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倫 理 審 査 申 請 書

TMGあさか医療センター
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I) 研究課題名

『骨髄線維症に対するルキシロチニブ、モメロチニブの有効性・安全性の検討』

II) 研究の種類

☐ 疫学研究

☐ 臨床研究 観察研究

☐ 臨床研究 介入あり

☐ その他

III) 研究代表者の氏名・所属・職名

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所 属：血液内科

職 名：血液内科部長

IV) 研究の概要（何がどこまで明らかにされているか）

(1) 研究の目的

原発性骨髄線維症(PMF)は 100 万人あたり 3 名程度と稀な骨髄増殖性腫瘍で、日本における生存期間中央値は 3.9 年とされ、比較的予後不良である。発症年齢中央値は 66 歳と比較的高齢で、男性に多い。貧血や脾腫に伴う腹部膨満感・食思不振、全身倦怠感などで発症する。予後指標に DIPSS, DIPSS-Plus などがあるが、中間-2 リスク、高リスクは同種造血幹細胞移植を行うか、JAK2 阻害剤による治療が推奨されている。

リスク群	IPSS		DIPSS		DIPSS-plus	
	原報	日本	原報	日本	原報	日本
低リスク	11.3	18.6	到達せず	18.6	15.4	18.6
中間-1 リスク	7.9	5.5	14.2	4.3	6.5	10.7
中間-2 リスク	4.0	3.2	4	3.0	2.9	3.7
高リスク	2.3	2.4	1.5	2.9	1.3	2.2

生存期間中央値(年)(診断時より)

(骨髄線維症診療の参照ガイド第6版より抜粋引用)

JAK2 阻害剤はルキシロチニブが 2014 年に日本国内で使用可能となった。2024 年 8 月にモメロチニブが発売され、骨髄線維症患者に対し使用されている。PMF が稀な疾患であることやモメロチニブが発売から日が浅いこともあり、実臨床での有効性、安全性は不明である。

(2) 研究の対象及び方法

・当院で 2020 年 8 月から 2026 年 3 月までに通院、治療を行なった PMF 患者 13 名を対象とする。特にモメロチニブを使用した 5 名の臨床経過、有効性、安全性について後方視的に検討する。また、ルキシロチニブを使用している患者、他の治療法を行なっている患者の有効性、安全性についても検討する。

(3) 実施場所

・TMG あさか医療センター 6B 病棟、及び外来

(4) 研究期間

西暦 倫理委員会承認 ～ 2026 年 12 月 31 日

V) 研究における倫理的配慮について

(1) 研究対象となる個人の人権擁護

・本研究は、治療介入を伴わない後方視的研究であるため、新たに採取する試料はない。本研究は当院単独研究であり、外部に情報を持ち出すことがないため匿名化は不要である。

(2) 研究対象となる個人への理解を求め、同意を得る方法

・本研究は侵襲を伴わず、治療介入を一切行わない後方視的研究であるため、「人を対象とする医学系研究に関する倫理指針」によると、患者個人に対しての同意取得は必要ないものとする。ただし、TMG あさか医療センターのホームページ上で、本研究が実施されていることを通知または公開し拒否機会の保障を確保する。

(3) 生じうる個人の利益及び不利益並びに危険性の予測

・本研究は治療介入を伴わない後方視的研究のため、研究に参加することによる不利益および危険性はない。利益についても後方視的研究のため直接的な利益はない。

(4) その他（判断能力の乏しい対象者への対処など）

・成人に対しての後方視的研究でありホームページ上での公開で対応する。

VI) 引用文献・その他参考文献など

1, Mesa RA, et al. SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor-Naïve Patients With Myelofibrosis. *J Clin Oncol*. 2017; 35:3844-3850.

SIMPLIFY-1: A Phase III Randomized Trial of Mometotinib Versus Ruxolitinib in Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis

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A B S T R A C T

Purpose

We evaluated the efficacy and safety of momelotinib, a potent and selective Janus kinase 1 and 2 inhibitor (JAKi), compared with ruxolitinib, in JAKi-naïve patients with myelofibrosis.

Patients and Methods

Patients (N = 432) with high risk or intermediate-2 risk or symptomatic intermediate-1 risk myelofibrosis were randomly assigned to receive 24 weeks of treatment with momelotinib 200 mg once daily or ruxolitinib 20 mg twice a day (or per label), after which all patients could receive open-label momelotinib. The primary end point was a $\geq 35\%$ reduction in spleen volume at 24 weeks of therapy. Secondary end points were rates of symptom response and effects on RBC transfusion requirements.

Results

A $\geq 35\%$ reduction in spleen volume at week 24 was achieved by a similar proportion of patients in both treatment arms: 26.5% of the momelotinib group and 29% of the ruxolitinib group (noninferior; $P = .011$). A $\geq 50\%$ reduction in the total symptom score was observed in 28.4% and 42.2% of patients who received momelotinib and ruxolitinib, respectively, indicating that noninferiority was not met ($P = .98$). Transfusion rate, transfusion independence, and transfusion dependence were improved with momelotinib (all with nominal $P \leq .019$). The most common grade ≥ 3 hematologic abnormalities in either group were thrombocytopenia and anemia. Grade ≥ 3 infections occurred in 7% of patients who received momelotinib and 3% of patients who received ruxolitinib. Treatment-emergent peripheral neuropathy occurred in 10% of patients who received momelotinib (all grade ≤ 2) and 5% of patients who received ruxolitinib (all grade ≤ 3).

