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Received: March 9, 2023.
Accepted: May 24, 2023.


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Author 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.

Running head: Momelotinib outcomes immediately after ruxolitinib

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Disclosures:
RM reports grants or contracts from AbbVie, Celgene, CTI Biopharma, Constellation Biopharma, Genotech, Incyte, Promedior, Samus Therapeutics, and the Mays Cancer Center P30 Cancer Center Support Grant from the National Cancer Institute (CA054174), and consulting fees from Constellation Biopharma, La Jolla, Novartis, and Sierra Oncology. SV reports consulting fees from Bristol Myers Squibb/Celgene, Incyte, Novartis, and Sierra Oncology; and research funding from AstraZeneca, Blueprint Medicines, Bristol Myers Squibb/Celgene, CTI BioPharma, Genentech, Gilead, Incyte, Italfarmaco, Novartis, NS Pharma, PharmaEssentia, and Promedior. UP reports consulting fees from AbbVie, Bristol Myers Squibb/Celgene, Janssen, and Novartis; honoraria from Amgen, Jazz Pharmaceuticals, and Takeda; and participation on data safety monitoring board or advisor board for AbbVie and Novartis. VG reports consulting fees from AbbVie, Bristol Myers Squibb/Celgene, Constellation Biopharma, Novartis, Pfizer, and Sierra Oncology; honoraria from Bristol Myers Squibb/Celgene, Constellation Biopharma, and Novartis; and participation on data safety monitoring board or advisory board for AbbVie, Bristol Myers Squibb/Celgene, Pfizer, and Roche. CR reports grants or contracts from AbbVie, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, and IQVIA; honoraria
and travel support from AbbVie, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, and Servier; and participation on a data safety monitoring board or advisory board for AbbVie, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Servier, and Takeda. J-JK reports honoraria from Novartis, and participation on a data safety monitoring board or advisory board for AbbVie, AOP Orphan, Bristol Myers Squibb, Incyte, and Novartis. STO reports consulting fees from AbbVie, Blueprint Medicines, Bristol Myers Squibb/Celgene, Constellation Pharmaceuticals, CTI BioPharma, Disc Medicine, Incyte, Kartos Therapeutics, PharmaEssentia, and Sierra Oncology. ATG reports consulting fees from AbbVie, Bristol Myers Squibb, Constellation/MorphoSys, CTI Biopharma, Novartis, PharmaEssentia, and Sierra Oncology. TD reports consulting fees from AOP Health, Bristol Myers Squibb/Celgene, Incyte, and MorphoSys, and honoraria from Novartis and Sobi. FP reports grants or contracts from Bristol Myers Squibb; consulting fees from AbbVie, AOP, Bristol Myers Squibb/Celgene, Janssen, Karyopharm Therapeutics, Kyowa Kirin, MEI Pharma, Novartis, Roche, and Sierra Oncology; and honoraria from AbbVie, Bristol Myers Squibb/Celgene, Janssen, Novartis, and Sierra Oncology. AMV reports honoraria from AbbVie, Blueprint Medicines, Bristol Myers Squibb, GSK, Incyte, and Novartis, and participation on a data safety monitoring board or advisory board for AbbVie, Blueprint Medicines, Bristol Myers Squibb, GSK, Incyte, MorphoSys, Novartis, and Roche. AP reports honoraria from Kedrion Biopharma. KS reports honoraria from Novartis and Takeda. DM reports grants or contracts from CPI, and honoraria from AbbVie, Bristol Myers Squibb/Celgene, Jazz Pharmaceuticals, and Novartis. JK reports employment at Sierra Oncology, and stock or stock options at Gilead Sciences and Sierra Oncology. BK and MH report employment and stock options at Sierra Oncology. BS reports employment at Sierra Oncology. CH reports grants or contracts from Bristol Myers Squibb/Celgene, Constellation Pharmaceuticals, and Novartis; consulting fees from AOP, Galecto, Keros, and Roche; honoraria from AbbVie, Celgene, Constellation Pharmaceuticals, CTI BioPharma, Janssen, and Novartis; participation in data safety monitoring board or advisory board for AbbVie, AOP, CTI BioPharma, Geron, Promedior, Roche, and Sierra Oncology; and leadership or fiduciary role in the European Hematology Association and MPN Voice. DL, PG, ME, EL-M, and LN declare no competing interests.

**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
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Word count: 1369/1500

Trial registration: ClinicalTrials.gov identifier: NCT01969838

Acknowledgments: We thank the patients and families who participated in the trial and all study investigators. Medical writing and editorial support was provided, based on the authors’ input and in accordance with ICMJE and GPP3 guidelines, by Second City Science, which was supported by Sierra Oncology, a GSK company.

