Clinical outcomes of patients with myelofibrosis after immediate transition to momelotinib from ruxolitinib

Janus kinase inhibitors (JAKi) such as ruxolitinib, approved for the treatment of myelofibrosis (MF), confer symptom and spleen improvements but can induce or worsen anemia and thrombocytopenia.[1-4] Although there is no consensus on the definition of JAKi treatment failure in MF, anemia and thrombocytopenia may require a reduction in JAKi dosing or discontinuation, which are associated with poor overall survival.[5-7] In addition, discontinuation from ruxolitinib is complicated by the potential for discontinuation syndrome characterized by acute relapse of symptoms, splenomegaly, anemia, thrombocytopenia, and risk of hemodynamic decompensation,[5,8] with approximately 40% of the cases being moderate or severe according to real-world evidence.[9] Given that discontinuation rates with ruxolitinib are high (up to 89% at 3 years) and dose modifications of ruxolitinib are associated with lower survival,[10,11] we sought to examine how transitioning directly from ruxolitinib to another therapy may be beneficial to patients with MF. Here, we present data from a retrospective analysis of a phase III clinical study (ClinicalTrials.gov identifier: NCT01969838) demonstrating that patients may be better served by a timely transition from ruxolitinib to momelotinib that can help improve anemia while maintaining or improving splenic and symptom responses.

Momelotinib is a potent and selective small-molecule inhibitor of JAK1, JAK2, and activin A receptor type 1 (ACVR1); the inhibition of JAK1 and JAK2 drives symptomatic and splenic benefits while the inhibition of ACVR1 promotes restoration of iron homeostasis and erythropoiesis, resulting in anemia benefits including increased hemoglobin (Hb) levels and reduced need for transfusions.[12-16] Notably, transfusion-independence response with momelotinib has been associated with improved overall survival.[6] Three phase III clinical studies of momelotinib in MF have provided extensive experience with momelotinib administered in more than 500 patients previously treated with ruxolitinib.[12-14] In the SIMPLIFY-1 study, patients in the ruxolitinib-randomized group who crossed over to receive momelotinib at week 24 were immediately administered momelotinib without ruxolitinib tapering or washout.[12] Here, we conducted a retrospective analysis to evaluate the clinical outcomes (i.e., dosing, spleen volume, frequency of transfusions, Hb levels, and occurrence of adverse events) of patients with MF who immediately transitioned from ruxolitinib to momelotinib in SIMPLIFY-1.

In SIMPLIFY-1, JAKi-naïve intermediate- and high-risk patients with primary MF, post-essential thrombocythemia MF, or post-polycythemia vera MF (N=432) were randomized 1:1 to receive momelotinib at 200 mg once daily or ruxolitinib twice daily across four starting doses (5, 10, 15, and 20 mg twice daily) based on baseline platelet counts and other laboratory values. After the 24-week (6-month) randomized treatment period, patients in the momelotinib-randomized group could continue momelotinib (momelotinib→momelotinib), and patients in the ruxolitinib-randomized group could crossover to open-label momelotinib (ruxolitinib→momelotinib) immediately without tapering or washout.[12] After the week 24 crossover into open-label treatment, clinical data including dosing, spleen volume, transfusions, and Hb levels, collected at weeks 4 and 8 after crossover and every 12 weeks thereafter, were analyzed to characterize the transition from ruxolitinib→momelotinib. Transfusion independence was defined as the absence of red blood cell (RBC) transfusion and no Hb level below 8 g/dL in the prior 12 weeks; transfusion dependence was defined as at least four units of RBC transfusions, or a Hb level below 8 g/dL in the previous eight weeks. In addition, safety assessments including recording of adverse events continued throughout open-label treatment.

