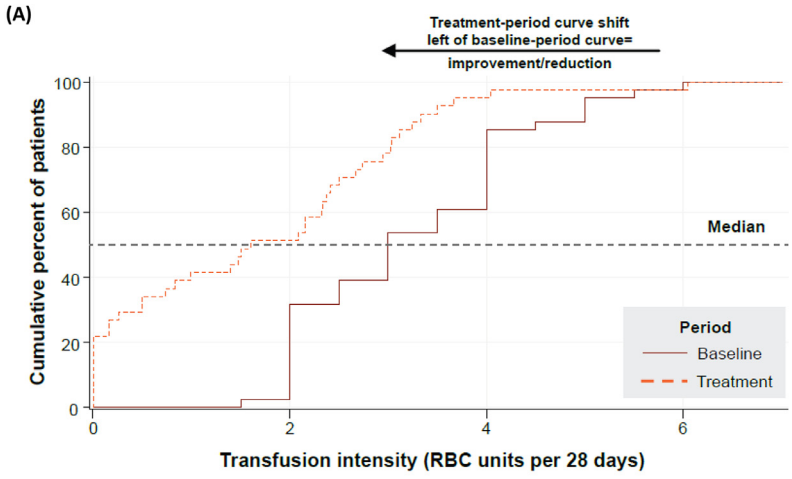
SIMPLIFY-2

In SIMPLIFY-2 (JAK inhibitor–experienced patients), 56% of evaluable patients (58/104) in the momelotinib arm and 52% of evaluable patients (27/52) in the BAT arm were TD at baseline; 74% and 89% of patients, respectively, had Hb levels of ≥80 g/L, and mean Hb levels were 94 and 95 g/L (Table 1).

Mean transfusion intensity decreased from 1.4 (range, 0-7.0) units per 28 days during the baseline period to 1.1 (range 0-6.0) units per 28 days during the treatment period with momelotinib, while there was no discernable effect on mean transfusion intensity from baseline (1.3 [range, 0-5.0] units per 28 days) during the treatment period with BAT (1.3 [range, 0-6.7] units per 28 days) (Supplemental Table 1). Overall, mean RBC transfusion burden per 28 days changed by −0.36 units (SD, 1.4) in the momelotinib arm and remained unchanged (0 units; SD, 1.3) in the BAT arm from the baseline to treatment periods (Table 2). As observed with SIMPLIFY-1, there was a decrease in RBC transfusion burden from baseline with momelotinib (leftward shift in cumulative distribution function curve), while the baseline- and treatment-period cumulative distribution functions for the BAT arm largely overlapped (Figure 4A).

During the baseline period, 36% [37/103] in the momelotinib arm and 37% [19/52] in the BAT arm were transfusion free (Table 1, Figure 4B). Using ordinal bins, a higher proportion of patients in the momelotinib arm (44% [45/103]) versus the BAT arm (27% [14/52]) were transfusion free for the entire treatment period, including a higher proportion of those who maintained this status from baseline (momelotinib, 76% [28/37]; BAT, 63% [12/19]) (Figure 4B). Among those with some transfusion burden at baseline, 26% (17/66) on momelotinib became transfusion free for the entire treatment period versus just 6% (2/33) in the BAT arm (Figure 4B). Overall, most patients in the momelotinib arm had improved (49% [50/103]) or stable (28% [29/103])

Figure 2 (A) Cumulative distribution function for RBC transfusion intensity and (B) shift table of change in RBC transfusion intensity in the phase 2 study. In panel A, mean transfusion intensity (RBC units per 28 days; x-axis) is plotted against the percentage of patients who had that mean transfusion intensity or less (y-axis); the percentage increases with increasing transfusion intensities until 100% of patients are accounted for. An overall leftward shift of the treatment-period curve versus baseline-period curve indicates decreased transfusion intensity overall with treatment. Median transfusion intensity (50th percentile in Supplemental Table 1) is indicated with the dotted grey line. In panel B, rows are patients with similar baseline-period transfusion intensities; columns show treatment-period transfusion intensities. Dark-shaded cells indicate baseline- to treatment-period worsening of transfusion burden, light-shaded cells indicate improvement in transfusion burden, and medium-shaded cells indicate stable transfusion burden. RBC, red blood cell.
[a]Percentage of baseline transfusion intensity category. [b]Rounding was applied to place patients in each ordinal bin/category; as a result, changes in intensity during treatment that did not result in a change in ordinal bin from baseline may not be apparent.



