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Impact of dual spleen response and transfusion independence on survival in JAK inhibitor–naive patients with myelofibrosis and anemia treated with momelotinib: a subgroup analysis of SIMPLIFY-1

Digital poster

Poster recording

Francesca Palandri,[1] Nicolaas P.M. Schaap,[2] Jerome Rey,[3] Nikolas von Bubnoff,[4] Andreas Reiter,[5] Juan Carlos Hernandez-Boluda,[6] Timothy Devos,[7] Lars Nilsson,[8] Bethan Psaila,[9] Donal P. McLornan,[10] Bryan Strouse,[11] Bharat Patel,[11] Dwaipayan Patnaik,[12] Stephen T. Oh[13]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia S. Orsola-Malpighi Hospital, Bologna, Italy; [2]Radboud University Medical Center, Nijmegen, the Netherlands; [3]Institut Paoli-Calmettes, Marseille, France; [4]University of Schleswig-Holstein, Lübeck, Germany; [5]University Hospital Mannheim, Heidelberg University, Mannheim, Germany; [6]Hospital Clínico de Valencia-INCLIVA, University of Medicine, Valencia, Spain; [7]University Hospitals Leuven and KU Leuven, Leuven, Belgium; [8]Skåne University Hospital, Lund, Sweden; [9]MRC Weatherall Institute of Molecular Medicine and Ludwig Cancer Institute, University of Oxford and Oxford University NHS Trust, Oxford, UK; [10]University College London Hospitals NHS Trust, London, UK; [11]GSK, Collegeville, PA, USA; [12]GSK, Baar, Switzerland; [13]Washington University School of Medicine, St Louis, MO, USA

Introduction

- Myelofibrosis (MF) is characterized by the key clinical manifestations of splenomegaly, constitutional symptoms, and cytopenias such as anemia and thrombocytopenia[1]
  - Spleen volume reduction (SVR) was the primary endpoint of the pivotal clinical trials leading to the approvals of Janus kinase (JAK) inhibitors such as ruxolitinib,[2-4] and management of splenomegaly is often prioritized as a result
  - However, splenomegaly often co-occurs with anemia (hemoglobin [Hb] <10 g/dL), which is present in approximately 40% of patients at diagnosis and will develop in the majority of patients as the disease progresses[7,8]; these patients may require prioritization of anemia management alongside SVR and symptom control
  - While JAK inhibitors provide spleen and symptom benefits in many patients, some such as ruxolitinib fail to address and may worsen anemia[9]
- In JAK inhibitor–naive patients in SIMPLIFY-1, the only direct head-to-head phase 3 trial of JAK inhibitors, momelotinib was noninferior to ruxolitinib for SVR ≥35% (SVR35; 27% vs 29%; *P*=.011) and nominally superior for transfusion independence (TI; 67% vs 49%; *P*<.001) at week 24[5]
  - While both SVR35 and TI have been associated with improved overall survival (OS), the relative impact of these endpoints on long-term outcomes in patients with MF and anemia has not been established[10-12]
- Momelotinib is initiated at full dose regardless of baseline platelet counts, while ruxolitinib is initiated at lowerdoses in patients with baseline platelet counts <200×10⁹/L; both JAK inhibitors are dose reduced in the event of on-treatment thrombocytopenia[13,14]
  - Ruxolitinib dosing is linked to response; patients receiving a higher dose are more likely to achieve SVR35, with doses of >20 mg daily considered optimal[15-17]
- In this post hoc analysis, we further characterized SVR35 rates with momelotinib vs ruxolitinib in the anemic subpopulation of JAK inhibitor–naive patients in SIMPLIFY-1, explored the differential clinical outcomes observed in patients with lower platelet counts, and evaluated the impact of dual SVR35 and TI at week 24 on OS with momelotinib

Methods

Patient Population

- These post hoc analyses were conducted in the subset of JAK inhibitor–naive patients with baseline anemia (Hb <10 g/dL) from SIMPLIFY-1:



- Within the baseline anemic subgroup, outcomes were further evaluated in subgroups defined by other key baseline characteristics

Endpoints

- The following were assessed in patients initially randomized to momelotinib vs ruxolitinib
  - SVR35: spleen volume reduction ≥35% at week 24
    - Spleen volume was assessed at baseline, week 12, week 24, and then every 12 weeks thereafter through week 168
  - TI: no transfusions and no Hb levels <8 g/dL in the 12 weeks immediately preceding week 24
    - Hb levels and transfusions were recorded at baseline, every 2 weeks through week 24, then every 4 weeks through week 36, and finally every 12 weeks thereafter through week 168
  - Dual response: both SVR35 and TI at week 24

Duration of Spleen Response and Survival

- Duration of spleen response was defined by the date of the first scan post response (ie, post week 24) that showed <35% reduction from baseline and with a 25% increase over on-study nadir
- OS was defined as time from treatment initiation to death due to any cause and was assessed by Kaplan-Meier analysis in responders (SVR35, TI, or dual response) vs nonresponders with momelotinib
- All patients who remained on study received open-label momelotinib after week 24; this crossover design precluded analysis of long-term survival and duration of response with ruxolitinib

Results

- Patient characteristics in the subgroup with baseline Hb <10 g/dL have been previously described and were generally consistent with the ITT (**Table 1**)[18]

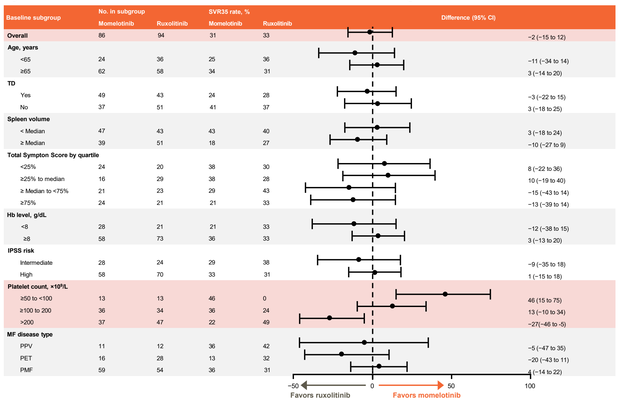
Table 1: **Baseline Characteristics of Patients With Baseline Hb <10 g/dL in SIMPLIFY-1 (JAK inhibitor naive)**[18]

	Momelotinib (n=86)	Ruxolitinib (n=94)
Age, mean (SD), years	68.5 (9.0)	65.9 (9.1)
≥65 years, n (%)	62 (72)	58 (62)
MF subtype, n (%)		
Primary	59 (69)	54 (57)
PPV	11 (13)	12 (13)
PET	16 (19)	28 (30)
IPSS, n (%)		
Int-1	2 (2)	4 (4)
Int-2	26 (30)	20 (21)
High	58 (67)	70 (74)
Spleen volume, median (range), cm³	1788.1 (352-4027)	1958.5 (686-9022)
TSS, mean (SD)	19.0 (13.7)	18.1 (11.9)
Hb, mean (SD), g/dL	8.6 (1.0)	8.7 (1.0)
<8, n (%)	28 (33)	21 (22)
Transfusion status, n (%)		
Transfusion dependent[a]	25 (29)	41 (44)
Transfusion dependent[b]	49 (57)	43 (46)
Transfusion requiring[c]	12 (14)	10 (11)
PLT, mean (SD), ×10⁹/L	229.3 (155.9)	292.3 (323.2)
<100, n (%)	13 (15)	13 (14)
100-200, n (%)	36 (42)	34 (36)
>200, n (%)	37 (43)	47 (50)

Hb, hemoglobin; int, intermediate; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; PET, post-essential thrombocythemia; PLT, platelet; PPV, post-polycythemia vera; RBC, red blood cell; TD, transfusion dependence; TI, transfusion independence; TSS, Total Symptom Score.
[a] SIMPLIFY-1 required palpable splenomegaly ≥5 cm below the left costal margin for enrollment. [b] Defined as no RBC transfusions and no Hb levels <8 g/dL in the last 12 weeks before randomization. [c] Defined as ≥4 RBC units transfused or Hb levels <8 g/dL in the 8 weeks before randomization.