During randomized treatment, there was no significant difference in mean spleen volume reduction between the momelotinib and ruxolitinib arms (P=0.9853 at week 24), whereas mean Hb level increased with momelotinib and decreased with ruxolitinib (Figure 1A). After 24 weeks of randomized treatment, 197 patients transitioned from ruxolitinib→momelotinib and 171 continued momelotinib→momelotinib. At the first assessment four weeks after crossover from ruxolitinib→momelotinib, mean Hb levels improved rapidly (approx. 1 g/dL), and mean spleen volume was maintained (approx. 1700 cm^3), similar to the mean spleen volume for momelotinib→momelotinib patients (Figure 1A). Patients continuing momelotinib treatment in the open-label phase maintained Hb levels that increased after two weeks of momelotinib treatment in the randomized phase. Mean platelet counts were generally maintained in patients randomized to momelotinib during both randomized and open-label treatment. For patients randomized to ruxolitinib, the mean platelet counts decreased by approximately $100x10^9$/L during the first four weeks of treatment from a mean baseline platelet count of $301x10^9$/L and remained at lower levels throughout the randomized phase; after crossover from ruxolitinib→momelotinib, mean platelet counts improved throughout open-label

momelotinib treatment and converged with momelotinib→momelotinib by week 48 (*Online Supplementary Figure S1*).

Of the patients in the ruxolitinib-randomized group, 70% were transfusion independent at baseline, which dropped to 49% at week 24.[12] Of the 92 ruxolitinib-randomized patients who were not transfusion independent at week 24 who crossed over to receive momelotinib, 42 (46%) became transfusion independent by week 12 after crossover (Figure 1B).

Among the 197 patients who completed 24 weeks of ruxolitinib treatment, 112 (57%) required a ruxolitinib dose modification (Figure 2A). Among patients who crossed over to receive open-label momelotinib from ruxolitinib after randomized treatment, 90% (177/197) initiated momelotinib at the 200 mg daily dose (Figure 2B), with the majority of patients maintaining full-dose treatment at 200 mg momelotinib after 12 weeks (Figure 2C). Notably, of the 71 patients who received a mean of ≤10 mg twice daily ruxolitinib over the four weeks before crossover, only 10% achieved a spleen response (≥35% volume reduction from baseline) at week 24 (before crossover); following crossover, 23% achieved or maintained spleen response at week 48.

Safety observations during the immediate 2-week period after ruxolitinib→momelotinib crossover revealed that the transition was well tolerated (Table 1); new onset grade 3/4 anemia and thrombocytopenia were experienced by

