Clinical Outcomes of Myelofibrosis Patients Following Immediate Transition to Momelotinib from Ruxolitinib (RUX)

Poster 1733

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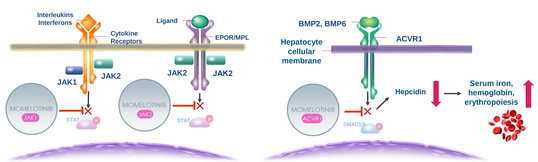
Introduction

- 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 Janus kinase inhibitor (JAKi)-naïve and JAKi-experienced patients with myelofibrosis in the SIMPLIFY-1 (NCT01969838), SIMPLIFY-2 (NCT02101268), and MOMENTUM (NCT04173494) phase 3 studies[1-3]
  - These phase 3 studies have provided extensive experience with momelotinib administered in over 500 patients after receiving RUX
  - This includes patients who transitioned immediately from RUX to momelotinib without tapering or washout of RUX
- Preclinical and clinical translational studies have demonstrated the ability of momelotinib to improve anemia and transfusion dependency via its differentiated suppression of ACVR1-mediated hepcidin production[4,5]
- A majority of patients are at risk for decreased overall survival (OS) after discontinuing RUX.[6] Also, prognostic negative risk factors of spleen length, RUX dose reduction, and red blood cell transfusion requirement predict decreased OS after 6 months of RUX treatment[7]
- Momelotinib has previously demonstrated that achievement of week 24 transfusion independence response (TI-R) is associated with prolonged OS[8]
- Here, we describe a retrospective analysis of data focusing on the timing and clinical outcomes of immediately transitioning patients from RUX to momelotinib



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**[9,10]

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.

Objective

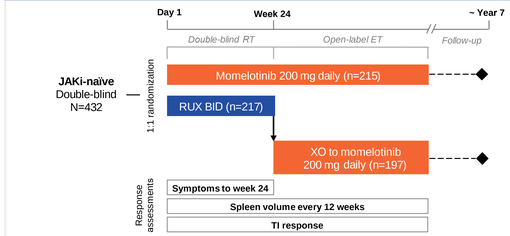
To conduct a retrospective analysis to evaluate the clinical outcomes of administering momelotinib immediately after stopping RUX, without tapering or washout of RUX

Methods

- In the phase 3 SIMPLIFY-1 study, JAKi-naïve patients with myelofibrosis (N=432) were randomized 1:1 to momelotinib or RUX
- After the 24-week (6-month) randomized treatment (RT) period, patients could continue momelotinib (momelotinib → momelotinib) and those randomized to RUX could cross over to open-label (OL) momelotinib (RUX → momelotinib) immediately, without tapering or washout, for up to day 168
- Clinical data including dosing, spleen volume, transfusions, hemoglobin, and safety assessments from week 24 (at crossover [XO]) through OL treatment were analyzed to characterize clinical outcomes after transitioning from RUX to momelotinib. Symptom scores were collected only during RT (baseline to week 24)

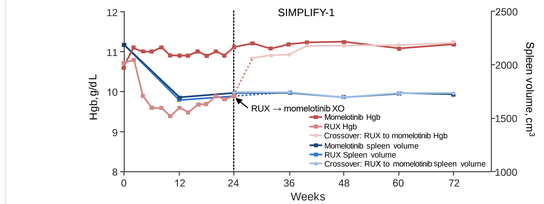
Results

Figure 1. Momelotinib Is the Only Drug Tested Head-To-Head Versus RUX and Has Extensive Experience With Immediate Transition After RUX (SIMPLIFY-1)



BID, twice a day; ET, extended treatment; JAKi, Janus kinase inhibitor; RT, randomized treatment; RUX, ruxolitinib; TI, transfusion independence; XO, crossover.

Figure 2. Momelotinib Provided Rapid Improvement in Hgb and Maintained Splenic Volume After the Transition From RUX to Momelotinib

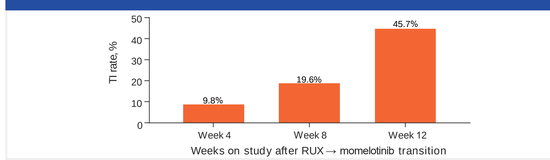


Hgb, n	Momelotinib	215	189	171	147	132	136	114
	RUX	216	208	199	156	139	141	123
Spleen, n	Momelotinib	214	195	184	154	144	128	110
	RUX	217	207	204	166	148	130	119

Hgb, hemoglobin; RUX, ruxolitinib; XO, crossover.

- Reduction in mean spleen volume between momelotinib and RUX was not statistically different over 24 weeks of treatment (*P*=.7853)
- After the RUX to momelotinib transition, mean spleen volume was maintained well beyond week 24

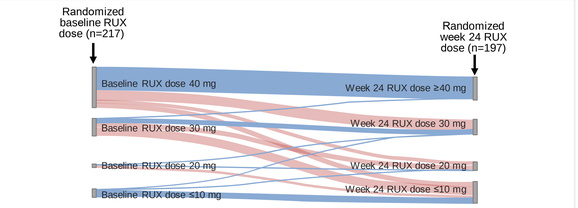
Figure 3. Approximately Half of the RUX-Randomized Patients With Non-TI[a] at Week 24 Converted to TI by 12 Weeks After the Transition to Momelotinib



[a]TD + TR.
RBC, red blood cell; RUX, ruxolitinib; TD, transfusion dependence (defined as requiring RBC transfusion ≥4 units in the 8 weeks before randomization); TI, transfusion independence; TR, transfusion-requiring (defined as patients who required transfusions but did not meet the criteria for TD).