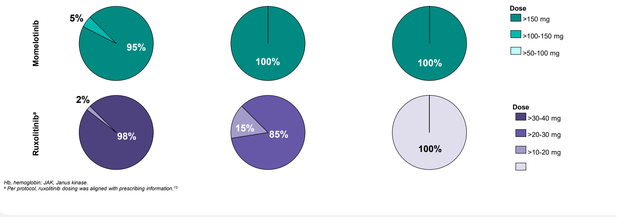
- At week 24, the overall SVR35 rate in JAK inhibitor–naive patients with Hb <10 g/dL was similar with momelotinib vs ruxolitinib (31% vs 33%; difference, −2; 95% CI, −15 to 12) (**Figure 1**)
  - SVR35 rates were comparable between arms across most subgroups but were notably higher with momelotinib in the baseline platelets <100×10⁹/L subgroup (46% vs 0) and with ruxolitinib in the baseline platelets >200×10⁹/L subgroup (22% vs 49%)
    - In the overall subgroup with baseline platelets <200×10⁹/L, SVR35 rates were 39% with momelotinib vs 17% with ruxolitinib
  - Per protocol, patients initiated momelotinib at the full 200-mg dose regardless of baseline platelet counts; consistent with prescribing information, while 98% of patients with baseline platelets ≥200×10⁹/L initiated ruxolitinib at >30 mg, all patients with baseline platelets <200×10⁹/L initiated ruxolitinib at ≤30 mg (**Figure 2**)
- Among the 27 patients with baseline Hb <10 g/dL who achieved SVR35 at week 24 with momelotinib, median duration of response was 35.7 months (95% CI, 27.6 months–not reached)
  - Among the 19 patients with baseline Hb <10 g/dL and platelet counts <200×10⁹/L, median duration was also 35.7 months (95% CI, 27.7-40.7 months)
- Overall, 40 momelotinib-randomized patients with baseline Hb <10 g/dL (47%) achieved SVR35 at any time on study, including an additional 13 patients after week 24; in addition, 15 of 63 patients initially randomized to ruxolitinib who did not achieve SVR35 did so after switching to momelotinib after week 24
  - In the subgroup with baseline platelet counts <200×10⁹/L, 26 momelotinib-randomized patients (53%) achieved SVR35 at any time on study, including an additional 7 patients after week 24; 9 of 39 ruxolitinib week 24 nonresponders achieved SVR35 after switching to momelotinib in the open-label phase of the study

Figure 1: **SVR35 at Week 24 in JAK Inhibitor–Naive Patients With Baseline Hb <10 g/dL**



Hb, hemoglobin; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post-polycythemia vera; SVR35, spleen volume reduction ≥35%; TD, transfusion dependence.

Figure 2: **Mean Daily Doses During Study Week 1 in JAK Inhibitor–Naive Patients With Baseline Hb <10 g/dL by Baseline Platelet Counts**



Hb, hemoglobin; JAK, Janus kinase.
** Per protocol, ruxolitinib dosing was aligned with prescribing information.*[17]