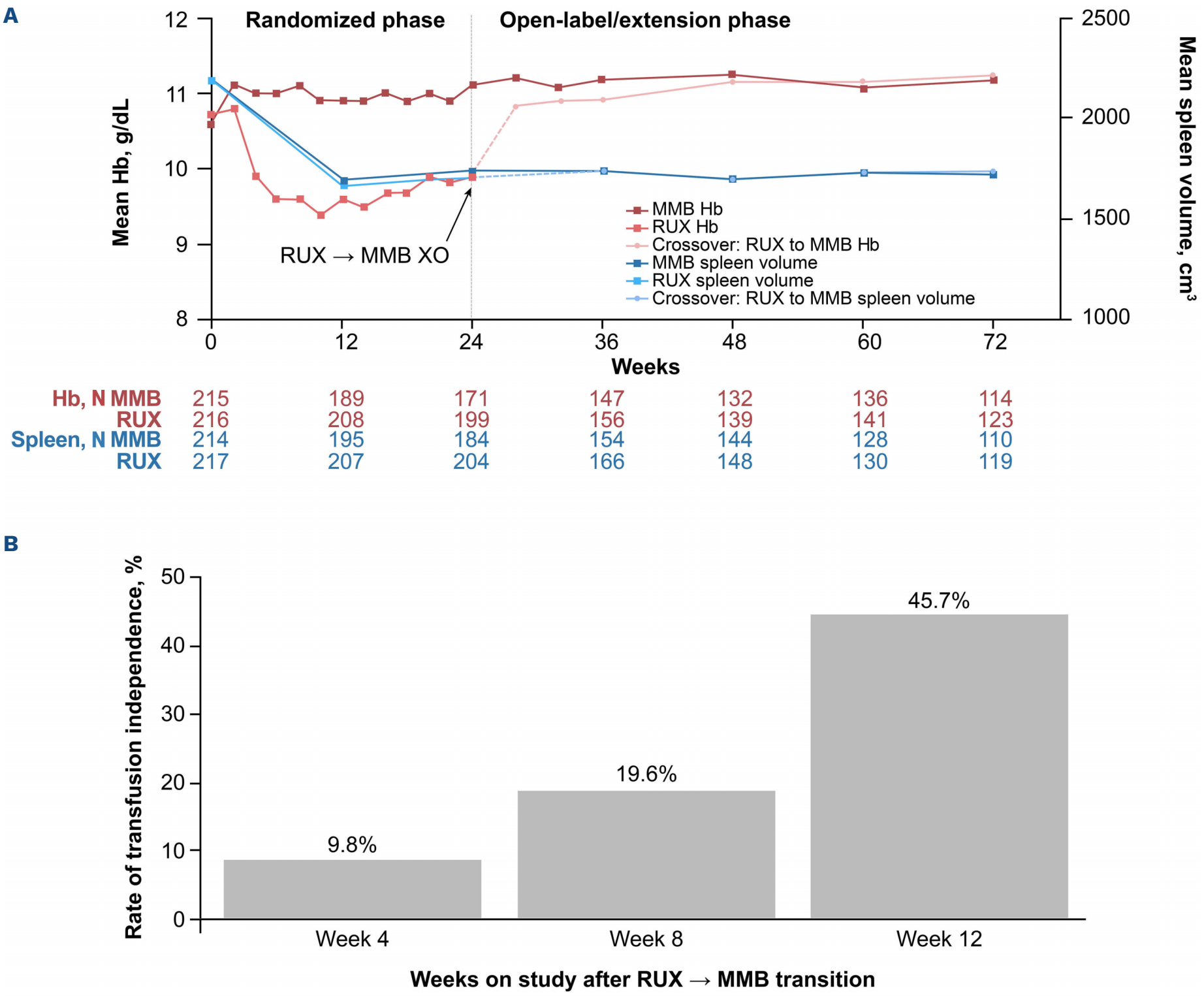

Figure 1. Clinical efficacy of momelotinib after immediate crossover from ruxolitinib in the SIMPLIFY-1 study. (A) Hemoglobin (Hb) and spleen volume dynamics in patients randomized to momelotinib→momelotinib or ruxolitinib→momelotinib. (B) Transfusion-independence rate after transition to open-label momelotinib at week 24 in non–transfusion-independent ruxolitinib-randomized patients (N=92). MMB: momelotinib; RUX: ruxolitinib; XO: crossover.

only 3% and 2% of patients, respectively, with no cases of ruxolitinib discontinuation syndrome, namely, no acute relapse of symptoms or splenomegaly, worsening of cytopenias, or hemodynamic decompensation, including acute respiratory distress syndrome and shock.[8] More broadly, the new onset adverse events (by preferred term) of any grade experienced within two weeks of ruxolitinib→momelotinib transition occurred at a rate of ≤7% each. Weight gain was higher with ruxolitinib than momelotinib during the randomized treatment period (weight change 0.9 ± 3.28 kg for momelotinib group *vs.* 3.3 ± 3.82 kg for ruxolitinib group [mean ± standard deviation]) but body weight remained