Conclusion

In JAKi-naïve patients with myelofibrosis, 24 weeks of momelotinib treatment was noninferior to ruxolitinib for spleen response but not for symptom response. Momelotinib treatment was associated with a reduced transfusion requirement.

J Clin Oncol 35:3844-3850. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by anemia, extramedullary hematopoiesis, splenomegaly, and often-debilitating constitutional symptoms.¹ Approximately 90% of patients with MF harbor mutations in *JAK2*, *CALR*, or *MPL* leading to constitutive activation of Janus kinase (JAK)–signal transducers and activators of transcription signaling.²⁻⁴ Currently, the only US Food and Drug Administration–approved treatment of MF is ruxolitinib, a JAK inhibitor (JAKi) that has demonstrated therapeutic benefit in the

control of symptomatic splenomegaly and constitutional symptoms in patients with or without the *JAK2* mutation.⁵⁻⁷ Common hematologic adverse events (AEs) with ruxolitinib treatment include anemia and thrombocytopenia, which can lead to dose reductions or treatment interruptions.^{6,7} Therefore, an unmet need exists for new therapeutic options that improve responses while reducing anemia and other toxicities associated with currently available therapies.

Mometotinib is an investigational, oral, small-molecule inhibitor of JAK1/2 with selectivity over other tyrosine and serine/threonine kinases.⁸⁻¹⁰ In preclinical studies, momelotinib has also demonstrated

ASSOCIATED CONTENT



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Appendix
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Data Supplement
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inhibition of the bone morphogenic protein receptor kinase activin A receptor, type I (ACVR1)–mediated expression of hepcidin in the liver, thereby increasing iron availability for erythropoiesis.¹⁰ Thus, there is a rationale for the use of mometotinib in patients with MF where anemia remains a challenging clinical problem. A phase I/II study evaluating mometotinib in MF demonstrated reduction in spleen volume, improvement of MF-associated symptoms, and reduction of RBC transfusion requirements in patients with MF.¹¹ In this analysis, we report the results of the phase III trial, Mometotinib Versus Ruxolitinib in Subjects With Myelofibrosis (SIMPLIFY-1) in JAKi-naïve patients with MF that compares the efficacy and safety of mometotinib versus ruxolitinib. A companion trial, SIMPLIFY-2, compares mometotinib with best available therapy in MF in patients who experienced either suboptimal responses or toxicity to ruxolitinib.¹²

PATIENTS AND METHODS

Patient Eligibility, Stratification, and Treatment

Patients were ≥ 18 years of age with palpable splenomegaly ≥ 5 cm below the left costal margin and a confirmed diagnosis of primary MF (WHO criteria¹³) or post-polycythemia vera or post-essential thrombocythemia MF (International Working Group for Myelofibrosis Research and Treatment [IWG-MRT] criteria¹⁴). Patients were classified as International Prognostic Scoring System¹⁵ high risk, intermediate-2 risk, or intermediate-1 risk with symptomatic splenomegaly or hepatomegaly or anemia (hemoglobin [Hb] < 10.0 g/dL) and/or unresponsive to available non-JAKi therapy. Within 14 days before the first dose of study treatment, the following laboratory tests were required: absolute neutrophil count $\geq 0.75 \times 10^9/L$ in the absence of growth factor therapy in the prior 7 days; platelet count $\geq 50 \times 10^9/L$ ($\geq 100 \times 10^9/L$ if AST or ALT $\geq 2 \times$ upper limit of normal [ULN]) in the absence of platelet transfusion(s) or thrombopoietin mimetics in the prior 7 days; peripheral blood blasts $< 10\%$, AST and ALT $\leq 3 \times$ ULN ($\leq 5 \times$ ULN if liver is involved by extramedullary hematopoiesis as judged by the investigator or if related to iron chelator therapy that was started within the prior 60 days); and creatinine clearance ≥ 45 mL/min and direct bilirubin $\leq 2.0 \times$ ULN. Patients had Eastern Cooperative Oncology Group performance status¹⁶ ≤ 2 and life expectancy > 24 weeks. Patients with prior use of a JAKi, prior splenectomy, spleen irradiation < 3 months before the first dose of study treatment, certain cancers (history or concurrent disease), or uncontrolled intercurrent illness that would limit study compliance as judged by the treating physician, or who were eligible for allogeneic stem-cell transplantation, were excluded.

This study had a 24-week double-blind double-dummy treatment phase. Patients were randomly assigned by an interactive web-based response system 1:1 to either mometotinib (200 mg once daily) or ruxolitinib 20 mg twice a day (or modified as per label). Treatment assignment was stratified by transfusion dependence (yes or no; defined as ≥ 4 units of RBCs or Hb level < 8 g/dL in the 8 weeks before random assignment, excluding patients associated with clinically overt bleeding) and by platelet count ($< 100 \times 10^9/L$, $\geq 100 \times 10^9/L$ and $\leq 200 \times 10^9/L$, or $> 200 \times 10^9/L$). After completion of the double-blind treatment phase, patients were eligible to receive mometotinib in an open-label phase.