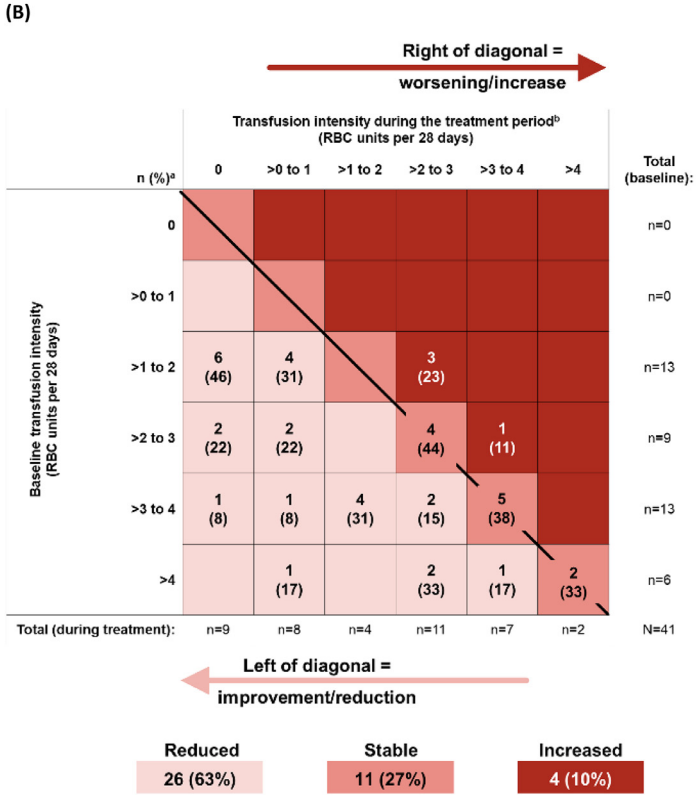


Figure 3 (A) Cumulative distribution function for RBC transfusion intensity and (B) shift table of change in RBC transfusion intensity in SIMPLIFY-1. In panel A, mean transfusion intensity (RBC units per 28 days; x-axis) is plotted against the percentage of patients who had that mean transfusion intensity or less (y-axis); the percentage increases with increasing transfusion intensities until 100% of patients are accounted for. An overall leftward shift of the treatment-period curve versus baseline-period curve for a given treatment indicates decreased transfusion intensity overall with that treatment. Median transfusion intensity (50th percentile in Supplemental Table 1) is indicated with the dotted grey line. In panel B, rows are patients with similar baseline-period transfusion intensities; columns show treatment-period transfusion intensities. Dark-shaded cells indicate baseline- to treatment-period worsening of transfusion burden, light-shaded cells indicate improvement in transfusion burden, and medium-shaded cells indicate stable transfusion burden.
RBC, red blood cell.
[a]Percentage of baseline transfusion intensity category. [b]Rounding was applied to place patients in each ordinal bin/category; as a result, changes in intensity during treatment that did not result in a change in ordinal bin from baseline may not be apparent. [c]Two patients in the momelotinib arm and 1 patient in the ruxolitinib arm were not evaluable for transfusion intensity (evaluable populations, n = 213 and n = 216, respectively).

