Transfusion Independence Response (TI-R) as a Potential Surrogate for Overall Survival (OS) in Janus Kinase Inhibitor (JAKi)-Experienced Patients with Myelofibrosis from MOMENTUM Trial

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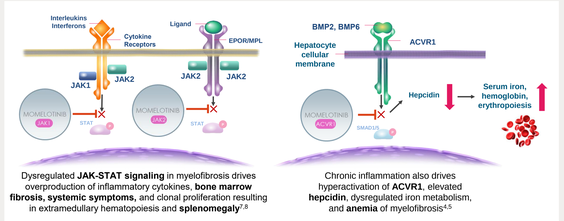
Introduction

- Anemia and transfusion requirements are major medical needs in myelofibrosis, associated with poor prognosis and frequently managed with repeated transfusions, which are costly in terms of reduced quality of life and OS as well as increased health care resource utilization
- Anemia is not addressed by currently approved JAKis and is commonly managed with recurrent red blood cell (RBC) transfusions and anti-anemic therapies
- Momelotinib, an oral activin A receptor type 1 (ACVR1), Janus kinase 1, and Janus kinase 2 inhibitor, has previously demonstrated clinical activity on symptoms, anemia, and spleen volume in JAKi-naïve and JAKi-experienced patients with myelofibrosis in the SIMPLIFY-1 (NCT01969838), SIMPLIFY-2 (NCT02101268), and MOMENTUM (NCT04173494) phase 3 studies[1-3]
- Preclinical and clinical translational studies have demonstrated the ability of momelotinib to address anemia and transfusion dependence (TD) is mechanistically linked to its differentiated suppression of ACVR1-mediated hepcidin production[4,5]
- Here, we describe data from the MOMENTUM study, which shows the achievement of week 24 TI-R on momelotinib is associated with prolonged OS, consistent with previously reported data[6]



Dysregulated **JAK-STAT signaling** in myelofibrosis drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms,** and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**[7,8]

Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of myelofibrosis[4,5]

ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; JAK1/2, Janus kinase 1/2; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription.

Objectives

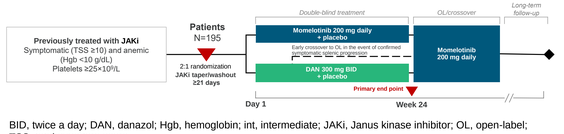
Employ data from the ongoing MOMENTUM study in JAKi-experienced patients to:

- Determine impact on transfusion independence (TI) and OS
- Describe transfusion burden reduction
- Better characterize reduction in transfusion requirements for momelotinib versus danazol (DAN)

Methods

- Eligible patients had Myelofibrosis Symptom Assessment Form total symptom score ≥10; hemoglobin (Hgb) <10 g/dL; prior JAKi for ≥90 days or ≥28 days RBC transfusions ≥4 units in 8 weeks or grade 3/4 thrombocytopenia, anemia, or hematoma; and palpable spleen ≥5 cm
- Anemia benefit was evaluated by:
  - Week 24 TI-R (defined as the absence of RBC transfusions and no Hgb measurements below 8 g/dL during the 12 weeks preceding week 24)
  - Consecutive 12-week TI-R (defined as absence of RBC transfusions and no Hgb measurement below 8 g/dL over any 12-week period through week 24)
  - Hgb response (defined as increases of ≥1 or ≥2 g/dL from baseline Hgb, as measured over any 12-week period through week 24)
  - Kaplan-Meier (KM) estimates of the proportion of patients who required zero units transfused
  - Hazard ratio (HR) of RBC units transfused
  - HR of time to first, third, and fifth transfusion unit
  - Odds ratio (OR) of having zero units transfused
- Survival was estimated using KM analysis

Figure 1. MOMENTUM Is a Double-Blind, Randomized, Phase 3 Study Comparing Momelotinib Versus DAN in Patients With High-Risk, Int-2, or Int-1 Myelofibrosis



BID, twice a day; DAN, danazol; Hgb, hemoglobin; int, intermediate; JAKi, Janus kinase inhibitor; OL, open-label; TSS, total symptom score.

