Time Without Transfusion Reliance or Anemia Worsening: a Novel Method for Integrating Transfusion Dependence, Anemia, and Survival With Myelofibrosis Therapies Based on the Phase 3 SIMPLIFY-1 and SIMPLIFY-2 Trials

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Introduction

- Patients with myelofibrosis (MF) often experience debilitating symptoms that profoundly impact their health-related quality of life (HRQOL) and functioning[1-3]
  - The presence of constitutional symptoms (eg, weight loss, fever, night sweats) is also a negative prognostic factor for survival[4]
- Anemia, as a key hallmark of MF, is also associated with negative HRQOL and prognostic impact; red blood cell (RBC) transfusion, an important component of anemia management in MF, further compounds these burdens[5-8]
- Janus kinase (JAK) inhibitors are a mainstay of MF treatment due to their ability to address both symptoms and splenomegaly in most patients[9-12]; however, JAK inhibitors such as ruxolitinib and fedratinib do not address, and may worsen, anemia[9,10]
  - While JAK inhibitors have also improved overall survival (OS) in MF,[13,14] traditional survival analyses do not consider the individual patient experience, which may be negatively impacted by factors including persistent symptoms, adverse events (AEs) such as anemia, and RBC transfusion dependence[15]
- Momelotinib is a JAK1/JAK2/activin A receptor type 1 (ACVR1) inhibitor recently approved by the US Food and Drug Administration for the treatment of patients with myelofibrosis and anemia[12]
  - Momelotinib has demonstrated consistent anemia benefits, including increased transfusion independence and reduced transfusion burden, as well as spleen and symptom improvements across 3 phase 3 trials in MF[16-18]
  - In all of these phase 3 trials, achieving transfusion independence with momelotinib was associated with prolonged OS[19,20]
- Here we applied novel time without transfusion reliance (TWiTR) analyses integrating transfusion-dependent (TD) status and OS[15] to better characterize the relative quality of survival with momelotinib vs comparators in these phase 3 trials

Objective

- To estimate time without transfusion reliance or anemia worsening, providing a measure of survival quality with momelotinib vs comparators in phase 3 trials

Methods

- Analyses were performed in the safety populations (all randomized patients who received ≥1 dose of study treatment), by treatment arm, over the 24-week randomized period of 3 phase 3 trials (**Table 1**)

Table 1. **Phase 3 Studies of Momelotinib in MF[16-18]**

	SIMPLIFY-1[16] (NCT01969838)		SIMPLIFY-2[17] (NCT02101268)		MOMENTUM[18] (NCT04173494)	
Patient population	JAK inhibitor naive		JAK inhibitor experienced		JAK inhibitor experienced, symptomatic (TSS ≥10), and anemic (Hb level <10 g/dL)	
Treatment	Momelotinib	Ruxolitinib	Momelotinib	BAT[a]	Momelotinib	Danazol
n (Safety)/n (ITT)	214/215	216/217	104/104	52/52	130/130	65/65

[a] BAT was ruxolitinib (alone or in combination) in 88.5% of patients.

- Baseline characteristics have been previously reported; key anemia-related characteristics are summarized in **Table 2**[16-18]
- Transfusion status was defined per the SIMPLIFY study protocols[16,17]:
  - **TD**: requiring ≥4 RBC transfusion units or having a hemoglobin (Hb) level <8 g/dL in the previous 8 weeks
    - In MOMENTUM, TD was defined as requiring ≥4 RBC transfusion units in the previous 8 weeks, each associated with Hb levels of ≤9.5 g/dL[18]; however, the SIMPLIFY definition was applied to the present analysis for consistency
  - **Transfusion independent (TI)**: no RBC transfusion units or Hb levels <8 g/dL in the previous 12 weeks
  - **Transfusion requiring (TR)**: not meeting criteria for TD or TI