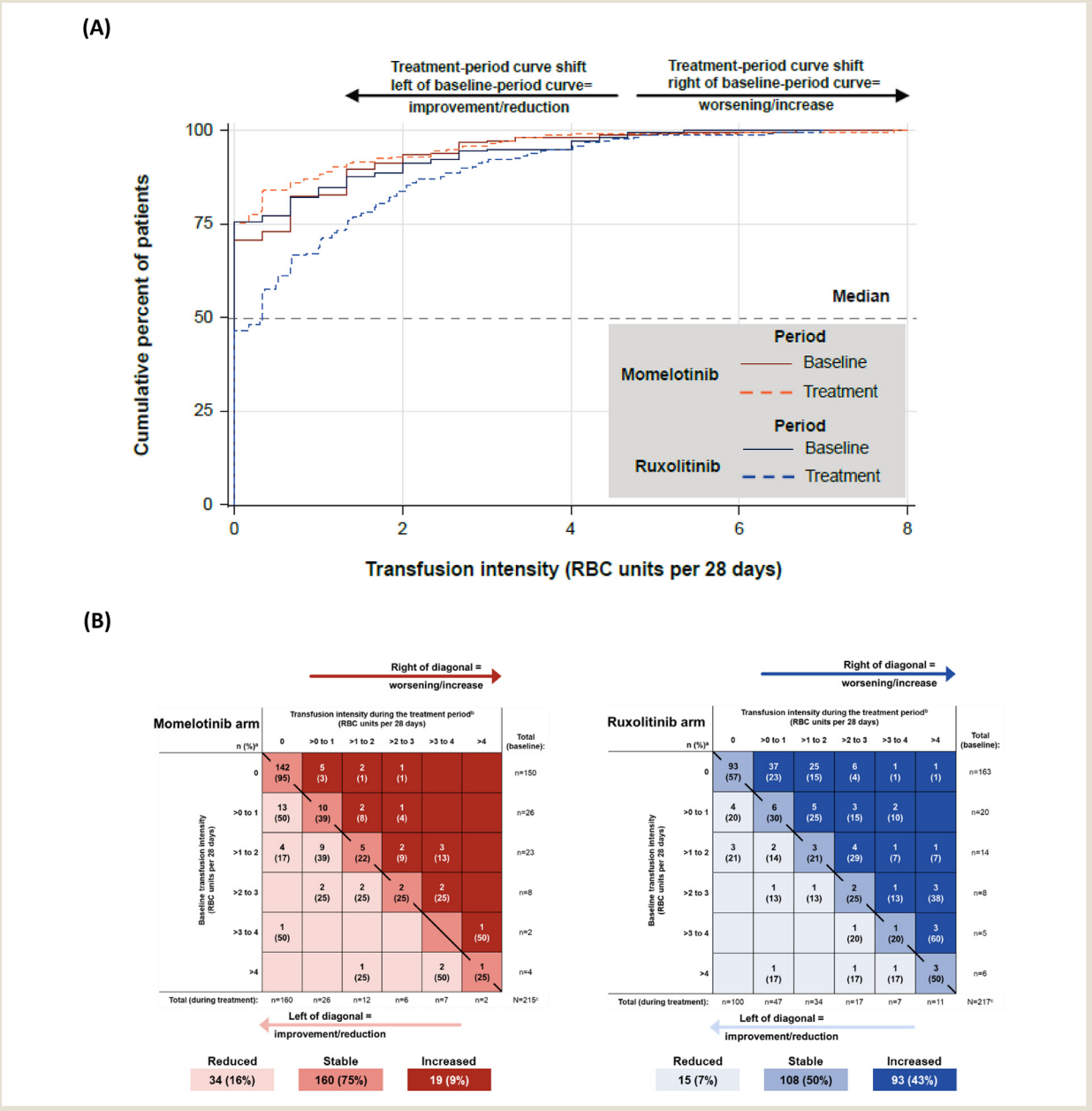


Figure 4 (A) Cumulative distribution function for RBC transfusion intensity and (B) shift table of change in RBC transfusion intensity in SIMPLIFY-2. In panel A, mean transfusion intensity (RBC units per 28 days; x-axis) is plotted against the percentage of patients who had that mean transfusion intensity or less (y-axis); the percentage increases with increasing transfusion intensities until 100% of patients are accounted for. An overall leftward shift of the treatment-period curve versus baseline-period curve for a given treatment indicates decreased transfusion intensity overall with that treatment. Median transfusion intensity (50th percentile in Supplemental Table 1) is indicated with the dotted grey line. In panel B, rows are patients with similar baseline-period transfusion intensities; columns show treatment-period transfusion intensities. Dark-shaded cells indicate baseline- to treatment-period worsening of transfusion burden, light-shaded cells indicate improvement in transfusion burden, and medium-shaded cells indicate stable transfusion burden.
BAT, best available therapy; RBC, red blood cell.
[a]Percentage of baseline transfusion intensity category. [b]Rounding was applied to place patients in each ordinal bin/category; as a result, changes in intensity during treatment that did not result in a change in ordinal bin from baseline may not be apparent. [c]One patient in the momelotinib arm was not transfusion intensity evaluable (evaluable population, n = 103).