- In SIMPLIFY-1, the proportion of RUX-randomized patients with transfusion independence (TI) decreased from 70% at baseline to 49% at Week 24
- Of the RUX non-TI[a] patients at week 24, 92 crossed over to momelotinib with 45.7% achieving TI at week 12

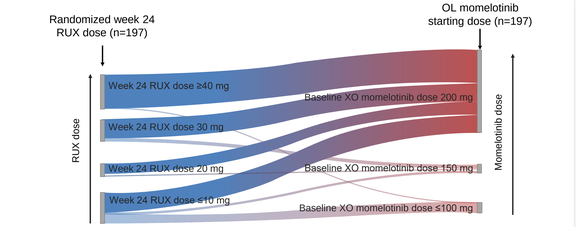
Figure 4A. Over Half of the RUX-Randomized Patients Required Dose Modification by Week 24



RUX, ruxolitinib.

- Of the 217 patients randomized to RUX, 197 crossed over to OL momelotinib. Dosing information was available for all 197 patients who completed 24 weeks of RT with RUX
- RUX patients were dosed twice daily across 4 starting doses (total daily doses of 10, 20, 30, and 40 mg) based on baseline platelets
- Among the 197 patients who completed 24 weeks of RUX treatment, 112 (57%) required a dose modification (interruption or reduction)

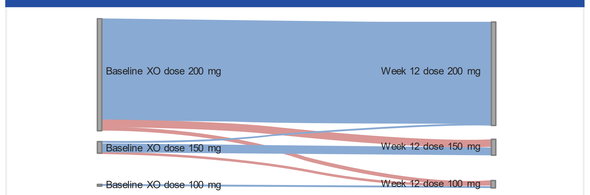
Figure 4B. Transition to Momelotinib Required Infrequent Dose Modifications and Was Very Well Tolerated During Initial Transition Period and Beyond



OL, open-label; RUX, ruxolitinib; XO, crossover.

- At XO to OL momelotinib, 90% (177/197) of patients initiated momelotinib at the full 200-mg daily dose

Figure 4C. OL Momelotinib Dosing Remained Relatively Constant From XO to 12 Weeks After XO



OL, open-label; XO, crossover.

- Of these 177 patients, 133 (75%) remained at 200 mg after 12 weeks

Table 1. Momelotinib Was Well Tolerated Two Weeks After XO From RUX

	RUX → momelotinib (n=197)			Momelotinib → momelotinib (n=171)		
n (%)	Total	Max grade 1/2	Max grade 3/4	Total	Max grade 1/2	Max grade 3/4
Overall	88 (44.7)	69 (35.0)	19 (9.6)	49 (28.7)	43 (25.1)	6 (3.5)
Nausea	14 (7.1)	13 (6.6)	1 (0.5)	3 (1.8)	3 (1.8)	0
Diarrhea	12 (6.1)	11 (5.6)	1 (0.5)	3 (1.8)	3 (1.8)	0
Fatigue	12 (6.1)	10 (5.1)	2 (1.0)	1 (0.6)	1 (0.6)	0
Dizziness	9 (4.6)	9 (4.6)	0	1 (0.6)	1 (0.6)	0
Headache	9 (4.6)	8 (4.1)	1 (0.5)	0	0	0
Pruritus	9 (4.6)	9 (4.6)	0	2 (1.2)	2 (1.2)	0
Anemia	8 (4.1)	2 (1.0)	6 (3.0)	4 (2.3)	1 (0.6)	3 (1.8)
Cough	8 (4.1)	8 (4.1)	0	0	0	0
Rash	6 (3.0)	6 (3.0)	0	1 (0.6)	1 (0.6)	0
Vitamin B1 deficiency	5 (2.5)	5 (2.5)	0	0	0	0
Back pain	4 (2.0)	4 (2.0)	0	0	0	0
Night sweats	4 (2.0)	4 (2.0)	0	2 (1.2)	2 (1.2)	0
Thrombocytopenia	4 (2.0)	0	4 (2.0)	4 (2.3)	4 (2.3)	0

AE, adverse event; RUX, ruxolitinib; XO, crossover.

- In both treatment arms, the majority of AEs within the two weeks after XO from RUX to momelotinib were grade 1-2
- No RUX cytokine release/withdrawal symptoms were observed after immediate transition to momelotinib from RUX

Conclusions

- Momelotinib has undergone unique and extensive analysis in patients who transitioned from RUX without tapering or washout of RUX
- Transitioning to momelotinib from RUX can rapidly improve anemia and shift patients to TI without compromising splenic control
- Momelotinib requires once-daily dosing, infrequent dose modifications, and is very well tolerated during the transition after RUX and beyond
- No symptoms associated with withdrawal were observed when patients transitioned from RUX, which is often a clinical issue when transitioning between JAKis
- Administering momelotinib immediately after RUX, without tapering or washout, is safe, maintains symptom benefit and spleen volume, and improves anemia in patients with myelofibrosis

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Further analysis of momelotinib can be accessed in the oral presentation **627** (MOMENTUM week 48 results) and in the poster presentation **3028** (TI-R and OS).

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