Results

Table 1. MOMENTUM Was Conducted in Symptomatic Anemic, Post-RUX Patients With Myelofibrosis and a Heavy Transfusion Burden at Baseline

Baseline characteristics	Momelotinib (N=130)	DAN (N=65)
Mean (SD) age, y	69.85 (8.24)	71.46 (6.99)
Male, n (%)	79 (60.8)	44 (67.7)
PMF/pPV MF/pET MF, %	60.0/20.8/19.2	70.8/16.9/12.3
DIPSS int-1/int-2/high, %	5.4/55.4/38.5	4.6/61.5/29.2
Mean prior JAKi therapy, weeks	138.5	124.8
Mean TSS	28.0	25.7
Mean Hgb, g/dL	8.1	7.9
Hgb <8 g/dL, %	47.7	49.2
TI,[a] n (%)	17 (13.1)	10 (15.4)
TR,[b] n (%)	50 (38.5)	21 (32.3)
TD,[c] n (%)	63 (48.5)	34 (52.3)
Mean (SD) platelets, × 10⁹/L	151.7 (130.9)	130.7 (101.0)

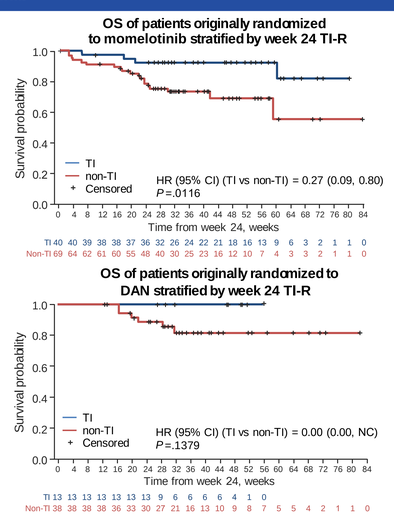
[a]TI defined as not requiring RBC transfusion for ≥12 weeks, with Hgb level ≥8 g/dL. [b]TR defined as patients who required transfusions but did not meet the criteria for TD. [c]TD defined as requiring RBC transfusion ≥4 units in the 8 weeks before randomization.
DAN, danazol; DIPSS, Dynamic International Prognostic Scoring System; Hgb, hemoglobin; int, intermediate; JAKi, Janus kinase inhibitor; pET MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; pPV MF, post-polycythemia vera myelofibrosis; RBC, red blood cell; RUX, ruxolitinib; TD, transfusion dependence; TI, transfusion independence; TR, transfusion-requiring; TSS, total symptom score.

Table 2. Week 24 Data Summary of Anemia-Related End Points Shows Momelotinib Is More Effective Versus DAN

	Momelotinib (N=130)	DAN (N=65)
Terminal week 24 TI-R[a]		
TI-R rate at week 24, n (%)	**40 (30.8)**	**13 (20.0)**
95% CI	(22.98, 39.46)	(11.10, 31.77)
Noninferiority difference (95% CI), 1-sided *P* value	14.77 (3.13, 26.41), ***P*=.0064**	
Superiority difference (95% CI), *P* value	10.99 (-0.80, 22.77), ***P*=.0861**	
Consecutive 12-week TI-R[b]		
TI-R rate by week 24, n (%)	58 (44.6)	19 (29.2)
95% CI	(35.90, 53.58)	(18.60, 41.83)
Noninferiority difference (95% CI), 1-sided *P* value	**22.68 (10.43, 34.94), *P*=.0001**	
Hgb response rate[c]		
Patients with ≥1 g/dL increase, n (%)	69 (53.1)	22 (33.8)
Patients with ≥2 g/dL increase, n (%)	38 (29.2)	13 (20.0)

[a]Terminal week 24 TI-R (defined as the absence of RBC transfusions and no Hgb measurements below 8 g/dL during the 12 weeks preceding week 24). [b]Consecutive 12-week TI-R (defined as absence of RBC transfusions and no Hgb measurement below 8 g/dL over any 12-week period through week 24). [c]Hgb response (defined as increases of ≥1 or ≥2 g/dL from baseline Hgb, as measured over any 12-week period through week 24).
DAN, danazol; Hgb, hemoglobin; RBC, red blood cell; TI-R, transfusion independence response.