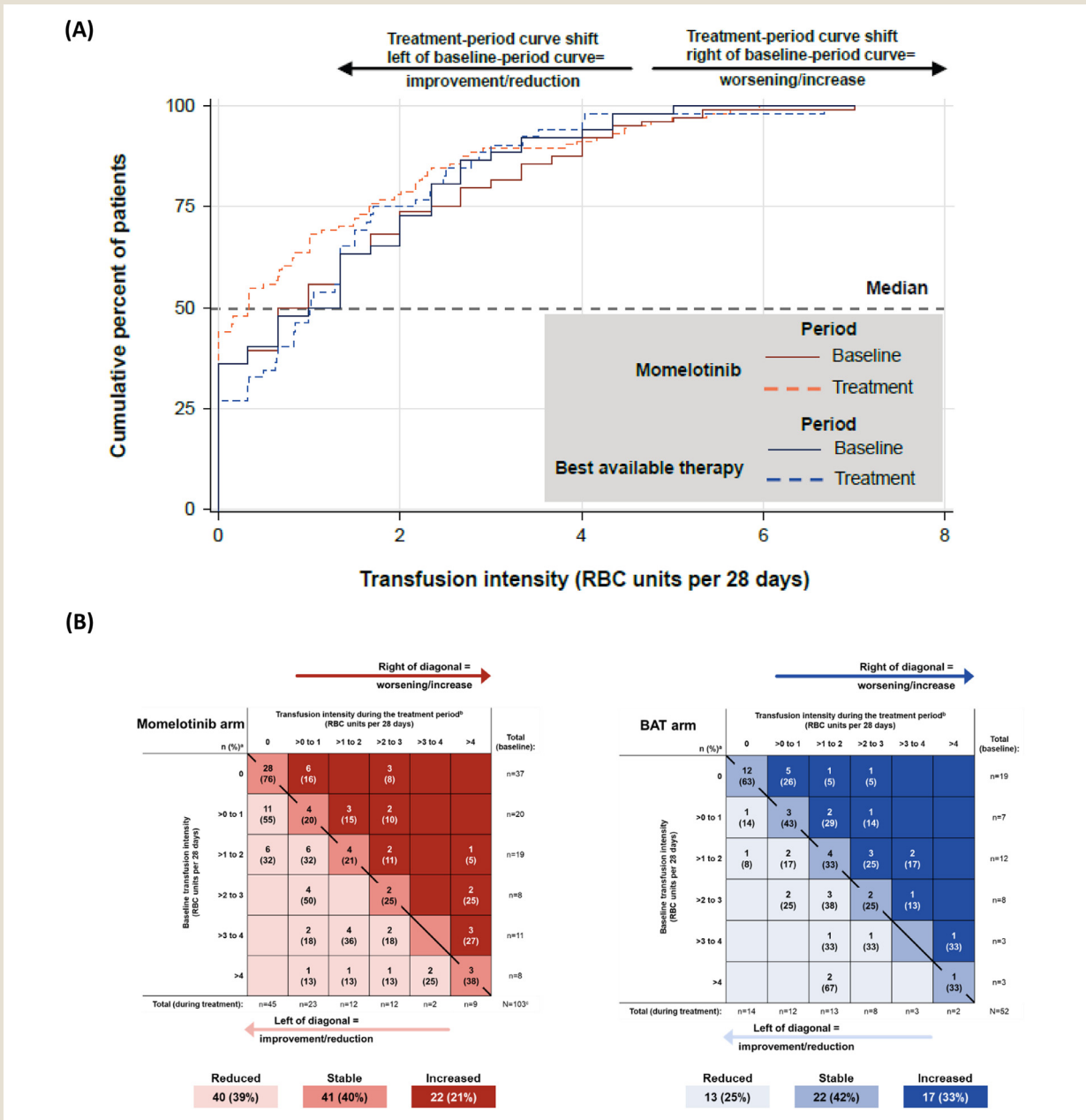


Table 2 Change From Baseline Period RBC Transfusion Intensity for the Phase 2 Study, SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM During the Treatment Period (ITT)

	Phase 2 study	SIMPLIFY-1		SIMPLIFY-2		MOMENTUM	
	Momelotinib (n = 41)[a]	Momelotinib (n = 215)	Ruxolitinib (n = 217)	Momelotinib (n = 104)	BAT (n = 52)	Momelotinib (n = 130)	Danazol (n = 65)
Transfusion intensity status, n (%)[b,c]	n = 41	n = 213[d]	n = 216[d]	n = 103[e]	n = 52	n = 130	n = 65
Improved from baseline	35 (85)	41 (19)	23 (11)	50 (49)	20 (39)	85 (65)	34 (52)
No change from baseline	0 (0)	144 (68)	94 (44)	29 (28)	12 (23)	25 (19)	7 (11)
Worsened from baseline	6 (15)	28 (13)	99 (46)	24 (23)	20 (39)	20 (15)	24 (37)
Change from baseline in transfusion intensity, mean (SD)	−1.5 (1.3)	−0.10 (0.7)	+0.39 (1.0)	−0.36 (1.4)	0.0 (1.3)	−0.86 (1.7)	−0.28 (1.6)