Study Design

This was a multicenter, randomized, double-blind phase III clinical trial. The study was approved by institutional review boards/independent ethics committees, and all participants provided written consent. Clinic visits were at screening (initial visit and ensuing assessments to determine eligibility), baseline (visit < 10 days before random assignment), random assignment (visit for administration of first dose of study drug), and every

2 weeks during the double-blind phase. Patients completed the modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (TSS) using an electronic diary daily from screening through the double-blind phase. Eastern Cooperative Oncology Group performance status and laboratory assessments were done during clinic visits, and abdominal magnetic resonance imaging (MRI) or computed tomography (CT) scans were performed every 12 weeks. A record of all transfusions received during screening and throughout the study was kept in the patients' diaries.

Statistical Analysis and End Points

The primary end point was a reduction of $\geq 35\%$ in spleen volume from baseline at week 24 (spleen response rate, SRR24), as assessed by MRI or CT scan and evaluated by a blinded central reader. The primary hypothesis was that mometotinib is noninferior to ruxolitinib. On the basis of the assumption of the common treatment effect on SRR being 34% (lower bound of the 95% CI on the ruxolitinib effect on SRR) that was observed in the Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment (COMFORT-1)⁷, a total sample size of 420 provides $> 90\%$ power for testing the noninferiority hypothesis on SRR24. Noninferiority of mometotinib was determined by whether the lower bound of the two-sided 95% CI for the noninferiority difference (SRR24 of mometotinib $- 0.6 \times$ SRR24 of ruxolitinib) was > 0 and was calculated based on the stratum-adjusted Cochran-Mantel-Haenszel (CMH) proportion.

Four end points at week 24 were designated as secondary end points for which sequential testing was performed in the order listed to control the type 1 error rate: TSS response rate (proportion of patients who achieved a $\geq 50\%$ reduction from baseline to week 24 on the basis of the modified Myeloproliferative Neoplasm Symptom Assessment Form TSS diary); RBC transfusion-independence rate (proportion of patients who were transfusion-independent at week 24 [absence of RBC transfusions and no Hb < 8 g/dL in the prior 12 weeks]); RBC transfusion-dependence rate (proportion of patients who were transfusion-dependent [≥ 4 units of RBC transfusions, or Hb < 8 g/dL in the prior 8 weeks]); and rate of RBC transfusion (average number of RBC units per subject-month during treatment). Most secondary end points were evaluated similarly to the primary end point (CMH approach), with the exception of the RBC transfusion rate, which was analyzed using a negative binomial regression method adjusted for stratification factors with an offset parameter to account for follow-up time. The primary end point analysis served as the gatekeeper for the secondary end point analyses, such that only if the primary efficacy hypothesis was rejected could the formal, statistical testing be undertaken for the four secondary efficacy end points sequentially in the order listed above. If a null hypothesis was not rejected, formal sequential testing was stopped and only nominal significance would be cited for the remaining secondary end points.

Exploratory end points included overall response rate, which was defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) according to the IWG-MRT and/or European LeukemiaNet (ELN)¹⁷ criteria. The composite clinical improvement rate was defined as the proportion of patients who achieved CR and PR on the basis of IWG-MRT and/or ELN response criteria or who achieved anemia response, MRI/CT spleen response, or TSS response at week 24.

Efficacy end points were analyzed in the intent-to-treat population consisting of all patients randomly assigned, except TSS response rate, which was analyzed in all randomly assigned patients with baseline TSS > 0 or with baseline TSS of 0, but week 24 TSS missing or > 0 . Patients without baseline and/or week 24 visit assessments for the corresponding end point were regarded as splenic nonresponders, TSS nonresponders, not transfusion independent, or transfusion dependent at week 24. Differences between treatment arms for continuous end points were assessed using analysis of covariance, with treatment and stratification factors as factors and baseline values as covariates. Differences between treatment arms were compared using CMH approach after adjusting for stratification factors. Sensitivity analyses for the primary end point included analysis on per-protocol analysis set, using last observation carried forward for missing data, unstratified method, and fixed margin method. Treatment-emergent AEs were monitored

continuously, graded for severity and relationship to treatment, and summarized by treatment group.

RESULTS

Patient Characteristics and Disposition

Between December 6, 2013 and September 12, 2016, 127 study centers enrolled patients in this international, multicenter trial. A total of 432 patients underwent random assignment, of whom 215 were assigned to receive momelotinib and 217 were assigned to receive ruxolitinib; 214 in the momelotinib group and 216 in the ruxolitinib group received one or more doses of study drug. Treatment discontinuation was reported for 18.6% and 7.4% of patients in the momelotinib and ruxolitinib groups, respectively. The baseline and demographic characteristics were similar between groups (Table 1). Most patients were white (82.6%), male (56.5%), and ≥ 65 years of age (57.2%), and 56.5% had primary MF. The median (first-third quartiles, Q1-Q3) time since diagnosis was 1.5 years (0.4 to 3.9 years). The 24-week double-blind phase was completed by 376 patients (momelotinib (n = 175), ruxolitinib (n = 201); 368 patients continued in the open-label phase of the study (171 from the momelotinib group and 197 from the ruxolitinib group switched to momelotinib). Patient disposition and availability for assessments are shown in Appendix Figure A1 (online only).