Funding: This study was sponsored by Sierra Oncology, a GSK company.
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.\textsuperscript{1-4} Although there is no consensus on the definition of JAKi treatment failure in MF, anemia and thrombocytopenia may necessitate attenuated JAKi dosing or discontinuation, which are associated with poor overall survival.\textsuperscript{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,\textsuperscript{5, 8} with approximately 40\% of the cases being moderate or severe according to real-world evidence.\textsuperscript{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,\textsuperscript{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 study, 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 levels and reduced need for transfusions.\textsuperscript{12-16} Notably, transfusion-independence response with momelotinib has been associated with improved overall survival.\textsuperscript{6} Three phase 3 clinical studies of momelotinib in MF have provided extensive experience with momelotinib administered in more than 500 patients previously treated with ruxolitinib.\textsuperscript{12-14} In SIMPLIFY-1, patients in the ruxolitinib-randomized group who crossed over to receive momelotinib at week 24 were immediately administered momelotinib without ruxolitinib tapering or washout.\textsuperscript{12} Here, we conducted a retrospective analysis to evaluate the clinical outcomes (ie, dosing, spleen volume, frequency of transfusions, hemoglobin 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 4 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 week 24 crossover into open-label treatment, clinical data including dosing, spleen volume, transfusions, and hemoglobin 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 transfusion and no hemoglobin level below 8 g/dL in the prior 12 weeks; transfusion dependence was defined as at least 4 units of red blood cell transfusions, or a hemoglobin level below 8 g/dL in the prior 8 weeks. In addition, safety assessments including recording of adverse events continued throughout open-label treatment.

During randomized treatment, mean spleen volume reduction was not significantly different between the momelotinib and ruxolitinib arms (p=0.9853 at week 24), whereas mean hemoglobin 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 4 weeks after crossover from ruxolitinib→momelotinib, mean hemoglobin levels improved rapidly (~1 g/dL), and mean spleen volume was maintained (~1700 cm³), similar to the mean spleen volume for momelotinib→momelotinib patients (Figure 1A). Patients continuing momelotinib treatment in the open-label phase maintained hemoglobin levels that increased after 2 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 ~100
× 10^9/L during the first 4 weeks of treatment from a mean baseline platelet count of 301 × 10^9/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 (Supplemental Figure 1).

Of the patients in the ruxolitinib-randomized group, 70% were transfusion independent at baseline, which dropped to 49% at week 24. 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 4 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 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. More broadly, the new onset adverse events (by preferred term) of any grade experienced within 2 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 of 0.9 ± 3.28 kg for momelotinib group vs 3.3 ± 3.82 kg for ruxolitinib group [mean ± standard deviation]) but body
weight remained stable and did not increase further after ruxolitinib→momelotinib crossover
(Supplemental Figure 2).

Momelotinib is a promising new therapy for MF. Data from the completed, randomized, phase 3 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 3 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 (Supplemental Figure 3); 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 modelled predictors of survival in patients with MF after 6 months of ruxolitinib.11 This multivariate model included negative risk factors of spleen length, ruxolitinib dose reduction, and red blood cell transfusion requirement; in this analysis, 45% were considered intermediate and 36% high risk of poor
survival after 6 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.
References

Table 1. Adverse events in the 2 weeks after crossover at week 24 in SIMPLIFY-1.

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Ruxolitinib→Momelotinib (n=197)</th>
<th>Momelotinib→Momelotinib (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Maximum Grade 1/2</td>
</tr>
<tr>
<td>Overall</td>
<td>88 (44.7)</td>
<td>69 (35.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (7.1)</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (6.1)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (6.1)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (4.6)</td>
<td>9 (4.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (4.6)</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (4.6)</td>
<td>9 (4.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (4.1)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (4.1)</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (3.0)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Vitamin B1 deficiency</td>
<td>5 (2.5)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (2.0)</td>
<td>4 (2.0)</td>
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<td>Night sweats</td>
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<td>Thrombocytopenia</td>
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</table>
Figure legends

**Figure 1.** Clinical efficacy of momelotinib after immediate crossover from ruxolitinib in SIMPLIFY-1. (A) Hemoglobin 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). Hgb, hemoglobin; MMB, momelotinib; RUX, ruxolitinib; XO, crossover.

**Figure 2.** Dosing in ruxolitinib-randomized patients in SIMPLIFY-1. (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.
Supplemental Figure 1.

**Randomized phase**

**Open-label/extension phase**

Mean platelet count, $\times 10^9/L$

- **MMB** 214 187 181 182 165 171 164 150 146 138 126
- **RUX** 216 204 200 202 192 190 189 174 164 151 132

Weeks
Supplemental Figure 2.

![Graph of mean weight over weeks for two phases: Randomized phase and Open-label/extension phase. The graph shows the mean weight in kg for MMB (brown squares) and RUX (pink squares). The data points are as follows:

**MMB**: 214, 201, 190, 190, 183, 179, 172, 166, 162, 158, 145
**RUX**: 216, 213, 207, 209, 207, 204, 200, 187, 176, 163, 144

Weeks range from 0 to 48 with measurements at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
Supplemental Figure 3.

![Graph showing the change in Hgb and spleen volume over weeks in two phases: Randomized and Open-label/extension. The graph includes data points for MMB Hgb, BAT Hgb, Crossover: BAT to MMB Hgb, MMB spleen volume, BAT spleen volume, and Crossover: BAT to MMB spleen volume.]

| Hgb, n MMB | BAT | 104 | 83 | 70 | 53 | 46 | 45 | 40 |
| Spleen, n MMB | BAT | 52 | 41 | 40 | 29 | 19 | 19 | 19 |
| Hgb, n MMB | BAT | 104 | 81 | 70 | 48 | 45 | 37 | 36 |
| Spleen, n MMB | BAT | 52 | 41 | 39 | 26 | 21 | 19 | 18 |