Abbreviations: BAT = best available therapy; ITT = intent to treat; RBC = red blood cell; SD = standard deviation.
[a] One patient in the momelotinib arm had insufficient transfusion intensity information.
[b] Transfusion intensity is calculated as the number of RBC units transfused divided by the number of days in an observation period and multiplied by 28. Improved means any decrease from the baseline RBC units transfused, and worsened means any increase from the baseline RBC units transfused; no change means neither improved nor worsened.
[c] Transfusion intensity status was determined using the absolute transfusion intensity numbers and may not fully align with the data presented in ordinal bin analyses.
[d] Two patients in the momelotinib arm and 1 patient in the ruxolitinib arm were not evaluable for transfusion intensity (evaluable populations, n = 213 and n = 216, respectively).
[e] One patient in the momelotinib arm was not evaluable for transfusion intensity (evaluable population, n = 103).

RBC transfusion intensities during the treatment versus baseline periods, compared with 39% (20/52) and 23% (12/52) in the BAT arm; conversely, transfusion intensities during the treatment period worsened from baseline in more patients treated with BAT (39% [20/52]) compared with momelotinib (23% [24/103]) (Table 2).

MOMENTUM

In MOMENTUM (JAK inhibitor–experienced, symptomatic, and anemic patients), approximately half of enrolled patients were TD at baseline (48% [63/130] in the momelotinib arm and 52% [34/65] in the danazol arm). Similarly, approximately half of the population, 52% and 51% of patients, respectively, had Hb levels of ≥80 g/L, and mean Hb levels were 81 and 79 g/L (Table 1).

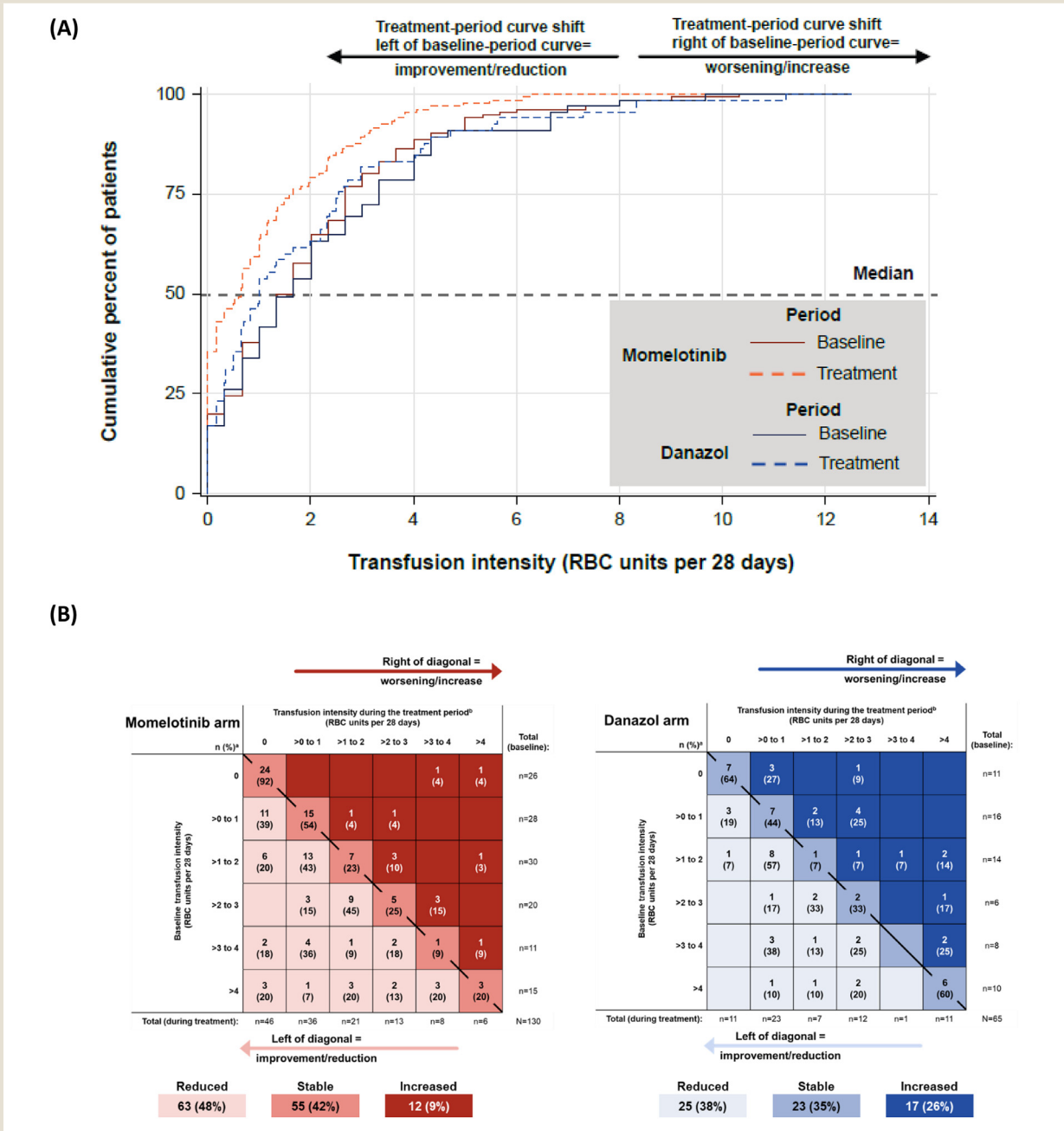
Consistent with this JAK inhibitor–experienced and anemic study population, patients in MOMENTUM had the highest mean baseline-period transfusion intensities (2.0 [range, 0-10.3] units per 28 days for momelotinib versus 2.2 [range, 0-9.7] units per 28 days for danazol) of the studies in this analysis. Mean transfusion intensity during the treatment period decreased by approximately 50% in the momelotinib arm (1.1 [range, 0-6.3] units per 28 days) versus a smaller decrease (approximately 15%) in the danazol arm (1.9 [range, 0-11.2] units per 28 days) (Supplemental Table 1). Overall, mean RBC transfusion burdens per 28 days changed by −0.86 units (SD, 1.7) in the momelotinib arm and −0.28 units (SD, 1.6) in the danazol arm from the baseline to treatment periods (Table 2). Cumulative distribution function curves further highlight the greater reduction in transfusion burden during the treatment period with momelotinib, with a larger leftward shift in the momelotinib versus danazol treatment-period curves compared with the baseline-period curves (Figure 5A).