Spleen Assessments

Overall, 184 patients who received momelotinib and 204 patients who received ruxolitinib had assessments available for SRR24. Figure 1 shows individual patients' spleen response as measured by MRI or CT scan. Spleen volume was reduced $\geq 35\%$ from baseline in 26.5% (57 of 215) of patients who received momelotinib and 29.0% (63 of 217) of patients who received ruxolitinib, with a noninferiority proportion difference of 0.09 (95% CI, 0.02 to 0.16). Because the lower bound of the two-sided 95% CI was > 0 , momelotinib met the primary end point of noninferiority to ruxolitinib ($P = .011$). Sensitivity analyses were consistent with the primary analysis.

Secondary End Points

A total of 175 patients who received momelotinib and 190 patients who received ruxolitinib had assessments available for TSS. Fewer patients who received momelotinib (28.4%, 60 patients) had a reduction in TSS of $\geq 50\%$ from baseline compared with those who received ruxolitinib (42.2%, 89 patients), indicating less symptomatic improvement in patients who received momelotinib (Fig 2A). The noninferiority proportion difference was 0.00 (95% CI, -0.08 to 0.08); because the lower bound of the two-sided 95% CI was not > 0 , noninferiority of momelotinib to ruxolitinib was not met ($P = .98$). Median scores for individual symptoms were generally low at baseline (medians ranged from 2 to 4 of a possible 10). Greatest improvements were seen in pain under left ribs, night sweats, and itching, and larger relative changes were seen with ruxolitinib compared with momelotinib (Fig 2B).

Because noninferiority of momelotinib to ruxolitinib on response rate in TSS at week 24 was not met, formal sequential

Table 1. Patient Baseline Characteristics

Characteristic	Momelotinib (n = 215)	Ruxolitinib (n = 217)
Mean age, years (SD)	65.0 (10.67)	64.4 (10.59)
Male	124 (57.7)	120 (55.3)
Mean body mass index, kg/m ² (SD)	24.9 (4.02)	25.3 (3.99)
Race		
White	179 (83.3)	178 (82.0)
Black	2 (0.9)	2 (0.9)
Asian	17 (7.9)	20 (9.2)
Ethnicity Hispanic or Latino	6 (2.8)	4 (1.8)
Myelofibrosis subtype		
Primary	128 (59.5)	116 (53.5)
Post-polycythemia vera	48 (22.3)	50 (23.0)
Post-essential thrombocythemia	39 (18.1)	51 (23.5)
IPSS risk category		
Intermediate-1	46 (21.4)	43 (19.8)
Intermediate-2	76 (35.3)	67 (30.9)
High	93 (43.3)	107 (49.3)
JAK2V617F mutation		
Previously tested	187 (87.0)	194 (89.4)
Positive	125 (58.1)	141 (65.0)
Negative	61 (28.4)	53 (24.4)
Not previously tested	28 (13.0)	23 (10.6)
TSS score, mean (SD)	19.4 (13.18)	17.9 (11.47)
ECOG performance status		
0	76 (35.3)	72 (33.2)
1	122 (56.7)	120 (55.3)
2	17 (7.9)	25 (11.5)
Mean Hb, g/dL (SD)	10.6 (2.10)	10.7 (2.38)
Hb ≥ 8 g/dL	186 (86.5)	195 (89.9)
Transfusion independent	147 (68.4)	152 (70.0)
Transfusion dependent	53 (24.7)	52 (24.0)
Mean platelet count, $\times 10^3/\mu\text{L}$ (SD)	301.1 (207.03)	301.5 (255.88)
Mean absolute neutrophil count, $\times 10^3/\mu\text{L}$ (SD)	12.0 (13.39)	11.3 (11.04)

NOTE. Data presented as No. (%) unless otherwise noted. No significant between-group differences in any of the listed baseline characteristics.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; IPSS, International Prognostic Scoring System; TSS, total symptom score.

testing was stopped and only nominal significance was reported for the remaining α -controlled secondary end points. More patients who received momelotinib were transfusion independent at week 24 (66.5%) compared with the ruxolitinib group (49.3%; nominal $P < .001$; Fig 3A). Fewer patients who received momelotinib were transfusion dependent at week 24 (30.2%) compared with those who received ruxolitinib (40.1%; nominal $P = .019$; Fig 3B). The median rate of RBC transfusion through week 24 was 0 units/mo in the momelotinib group compared with 0.4 units/mo in the ruxolitinib group (nominal $P < .001$; Fig 3C).

More patients achieved two or more of the predefined end points (SRR24, TSS response, or transfusion independence) at week 24 in the momelotinib group (38.6%) than in the ruxolitinib group (34.6%). The proportion of patients who achieved all three end points was also higher with momelotinib (10.2%) than with ruxolitinib (7.8%; Fig 4).