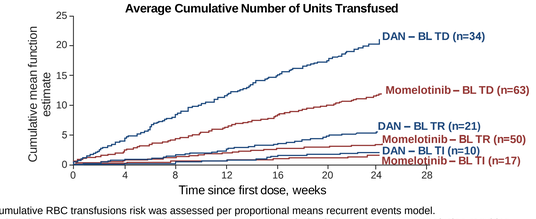
Figure 2. OS Was Improved in Patients Who Achieved Week 24 TI-R on Momelotinib, Including Those Randomized to DAN and Crossed Over to Momelotinib



DAN, danazol; HR, hazard ratio; NC, not calculable; OL, open-label; OS, overall survival; TI, transfusion independence; TI-R, transfusion independence response; TR, transfusion-requiring.

- For those patients randomized to momelotinib achieving week 24 TI-R, OS was significantly improved, consistent with observations in the SIMPLIFY studies
- Patients randomized to DAN achieving week 24 TI-R who then crossed over to momelotinib also trended toward longer OS

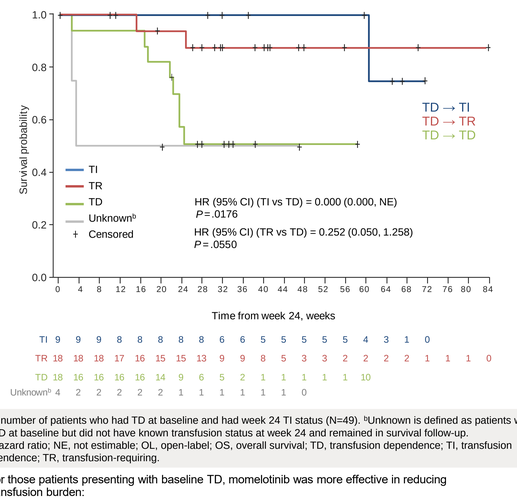
Figure 3. Momelotinib Is More Effective Than DAN at Reducing Transfusion Burden for Anemic TI, Non-TI, TD, and TR Subpopulations



[a]Cumulative RBC transfusions risk was assessed per proportional means recurrent events model.
BL, baseline; DAN, danazol; TD, transfusion dependence; TI, transfusion independence; TR, transfusion-requiring.

- In the intent-to-treat population, mean cumulative RBC transfusion risk[a] was 6.55 versus 10.86 (*P*=.006) for patients treated with momelotinib and DAN, respectively
- In the baseline non-TI subpopulation, mean cumulative RBC transfusion risk[a] was 7.34 versus 12.47 (*P*=.008) for patients treated with momelotinib and DAN, respectively
- Over the 24-week randomized treatment period, 35% of momelotinib patients had zero units transfused compared with 17% of DAN patients (OR=2.7; *P*=.0107)

Figure 4. Transitioning to TR or TI by Week 24 Is Associated With Prolonged OS for Patients Who Have TD at Baseline Randomized to Momelotinib[a]



[a]Total number of patients who had TD at baseline and had week 24 TI status (N=49). [b]Unknown is defined as patients who had TD at baseline but did not have known transfusion status at week 24 and remained in survival follow-up.
HR, hazard ratio; NE, not estimable; OL, open-label; OS, overall survival; TD, transfusion dependence; TI, transfusion independence; TR, transfusion-requiring.

- For those patients presenting with baseline TD, momelotinib was more effective in reducing transfusion burden:
  - Momelotinib baseline TD: 44% transitioned to TI (n=9) or transfusion-requiring (TR) (n=19)
  - DAN baseline TD: 18% transitioned to TI (n=3) or TR (n=3)

Conclusions

- In MOMENTUM, in symptomatic and anemic patients with myelofibrosis, momelotinib showed significant benefit with higher TI response rates and lower transfusion burden compared with DAN
- In patients achieving week 24 TI-R, OS was significantly improved compared with patients who were non-TI
- Both MOMENTUM and the SIMPLIFY studies suggest that achieving week 24 TI-R on momelotinib may be a potential surrogate for improved OS
- TD patients not achieving TI on-study were still more likely to have reduced transfusion burden (become TR) on momelotinib when compared with DAN
- TD patients becoming TR by week 24 also demonstrated a significant improvement in OS
- Given the association of improved OS with reduced transfusion burden, this provides a potential signal of disease modification

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Further analyses of momelotinib can be accessed in the oral presentations **627** (MOMENTUM week 48 results) and **337** (bone marrow fibrosis changes), and poster presentations **1729** (the burden of myelofibrosis and TD), **1733** (transition to momelotinib from ruxolitinib), **4348** (momelotinib long-term safety), and **4351** (impact of momelotinib on patient-reported quality of life).

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