Table 2. **Anemia-Related Baseline Characteristics[16-18]**

	SIMPLIFY-1[16]		SIMPLIFY-2[17]		MOMENTUM[18]	
	Momelotinib (n=215)	Ruxolitinib (n=217)	Momelotinib (n=104)	BAT/ Ruxolitinib (n=52)	Momelotinib (n=130)	Danazol (n=65)
Hb level						
Mean (SD)	10.6 (2.1)	10.7 (2.4)	9.4 (1.9)	9.5 (1.6)	8.1 (1.1)	7.9 (0.8)
<8 g/dL, n (%)	28 (13)	21 (10)	27 (26)	6 (12)	62 (48)	32 (49)
TD, n (%)	53 (25)	52 (24)	58 (56)	27 (52)	63 (48)	34 (52)
TI, n (%)	147 (68)	152 (70)	32 (31)	19 (37)	17 (13)	10 (15)
TR, n (%)	15 (7)	13 (6)	14 (13)	6 (12)	50 (38)	21 (32)

Methods

- TWiTR is based on the established time without symptoms and toxicity (TWiST) analysis, which assesses survival quality by subtracting from OS those periods during which treatment toxicity or disease reduces QOL; in TWiTR, toxicity is replaced with TD status[15,21]
- The main TWiTR analysis partitioned survival duration into 3 health states:
  - **TD:** the number of days on which patients were TD (defined per the SIMPLIFY protocol) before experiencing a leukemia-free survival (LFS) event (leukemic transformation or death)
  - **Post-LFS:** the number of days from an LFS event to death or censoring (OS)
    - Post-LFS = OS − LFS
  - **TWiTR:** the number of days without post-LFS or TD
    - TWiTR = LFS − TD
- An additional analysis incorporated the number of days on which patients had any-grade anemia events into the TD state (TD-Anemia [**TD-An**]) to define time without transfusion reliance or anemia worsening (TWiTR-An)
  - Overlapping periods were counted only once
- Health state durations were estimated via Kaplan-Meier curves of the survival distribution function, with mean duration in each state calculated as the area under the curve and visualized via partitioned survival plots

Discussion/Limitations

- These TWiTR and TWiTR-An analyses are, to our knowledge, the first assessment of survival quality associated with JAK inhibitors in MF, integrating the patient experience into OS by considering the impact of RBC transfusion dependence and anemia
- A limitation of these analyses is that the definition of TD varied between the SIMPLIFY trials and MOMENTUM; while the SIMPLIFY definition was applied to all trials in these analyses, it was not possible to align the MOMENTUM data completely with this definition, potentially impacting the results of that analysis
  - Scenario analyses applying alternative definitions of transfusion status (eg, rolling 12-week) may be explored in the future pending feasibility assessment
- Furthermore, only data from the 24-week randomized periods of each trial were available for analysis of momelotinib vs comparators, so mean changes in the number of days spent in each health state must be considered in the context of this time frame; due to the crossover design of all 3 trials, all patients received open-label momelotinib after week 24, so additional analyses will be required to validate long-term survival outcomes
- As these clinical trials may not be fully representative of real-world clinical practice, application of TWiTR/TWiTR-An to real-world patient populations in the future may provide further insights into the quality of survival in patients with MF under diverse clinical scenarios

Conclusion

- Across 3 phase 3 trials, patients treated with momelotinib spent less time reliant on RBC transfusions and more time free from transfusions and anemia events compared with those treated with ruxolitinib, BAT, or danazol
  - The largest differences were observed with momelotinib vs ruxolitinib (SIMPLIFY-1) or BAT (88.5% ruxolitinib; SIMPLIFY-2)
  - However, momelotinib was also associated with less time reliant on RBC transfusions than danazol, a guideline-recommended supportive therapy for anemia management in MF, in MOMENTUM[18]
- Incorporating anemia events into the TWiTR-An analyses had minimal impact on health state durations vs the TWiTR analyses, particularly in the JAK inhibitor–experienced setting (SIMPLIFY-2, MOMENTUM), consistent with the fact that more patients were TD at baseline in those trials
- Given the negative QOL and prognostic impact of RBC transfusion dependence, these analyses collectively suggest that prevention of transfusion dependence and achievement of transfusion independence with momelotinib may lead to improved quality of survival for patients with MF