Exploratory End Points

The best overall response rate at any time on the basis of IWG-MRT and/or ELN criteria was 5.1% (11 patients, two with CR and nine with PR) in the momelotinib group and 3.2% (seven patients, two with CR and five with PR) in the ruxolitinib group. Composite clinical improvement was numerically greater in the momelotinib

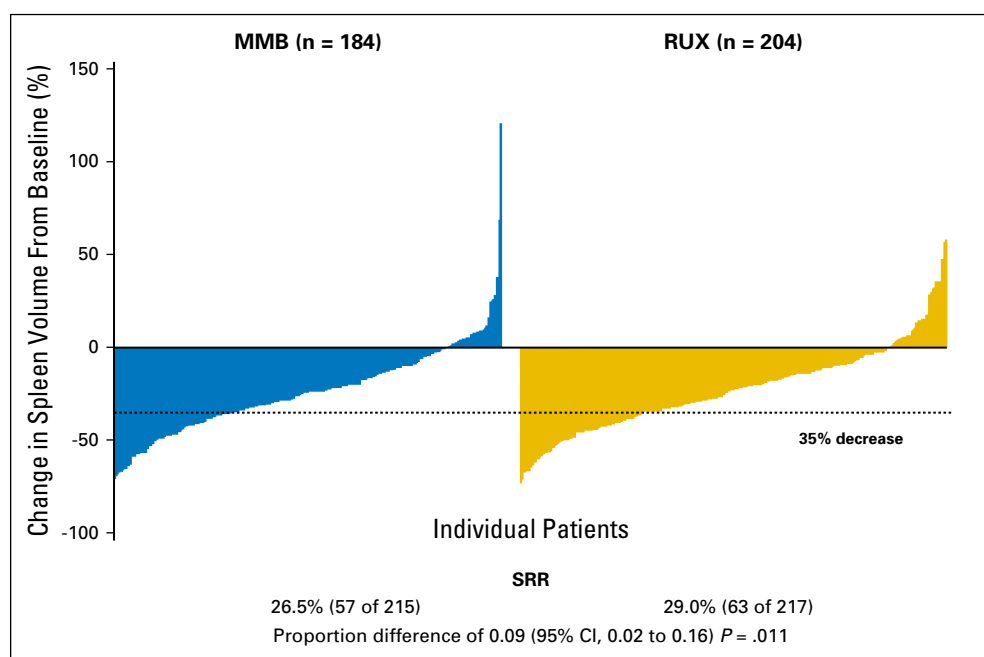


Fig 1. Change in spleen volume and spleen response rate (percentage of patients with a $\geq 35\%$ reduction in spleen volume) at week 24. MMB, momelotinib; RUX, ruxolitinib; SRR, spleen response rate.

group at 35.3% (76 patients) compared with the ruxolitinib group at 27.2% (59 patients).

Safety

During the 24-week treatment phase, the mean duration of exposure to study drug was 21.3 weeks (range, 0.3 to 26.1 weeks) for momelotinib and 23.3 weeks (range, 1.3 to 26.9 weeks) for ruxolitinib; 26.2% of patients who received momelotinib and 56.0% of patients who received ruxolitinib had dose reductions or interruptions of active study drug, most frequently for AEs (17.3% and 35.6%, respectively). Most patients (momelotinib, 92.1%; ruxolitinib, 95.4%) had one or more AE. The most common treatment-emergent AEs are listed in Table 2. AEs that were grade ≥ 3 were reported for 35.5% of patients who received momelotinib and 43.5% of patients who received ruxolitinib; the most commonly reported grade 3 or 4 AEs with momelotinib were thrombocytopenia (7.0%), anemia (5.6%), and diarrhea, hypertension, and neutropenia (2.8% each). The most commonly reported grade 3 or 4 AEs with ruxolitinib were anemia (23.1%), neutropenia and thrombocytopenia (4.6% each), and hypertension (4.2%). Serious AEs were reported for 22.9% of patients who received momelotinib and 18.1% of patients who received ruxolitinib. AEs that lead to discontinuation of active study drug were reported for 13.1% of patients who received momelotinib and 5.6% of patients who received ruxolitinib. AEs that lead to dose reduction or temporary interruption of active study drug were reported for 17.8% of patients who received momelotinib and 36.6% of patients who received ruxolitinib.

A smaller proportion of patients died or had leukemic transformation in the momelotinib group (15 patients [7.0%]) compared with the ruxolitinib group (20 patients [9.2%]), although the difference was not statistically significant. Deaths were reported for seven (3.3%) patients who received momelotinib

(enteritis, mesenteric vein thrombosis, death, sudden death, sepsis, renal failure, and aortic dissection [one patient each]) and seven (3.2%) patients who received ruxolitinib (melena, sepsis, pneumonia, head injury, acute myeloid leukemia, recurrent mantle cell lymphoma, and coma [one patient each]). Transformation to acute myeloid leukemia occurred in one patient who received momelotinib (grade 4) and two patients who received ruxolitinib (grade 3 and grade 5).

Peripheral neuropathy was reported in both groups (momelotinib, 22 patients [10.3%], 28 events; ruxolitinib, 10 patients [4.6%], 11 events). Two patients in the momelotinib group and one patient in the ruxolitinib group had peripheral neuropathy at baseline. The most frequently reported term was peripheral sensory neuropathy (8.4% in the momelotinib group and 4.6% in the ruxolitinib group); additional reported terms were neuropathy peripheral, neuralgia, and peripheral motor neuropathy (momelotinib group only). These AEs were grade 1 to 2, with the exception of grade 3 peripheral sensory neuropathy, reported for one patient (0.5%) in the ruxolitinib group. No patients discontinued momelotinib or ruxolitinib because of peripheral neuropathy.