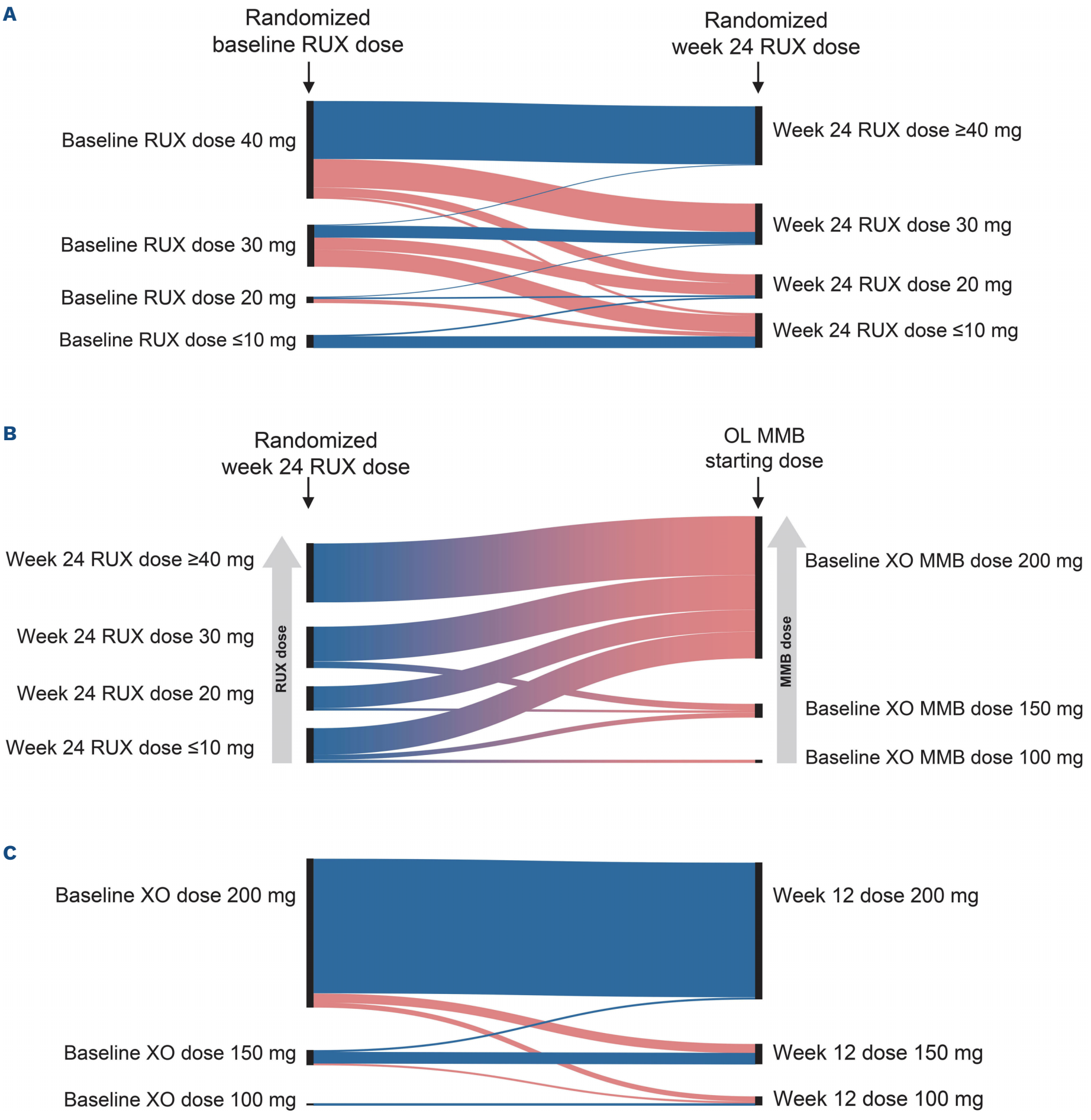

Figure 2. Dosing in ruxolitinib-randomized patients in the SIMPLIFY-1 study. (A) Dosing from baseline to week 24 of ruxolitinib treatment. (B) Dosing at crossover from ruxolitinib→momelotinib. (C) Dosing from baseline momelotinib at crossover to week 12 of open-label momelotinib treatment. MMB: momelotinib; OL: open label; RUX: ruxolitinib; XO: crossover.

Table 1. Adverse events in the two weeks after crossover at week 24 in the SIMPLIFY-1 study.

Adverse events, N (%)	Ruxolitinib→Momelotinib N=197			Momelotinib→Momelotinib N=171		
	Overall	Maximum grade 1/2	Maximum grade 3/4	Overall	Maximum grade 1/2	Maximum 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

stable and did not increase further after ruxolitinib→momelotinib crossover (*Online Supplementary Figure S2*).