Results

TWiTR Analysis

- Across all 3 trials, patients in the momelotinib arms spent less time in the TD state and more time in the TWiTR state on average vs patients in the comparator arms, with mean differences of >30 days in SIMPLIFY-1, >20 days in SIMPLIFY-2, and >7 days in MOMENTUM (**Table 3; Figures 1-3**)

Table 3. **Summary of TWiTR Analysis Results**

Duration in health state, mean (95% CI), days	SIMPLIFY-1		SIMPLIFY-2		MOMENTUM	
	Momelotinib (n=214)	Ruxolitinib (n=216)	Momelotinib (n=104)	BAT/ Ruxolitinib (n=52)	Momelotinib (n=130)	Danazol (n=65)
TD	28.3 (20.8-35.8)	62.7 (53.5-72.0)	69.4 (55.4-83.4)	89.9 (70.1-109.7)	80.5 (69.5-91.6)	88.0 (73.6-102.5)
Difference with momelotinib	−34.4 (−46.3 to −22.5)		−20.5 (−44.5 to 3.5)		−7.5 (−26.0 to 11.0)	
TWiTR	163.4 (157.4-169.4)	131.1 (124.1-138.0)	118.3 (107.0-129.5)	95.9 (80.0-111.8)	104.2 (95.2-113.3)	83.2 (68.9-97.5)
Difference with momelotinib	32.3 (23.2-41.5)		22.4 (3.0-41.7)		21.0 (4.8-37.2)	
Post-LFS	0.2 (−3.8 to 4.3)	0.4 (−2.7 to 3.6)	1.0 (−6.6 to 8.5)	0.7 (−10.1 to 11.6)	0.8 (−5.7 to 7.2)	2.4 (−11.6 to 16.3)
Difference with momelotinib	−0.2 (−5.3 to 4.9)		0.2 (−12.8 to 13.3)		−1.6 (−16.9 to 13.7)	

Shorter times in the TD state and longer times in the TWiTR state suggest improved survival quality.

Figure 1. **TWiTR Health State Durations in SIMPLIFY-1**

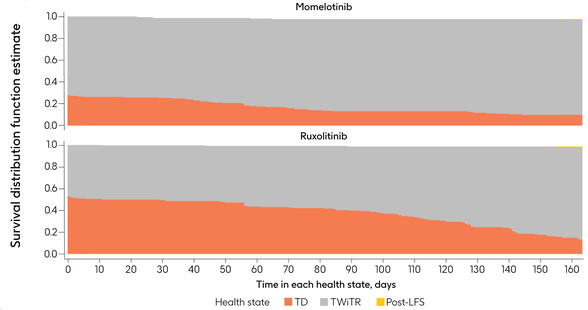


Figure 2. **TWiTR Health State Durations in SIMPLIFY-2**

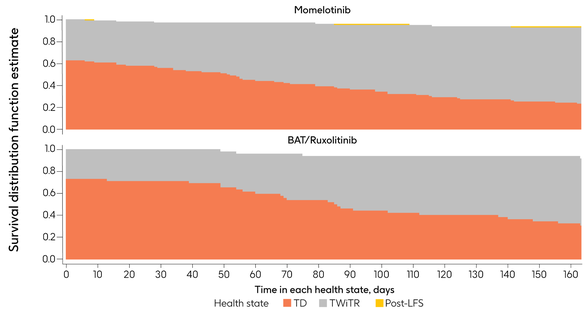
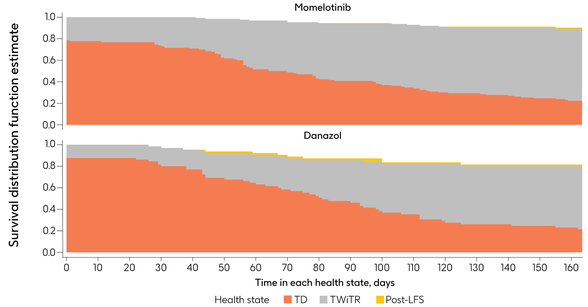