A total of 17 events considered related to first-dose effects were reported for 14 patients (6.5%) in the momelotinib group: hypotension (3.3%), dizziness (1.9%), flushing (1.4%), nausea (0.9%), and headache (0.5%). All events considered related to first-dose effects were grade 1 to 2, with the exception of one grade 3 event (hypotension), which was also reported as serious and resulted in a dose reduction. In the ruxolitinib group, AEs considered related to first-dose effects were reported for two patients (0.9%) who experienced grade 1 dizziness. No event in the ruxolitinib group was reported as serious.

DISCUSSION

SIMPLIFY-1 evaluated the efficacy and safety of momelotinib compared with ruxolitinib in patients who had not received prior

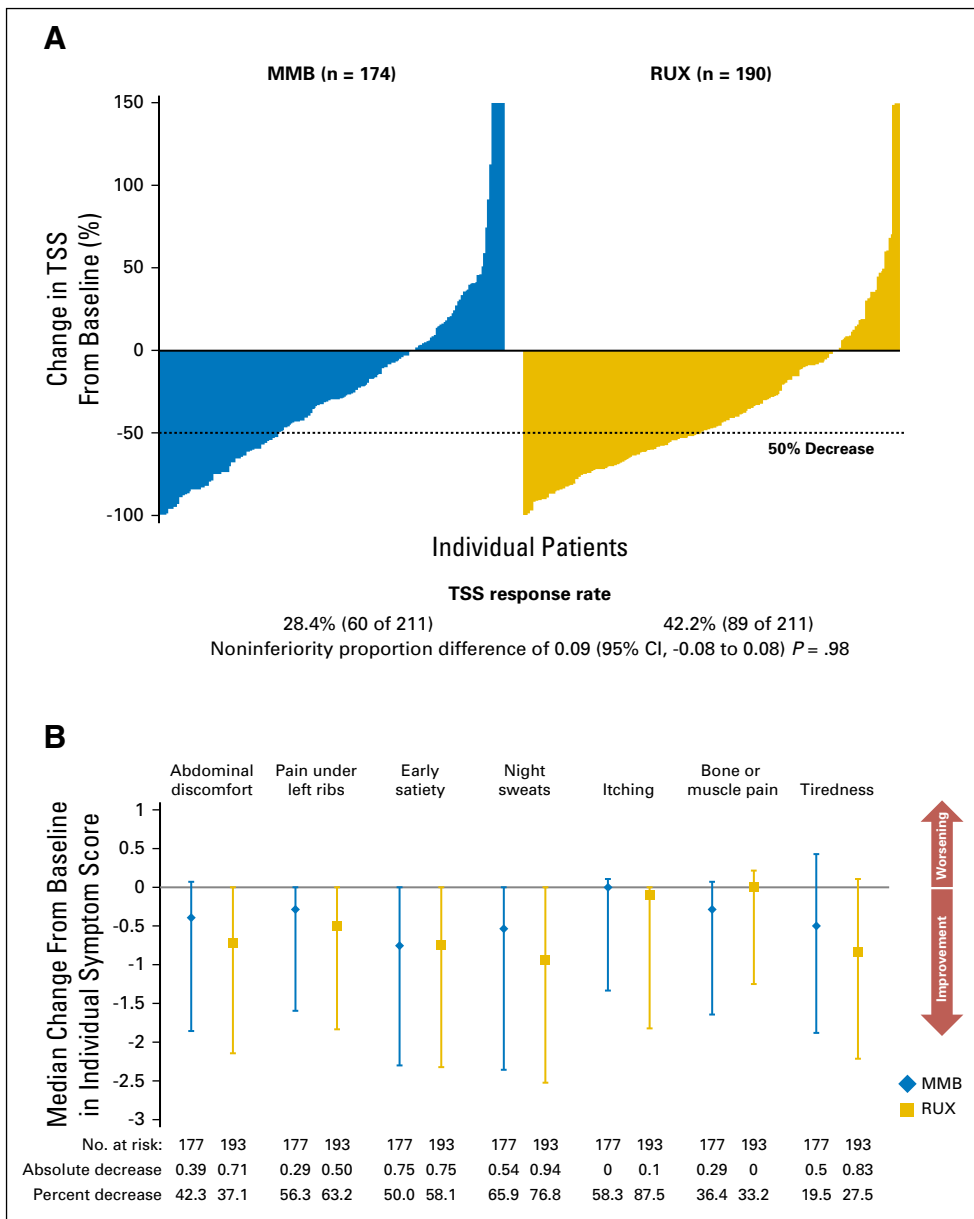


Fig 2. (A) Change in Total Symptom Score (TSS) from baseline and TSS response rate (percentage of patients with $\geq 50\%$ reduction in TSS) at week 24. (B) Absolute and percent changes in individual symptoms of the Myeloproliferative Neoplasm Symptom Assessment Form from baseline to week 24. MMB, momelotinib; RUX, ruxolitinib.