During the baseline period, only 20% (26/130) in the momelotinib arm and 17% (11/65) in the danazol arm were transfusion free (Table 1, Figure 5B). Similar to the ordinal bin results from SIMPLIFY-1 and SIMPLIFY-2, during the entire treatment period, a higher proportion of patients in the momelotinib arm (35% [46/130]) versus the danazol arm (17% [11/65]) were transfusion free, including a higher proportion of those who maintained this status from baseline (momelotinib, 92% [24/26]; danazol, 64% [7/11]) (Figure 5B). Among patients with some transfusion burden during the baseline period, 21% (22/104) in the momelotinib arm became transfusion free for the entire treatment period versus 7% (4/54) in the danazol arm (Figure 5B). Overall, 65% (85/130) in the momelotinib arm had improved and 19% (25/130) had stable RBC transfusion intensities during the treatment versus baseline periods, compared with 52% (34/65) and 11% (7/65), respectively, in the danazol arm; in contrast, more patients had worsened transfusion intensities compared with baseline during the treatment period with danazol (37% [24/65]) versus momelotinib (20% [15/130]) (Table 2).

Discussion

These post hoc clinical trial analyses applied novel methodology to quantify longitudinal RBC transfusion burden in a broad spectrum of both JAK inhibitor–naive and –experienced patients with MF, demonstrating that momelotinib provides anemia-related benefit in the form of reduced or stable transfusion intensity to

Figure 5 (A) Cumulative distribution function for RBC transfusion intensity and (B) shift table of change in RBC transfusion intensity in MOMENTUM. In panel A, mean transfusion intensity (RBC units per 28 days; x-axis) is plotted against the percentage of patients who had that mean transfusion intensity or less (y-axis); the percentage increases with increasing transfusion intensities until 100% of patients are accounted for. An overall leftward shift of the treatment-period curve versus baseline-period curve for a given treatment indicates decreased transfusion intensity overall with that treatment. Median transfusion intensity (50th percentile in Supplemental Table 1) is indicated with the dotted grey line. In panel B, rows are patients with similar baseline-period transfusion intensities; columns show treatment-period transfusion intensities. Dark-shaded cells indicate baseline- to treatment-period worsening of transfusion burden, light-shaded cells indicate improvement in transfusion burden, and medium-shaded cells indicate stable transfusion burden.
RBC, red blood cell.
[a]Percentage of baseline transfusion intensity category. [b]Rounding was applied to place patients in each ordinal bin/category; as a result, changes in intensity during treatment that did not result in a change in ordinal bin from baseline may not be apparent.