Conclusions

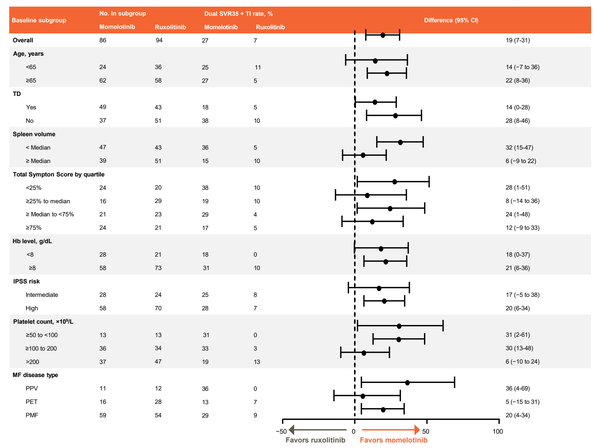
- In this trial population of JAK inhibitor–naive patients with baseline Hb <10 g/dL, most responders achieved dual SVR35+TI responses with momelotinib, illustrating its combined benefits for spleen reduction and anemia in MF, while similar SVR35 rates with ruxolitinib often came at the expense of transfusion need
  - Momelotinib provided comparable SVR35 rates to ruxolitinib across most patient subgroups
    - Splenic responses with momelotinib were durable, with a median duration of >3 years, and new responses after week 24 were observed with open-label momelotinib in patients previously treated with either momelotinib or ruxolitinib during the 24-week randomized period
  - In the momelotinib arm, the OS HR vs nonresponders was lower for TI alone (0.19) than for SVR35+TI (0.40), suggesting that TI in anemic patients with MF may contribute to long-term outcomes with momelotinib
- SVR35 rates were notably higher with momelotinib in patients with baseline platelet counts <200×10⁹/L
  - In patients with baseline Hb <10 g/dL and platelet counts <200×10⁹/L, more than half of patients initially randomized to momelotinib achieved SVR35 on study, and another 9 patients did so after switching from ruxolitinib after week 24
  - As momelotinib was able to be initiated at full dose (200 mg daily) in patients with lower platelet counts, while ruxolitinib was initiated at daily doses ≤30 mg compared with a full daily dose of 40 mg, these data illustrate the importance of full-dose JAK inhibition for optimal splenic activity
- Based on these data, momelotinib may be a preferred initial JAK inhibitor vs ruxolitinib in patients with anemia and low platelet counts, which may warrant further exploration in a prospective study

Discussion/Limitations

- While this analysis is consistent with previous reports linking lower ruxolitinib starting doses in patients with baseline platelet counts <200×10⁹/L to lower SVR35 rates, future studies may be warranted to explore the impact of dose reductions over time in JAK inhibitor–naive patients; most patients with anemia or thrombocytopenia in SIMPLIFY-1 maintained full or near-full doses of momelotinib over time, while use of lower ruxolitinib doses increased[18,19]
- OS results with momelotinib were similar in patients who were transfusion independent at week 24 regardless of whether they also achieved SVR35; interpretation of the impact of SVR35 alone on OS with momelotinib is limited by the fact that only 4 patients achieved SVR35 but not TI
- While these analyses suggest an OS benefit in SVR35+TI responders with momelotinib, formal statistical analysis and adjustment for potential baseline confounders were not feasible due to small sample sizes, and results should be interpreted accordingly; potential interactions between these endpoints cannot be definitively determined
- Given the crossover design of SIMPLIFY-1, evaluation of outcomes beyond week 24 in the ruxolitinib arm was not possible; future prospective studies may be warranted to evaluate comparative response rates and durations with momelotinib vs ruxolitinib and the relative OS impacts of TI and SVR35, particularly in anemic patients with platelet counts <200×10⁹/L

- The overall SVR35 rate with momelotinib (31%) was largely maintained when considering patients who were also transfusion independent at week 24 (SVR35+TI rate, 27%), but few patients achieved dual responses with ruxolitinib (SVR35+TI rate, 7%; difference vs momelotinib, 19; 95% CI, 7-31) (**Figure 3**)
  - SVR35+TI rates were higher with momelotinib across all subgroups
- The combined effects of baseline Hb levels and platelet counts on SVR35 and TI responses are illustrated in **Table 2**
  - In patients with baseline anemia (Hb <10 g/dL), SVR35 rates were higher with momelotinib in patients with baseline platelet counts <200×10⁹/L, and spleen response with ruxolitinib was associated with transfusion need, as dual response rates with transfusion independence were low
    - Notably, no patients with baseline platelet counts of ≥50 to <100×10⁹/L achieved SVR35 with ruxolitinib regardless of baseline anemia status, while the SVR35 rate with momelotinib was 39%

Figure 3: **Dual SVR35+TI Responses at Week 24 in JAK Inhibitor–Naive Patients With Baseline Hb <10 g/dL**



Hb, hemoglobin; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post-polycythemia vera; SVR35, spleen volume reduction ≥35%; TD, transfusion dependence; TI, transfusion independence.