treatment with a JAKi. The study met the prespecified primary end point of noninferiority for spleen response but not the key secondary end point of symptomatic improvement. The proportion of patients who achieved a $\geq 50\%$ reduction in TSS with ruxolitinib in this study (42%) was comparable to that in the registrational COMFORT-1 study (46%), whereas momelotinib here achieved this response in only 28%. Note that the COMFORT-1 control group TSS response rate was 5%.⁷ The reduction in TSS by momelotinib here was also consistent with that observed in the second-line study, SIMPLIFY-2 (ClinicalTrials.gov identifier: NCT02101268).¹² One possible explanation is that momelotinib and ruxolitinib differ in inhibition of cytokines mediating disease-related symptoms. Both drugs decreased inflammatory cytokines, but neither the baseline level of the cytokines nor the extent of decrease of the cytokines was associated with TSS response for either treatment (data not shown). Despite the anemia benefit of

momelotinib, there was a greater reduction in fatigue with ruxolitinib, which suggests that fatigue is multifactorial and not only related to anemia.

Although momelotinib did not demonstrate an improvement over ruxolitinib for TSS, it did improve all three anemia end points and the composite clinical improvement (composite of SRR24, TSS response, and transfusion independence end points). Furthermore, more patients treated with momelotinib achieved two or more clinical improvements (SRR, TSS, or transfusion independence) than patients treated with ruxolitinib. Objective laboratory measures such as Hb, serum iron, and transferrin saturation also favored momelotinib (Appendix, online only). Momelotinib is a negative regulator of hepcidin in the liver through its inhibitory effect on the ACVR1 pathway, increasing the release of iron from sequestered cellular stores and enhancing erythropoiesis in a nonclinical study.¹⁰ This may be one mechanism underlying the anemia

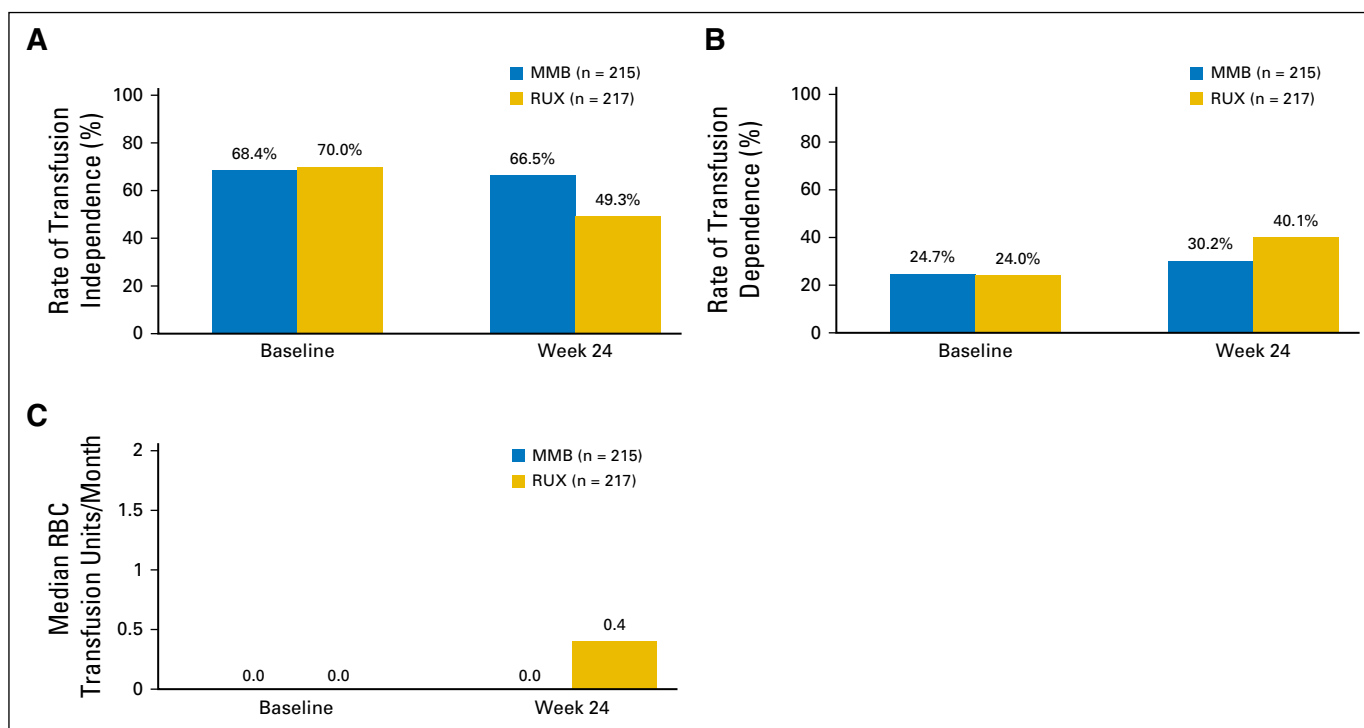


Fig 3. Comparison of momelotinib (MMB) and ruxolitinib (RUX) effects on transfusion requirements at week 24. (A) RBC transfusion independence rate (no RBC transfusion and no hemoglobin [Hb] < 8 g/dL in the prior 12 weeks; nominal $P < .001$). (B) RBC transfusion dependence rate (≥ 4 units of RBC transfusion or Hb < 8 g/dL in the prior 8 weeks; nominal $P = .019$). (C) Rate of RBC transfusions through week 24 (nominal $P < .001$).

response observed in patients who received momelotinib. In contrast, ruxolitinib has no activity associated with the ACVR1 pathway.