most patients. Results from a single-arm phase 2 study—in which almost all patients were TD with high baseline-period transfusion intensity, allowing visualization of substantial decreases in individual and mean treatment-period intensities—provided initial proof-of-concept for this approach to assessment of transfusion burden. Similar analyses were subsequently applied to the larger, randomized controlled, phase 3 studies of momelotinib (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM) to facilitate evaluation versus comparators and in the context of more diverse baseline transfusion burdens. Momelotinib was associated with greater reductions in mean RBC transfusion burden versus comparators across trials; mean RBC transfusion burden increased with ruxolitinib, while mean reductions with BAT and danazol—a standard anemia therapy[2]—were less than what was observed with momelotinib.

Transfusion independence is an increasingly common endpoint in MF trials that assess anemia-related benefit; reported response rates can vary substantially depending on the stringency of the definition applied.[17] All 3 momelotinib phase 3 trials predefined TI response using the most stringent terminal 12-week definition (versus the alternative rolling 12-week definition not restricted to the last 12 weeks before week 24) and found higher rates of transfusion independency with momelotinib versus the comparator arms.[14-16] Notably, however, all definitions are binomial and thus do not reflect any anemia-related benefits of a given treatment that, while still potentially meaningful, do not meet the definition of response.[17] A key feature of these time-dependent analyses is that they make use of all data related to transfusions received during the baseline and 24-week treatment periods to provide insight into longitudinal changes in transfusion burden. This further contrasts with the TI endpoint, which typically only considers transfusion-related data from a discrete duration (eg, the 12 weeks immediately preceding week 24).[14-16] These time-dependent analyses demonstrate that mean transfusion intensity was decreased, and individual transfusion intensities were reduced or stable for most patients, with momelotinib throughout the entire 24-week treatment period versus baseline, providing evidence of the durability of momelotinib's anemia-related benefits. These results are particularly notable in the context of the previously reported mean Hb levels over time in SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM, which increased rapidly in the momelotinib arm before stabilizing.[18] Since patients receiving transfusions were included in those analyses, the present analyses illustrate that these increased mean hemoglobin levels were not the result of increased transfusion burden. In contrast, mean hemoglobin levels in the ruxolitinib arm of SIMPLIFY-1 initially decreased before stabilizing.[18] The present analyses suggest that this stabilization may be the result of increased transfusion burden, which was still insufficient to restore mean hemoglobin levels to their baseline value.

These analyses leveraged data from 4 momelotinib studies, providing an opportunity to evaluate a diverse array of patients across both the JAK inhibitor–naive and –experienced settings. JAK inhibitor–naive patients who are TD are an often underappreciated group, with greater focus typically placed on the management of patients with worsening anemia on treatment.[19,20] However, results from the phase 2 study and SIMPLIFY-1—consisting of primarily and only JAK inhibitor–naive patients, respectively—suggest that there are JAK inhibitor–naive patients with high transfusion burden, and that momelotinib can offer anemia-related benefits to this population. All patients in the phase 2 study were TD at baseline, but >20% were transfusion free on momelotinib; while only approximately 25% of patients in SIMPLIFY-1 were TD at baseline, a similar percentage of those with some baseline transfusion burden were transfusion free during momelotinib treatment. The benefits of momelotinib were further demonstrated in JAK inhibitor–experienced patients with varying baseline transfusion burdens and comparators in SIMPLIFY-2 and MOMENTUM; momelotinib was associated with larger decreases in transfusion intensity and mean transfusion burden with momelotinib versus the BAT or danazol comparator arms. These results build on a previous analysis of SIMPLIFY-2 that suggested switching to momelotinib might be associated with greater anemia-related benefits in JAK inhibitor–experienced patients receiving transfusions than the traditional approach of adding anemia supportive therapies such as erythropoiesis-stimulating agents to dose-reduced ruxolitinib.[21] Taken together, these findings collectively demonstrate that momelotinib can provide substantial anemia benefit for both JAK inhibitor–naive and –experienced patients with MF.