Figure 3. **TWiTR Health State Durations in MOMENTUM**



TWiTR-An Analysis

- In SIMPLIFY-1, fewer patients in the momelotinib arm vs the ruxolitinib arm had treatment-emergent anemia events; anemia event rates were comparable between arms in SIMPLIFY-2 and MOMENTUM (**Table 4**)[16-18]
- Across all 3 trials, health state trends were similar to those observed in the main TWiTR analysis, with patients in the momelotinib arms spending less time in the TD-An state and more time in the TWiTR-An state vs comparator arms (**Table 5**)
  - In JAK inhibitor–naive patients (SIMPLIFY-1), incorporation of anemia events into the analysis resulted in greater mean time in the TD-An state compared with the TD state in all treatment arms, although this increase was smaller in the momelotinib arm
  - Incorporation of anemia events had less impact in JAK inhibitor–experienced patients (SIMPLIFY-2, MOMENTUM)

Table 4. **Anemia TEAEs[16-18]**

	SIMPLIFY-1				SIMPLIFY-2				MOMENTUM			
	Momelotinib (n=214)		Ruxolitinib (n=216)		Momelotinib (n=104)		BAT/ Ruxolitinib (n=52)		Momelotinib (n=130)		Danazol (n=65)	
Grade:	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3
Any TEAE, n (%)	198 (93)	77 (36)	206 (95)	94 (44)	101 (97)	60 (58)	46 (88)	22 (42)	122 (94)	70 (54)	62 (95)	42 (65)
Anemia TEAEs, n (%)	31 (14)	13 (6)	81 (38)	49 (23)	16 (15)	14 (13)	10 (19)	9 (17)	15 (12)	10 (8)	10 (15)	7 (11)

Table 5. **Summary of TWiTR-An Analysis Results**

Duration in health state, mean (95% CI), days	SIMPLIFY-1		SIMPLIFY-2		MOMENTUM	
	Momelotinib (n=214)	Ruxolitinib (n=216)	Momelotinib (n=104)	BAT/ Ruxolitinib (n=52)	Momelotinib (n=130)	Danazol (n=65)
TD-An	32.0 (24.2-39.7)	74.8 (65.6-84.0)	69.6 (55.7-83.6)	89.9 (70.1-109.7)	80.5 (69.5-91.6)	88.0 (73.6-102.5)
Difference with momelotinib	−42.8 (−54.8 to −30.8)		−20.3 (−44.3 to 3.7)		−7.5 (−26.0 to 11.1)	
TWiTR-An	159.7 (153.5-165.9)	119.0 (112.2-125.9)	118.0 (106.8-129.3)	95.9 (80.0-111.8)	104.2 (95.1-113.3)	83.2 (68.9-97.5)
Difference with momelotinib	40.7 (31.5-49.9)		22.2 (2.8-41.5)		21.0 (4.8-37.2)	
Post-LFS	0.2 (−3.8 to 4.3)	0.4 (−2.7 to 3.6)	1.0 (−6.6 to 8.5)	0.7 (−10.1 to 11.6)	0.8 (−5.7 to 7.2)	2.4 (−11.6 to 16.3)
Difference with momelotinib	−0.2 (−5.3 to 4.9)		0.2 (−12.8 to 13.3)		−1.6 (−16.9 to 13.7)	

Shorter times in the TD-An state and longer times in the TWiTR-An state suggest improved survival quality.

Abbreviations

ACVR1, activin A receptor type 1; AE, adverse event; BAT, best available therapy; Hb, hemoglobin; HRQOL, health-related quality of life; ITT, intent to treat; JAK, Janus kinase; LFS, leukemia-free survival; MF, myelofibrosis; OS, overall survival; QOL, quality of life; RBC, red blood cell; TD, transfusion dependent; TD-An, transfusion dependent or anemia worsening; TEAE, treatment-emergent adverse event; TI, transfusion independent; TR, transfusion requiring; TSS, Total Symptom Score; TWiST, time without symptoms and toxicity; TWiTR, time without transfusion reliance; TWiTR-An, time without transfusion reliance or anemia worsening.

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