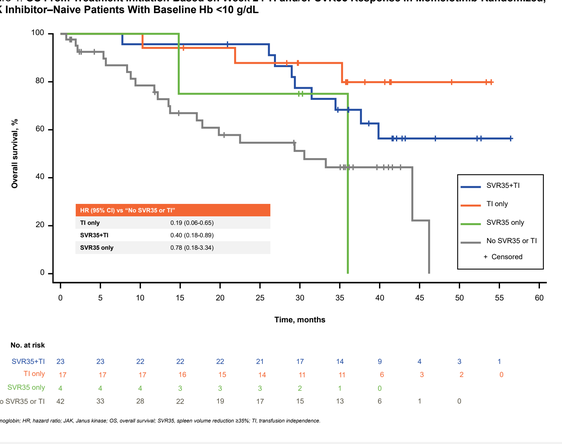
Table 2: **SVR35 and TI at Week 24 in JAK Inhibitor–Naive Patients With Baseline Hb <10 g/dL by Baseline Platelet Counts**

Baseline platelet subgroup	Week 24 endpoint			
		Momelotinib (n=49)	Ruxolitinib (n=47)	Δ with momelotinib
<200×10⁹/L*	SVR35	39%	17%	+22%
	TI[a]	51%	21%	+30%
	SVR35+TI	33%	2%	+31%
		(n=36)	(n=34)	
≥100 to <200×10⁹/L	SVR35	36%	24%	+12%
	TI[a]	50%	24%	+26%
	SVR35+TI	33%	3%	+30%
		(n=13)	(n=13)	
≥50 to <100×10⁹/L	SVR35	46%	0	+46%
	TI[a]	54%	15%	+39%
	SVR35+TI	31%	0	+31%
		Momelotinib (n=37)	Ruxolitinib (n=47)	Δ with momelotinib
>200×10⁹/L	SVR35	22%	49%	−27%
	TI[a]	41%	32%	+9%
	SVR35+TI	19%	13%	+6%

Hb, hemoglobin; JAK, Janus kinase; SVR35, spleen volume reduction ≥35%; TI, transfusion independence.
** Minimum platelet count for enrollment was 50×10⁹/L. [a] The prespecified definition of TI at week 24 was no transfusions and no Hb levels <8 g/dL in the 12 weeks immediately preceding week 24 assessments.*

- OS was longer in patients who were transfusion independent and/or achieved SVR35 with momelotinib at week 24 vs those who did not meet either endpoint, and was similar in patients who were transfusion independent alone or in combination with achieving SVR35 (**Figure 4**)

Figure 4: **OS From Treatment Initiation Based on Week 24 TI and/or SVR35 Response in Momelotinib-Randomized, JAK Inhibitor–Naive Patients With Baseline Hb <10 g/dL**



Hb, hemoglobin; HR, hazard ratio; JAK, Janus kinase; OS, overall survival; SVR35, spleen volume reduction ≥35%; TI, transfusion independence.

Abbreviations

Hb, hemoglobin; HR, hazard ratio; int, intermediate; IPSS, International Prognostic Scoring System; ITT, intent to treat; JAK, Janus kinase; MF, myelofibrosis; NA, not available; OS, overall survival; RBC, red blood cell; PET, post–essential thrombocythemia; PLT, platelet; PPV, post–polycythemia vera; RUX, ruxolitinib; SRR, splenic response rate; SVR, spleen volume reduction; SVR35, spleen volume reduction ≥35%; TD, transfusion dependence; TI, transfusion independence; TR, transfusion requiring; TSS, Total Symptom Score.

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Disclosures

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Presenting author: Francesca Palandri, Francesca.Palandri@unibo.it