Another important finding from these analyses is that momelotinib can maintain and/or reduce transfusion burden in patients who start off with less severe anemia (ie, low or no baseline transfusion burden), in addition to reducing transfusion burden in TD patients with high baseline intensities. Early momelotinib initiation even in anemic patients with low transfusion burden is further supported by a post hoc analysis of SIMPLIFY-1 that used the same longitudinal transfusion burden analyses to evaluate the impact of momelotinib versus ruxolitinib in subgroups defined by baseline anemia severity.[22] Reduction in transfusion intensity with momelotinib was not only observed in patients with moderate to severe anemia (baseline Hb <100 g/L), but also in those with mild anemia (baseline Hb ≥100 to <120 g/L), with 93% of those on momelotinib having stable or reduced transfusion intensities versus 51% of those on ruxolitinib in that subgroup.[22] Moreover, momelotinib enabled all patients who were nonanemic (baseline Hb ≥120 g/L) to maintain their transfusion-free status during treatment, while some patients became transfusion requiring during ruxolitinib treatment.[22] Reduced transfusion burden in patients with transfusion needs at baseline and avoidance of worsening burden in baseline transfusion-free patients suggests that momelotinib may address both disease- and treatment-related anemia. Although a mechanistic differentiation between these types of anemia in myelofibrosis has not been established, categorization based on timing (present at baseline or developing on treatment) suggests that disease-related anemia may have a stronger negative impact on clinical outcomes and survival.[23,24] However, in an analysis of the ruxolitinib expanded access JUMP study, patients who developed new or worsening anemia on treatment (although not necessarily related to treatment) had worse survival regardless of their baseline anemia status.[25] These findings reinforce avoidance of both anemia worsening, and, by extension, avoidance of increasing transfusion dependency, as a treatment priority in MF.

The use of anemia-related benefits as efficacy endpoints in trials of MF, and evolving methodology to describe these benefits, are reflec-

tive of an increasing appreciation for the importance of addressing anemia in MF.[17] Although the analyses described here demonstrate a lower transfusion burden for patients with MF treated with momelotinib, whether this translates to a clinically meaningful reduction or symptom and QOL improvement could not be addressed and awaits future studies. Furthermore, these analyses were limited to transfusion outcomes within a 24-week treatment period due to the crossover design of the phase 3 trials, and their post hoc nature precluded any statistical comparisons. A previous analysis of SIMPLIFY-1 found that median time to loss of week 24 transfusion independence with momelotinib was not reached after >3 years of follow-up; however, durability of transfusion burden changes over such extended follow-up, and the relative benefits of momelotinib versus comparators in the long term, have not been extensively evaluated.[26] In the future, this methodology could also be applied prospectively to deepen the understanding of how momelotinib used in combination with emerging therapies could provide additional anemia benefits.

Conclusion

This study demonstrates that, across all 3 phase 3 trials of momelotinib in MF to date, ≥75% of patients treated with momelotinib either maintained or experienced improved transfusion intensities versus baseline. These results provide evidence that underscores the consistent anemia benefits provided by momelotinib for the majority of patients.

Clinical Practice Points

- In this novel transfusion burden analyses of JAK inhibitor–naive and –experienced patients treated with momelotinib, ≥77% of patients from the phase 2 and 3 momelotinib trials achieved a numeric reduction in RBC transfusion requirements on treatment compared with baseline.
- Ordinal bin analyses, used to group patients based on baseline-period and treatment-period intensity of RBC units transfused per 28 days, showed that most patients experienced a decrease or stabilization of transfusion requirements on momelotinib treatment; mean change in transfusion intensity also showed a numeric decrease from baseline.
- These results highlight that binary transfusion independence response/nonresponse may not fully capture the anemia benefits of momelotinib; future studies incorporating this novel methodology will be increasingly important for characterizing anemia-related benefits in myelofibrosis therapies.

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curation. **Catherine Ellis:** Writing – review & editing, Conceptualization. **Bryan Strouse:** Writing – review & editing, Conceptualization. **Francisco J. Gonzalez Carreras:** Writing – review & editing, Conceptualization. **Stephen T. Oh:** Writing – review & editing, Data curation.

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Data Availability Statement

Data are available upon reasonable request. Information on GSK's data-sharing commitments and requesting access to anonymized individual participant data and associated study documents can be found at https://www.gsk-studyregister.com/en/.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2024.10.001.

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