Momelotinib is a promising new therapy for MF. Data from the completed, randomized, phase III SIMPLIFY-1 study of momelotinib *versus* ruxolitinib provide a unique opportunity to evaluate transition to open-label momelotinib therapy in the extended treatment phase without tapering or washout of prior randomized treatment with ruxolitinib. Transition to momelotinib from ruxolitinib did not result in symptoms associated with ruxolitinib withdrawal, and control of spleen volume was maintained. Most patients tolerated full-dose momelotinib including those previously on low-dose ruxolitinib. In addition, transition to momelotinib was associated with rapid improvement in anemia and a shift toward transfusion independence. These data are consistent with those of SIMPLIFY-2, an international, randomized, open-label, phase III study conducted to evaluate the efficacy and safety of momelotinib *versus* best available therapy (ruxolitinib accounting for 88.5% of best available therapy) in patients with intermediate- or high-risk primary MF, post-essential thrombocythemia MF, or post-polycythemia vera MF whose prior treatment with ruxolitinib was associated with anemia or thrombocytopenia.[13] Washout was prohibited for patients receiving active MF therapy at screening; 72% of those randomized to momelotinib (75 of 104) continued ruxolitinib until the day of randomization. Similar to SIMPLIFY-1, spleen volume control was maintained with transition to momelotinib treatment (*Online Supplementary Figure S3*); transition to momelotinib also provided symptom and anemia improvements in conjunction with an acceptable safety profile.[13]

These analyses provide confidence in an immediate transition to momelotinib from ruxolitinib without washout or tapering, which is likely to rapidly improve anemia without compromising safety or control of symptoms and spleen. The recently published Response to Ruxolitinib After 6 Months criteria modeled predictors of survival in patients with MF after six months of ruxolitinib.[11] This multivariate model included negative risk factors of spleen length, ruxolitinib dose reduction, and RBC transfusion requirement; in this analysis, 45% were considered at intermediate risk and 36% at high risk of poor survival after six months of ruxolitinib therapy. These findings suggest that most patients with anemia on ruxolitinib therapy or those receiving low-dose ruxolitinib therapy should transition to a different therapy that can improve anemia and maintain recommended dose levels while also maintaining or improving on splenic and symptom responses.

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Contributions

JK, BK, MH and BS contributed to the study design. RM, SV, UP, VG, DL, PG, CR, J-JK, STO, ATG, TD, FP, AMV, ME, EL-M, AP, LN, DM, MH and CH contributed to data acquisition. JK, BK, MH and BS conducted the data analysis. MH performed the statistical analysis. All authors contributed to data interpretation, reviewed and provided important intellectual contributions to the manuscript, and approved the final version for publication.

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Data-sharing statement

Sierra Oncology commits to sharing clinical study data with qualified researchers to enable enhancement of public health. As such, Sierra will share anonymized patient-level data on request or if required by law or regulation. Qualified scientific and medical researchers can request patient-level data for studies of Sierra pharmaceutical substances listed on ClinicalTrials.gov and approved by health authorities in the USA and the EU. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after US Food and Drug Administration and European Medicines Agency approvals. Such requests are assessed at Sierra's discretion, and the decisions depend on the scientific merit of the proposed request, data availability, and the purpose of the proposal. If Sierra agrees to share clinical data for research purposes, the applicant is required to sign an agreement for data sharing before data release, to ensure that the patient data are deidentified. In case of any risk of reidentification on anonymized data despite measures to protect patient confidentiality, the data will not be shared. The patients' informed consent will always be respected. If the anonymization process will provides futile data, Sierra will have the right to refuse the request. Sierra will provide access to patient-level clinical trial analysis datasets in a secured environment upon execution of the data-sharing agreement. Sierra will also provide the protocol, statistical analysis plan, and the clinical study report synopsis if needed. For additional information or requests for access to Sierra clinical trial data for research purposes, please contact us at GSKClinicalSupportHD@gsk.com.

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