The safety profile of momelotinib in patients with MF showed fewer events of anemia and thrombocytopenia compared with ruxolitinib and a higher incidence of nausea. Peripheral neuropathy, a predominant nonhematologic AE in earlier studies, was not substantially more common with momelotinib than with ruxolitinib,

nor did it lead to discontinuation for patients in either group. The mechanism of action driving peripheral neuropathy is not known, and there do not seem to be specific risk factors for momelotinib-associated peripheral neuropathy.¹⁸

In sum, these results were mixed and indicate that although momelotinib may offer less symptom control than ruxolitinib, there is a comparable spleen response and a potential benefit in terms of anemia. Given the broad range of phenotypes in MF and

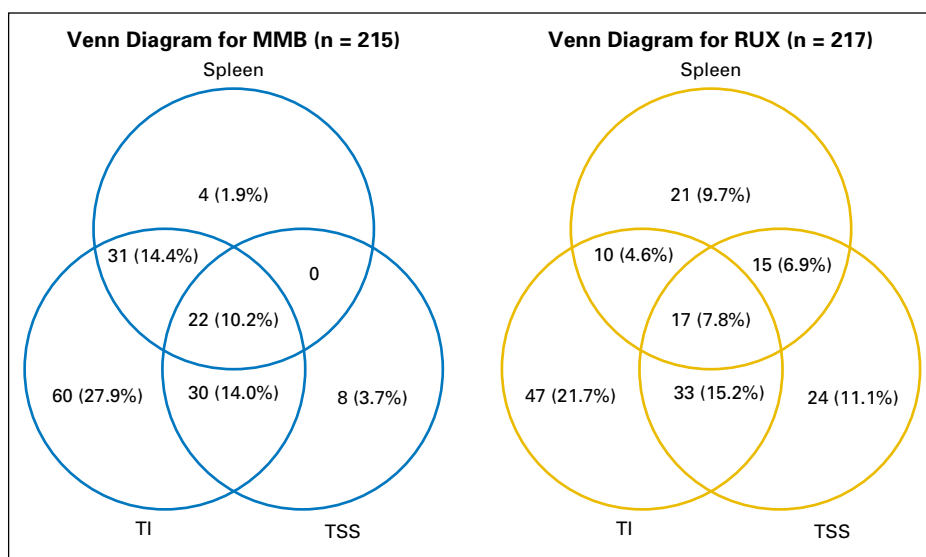


Fig 4. Patients (n, %) who achieved spleen response ($\geq 35\%$ reduction in spleen volume), Total Symptom Score (TSS) response ($\geq 50\%$ reduction in score), and transfusion independence (TI; no RBC transfusion and no Hb < 8 g/dL in the prior 12 weeks) at week 24. MMB, momelotinib; RUX, ruxolitinib.

Table 2. Treatment-Emergent Adverse Events Occurring in $\geq 10\%$ of Either Treatment Group

Treatment-Emergent Adverse Event	Double-Blind Phase	
	Momelotinib (n = 214)	Ruxolitinib (n = 216)
Thrombocytopenia	40 (18.7)	63 (29.2)
Diarrhea	38 (17.8)	43 (19.9)
Headache	37 (17.3)	43 (19.9)
Dizziness	34 (15.9)	25 (11.6)
Nausea	34 (15.9)	8 (3.7)
Fatigue	31 (14.5)	26 (12.0)
Anemia	29 (13.6)	82 (38.0)
Abdominal pain	22 (10.3)	24 (11.1)

NOTE. Data presented as No. (%).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTERESTDisclosures provided by the authors are available with this article at jco.org.**AUTHOR CONTRIBUTIONS****Conception and design:** Ruben A. Mesa, Wei Deng, Jason Gotlib**Provision of study materials or patients:** Ruben A. Mesa, John V.

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different treatment needs for individual patients, treatment decisions might also consider these tradeoffs, should momelotinib gain approval for this indication. Long-term efficacy and safety studies are warranted in the JAKi-naïve patient population and in patients who have received prior JAKi treatment.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis

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Appendix

Methods

The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Total Symptom Score (TSS) is a validated instrument developed to assess symptom severity in patients with myeloproliferative neoplasms (Emanuel RM, et al: J Clin Oncol 30:4098-4103, 2012). The MPN-SAF TSS was originally derived from the MPN-SAF that evaluates symptom experience and quality of life among patients with MPNs as the total score of 10 symptom items from the larger measure (Scherber R, et al: Blood 118:401-408, 2011). The MPN-SAF is a modified myelofibrosis symptom assessment form that captures the symptom and effect experience of the entire spectrum of patients with MPNs, including patients with polycythemia vera and essential thrombocythemia. The 10-item MPN-SAF TSS was revised to result in the modified MPN-SAF TSS used in this study. The modified MPN-SAF TSS v2.0 used in this study contained eight questions, only seven of which were used to generate the score. The included questions were related to tiredness, early satiety, abdominal discomfort, night sweats, itching, bone pain, and pain under the ribs on the left side.

Safety

Objective laboratory measures such as hemoglobin (Hb), serum iron, and transferrin saturation all favored momelotinib over ruxolitinib. Mean serum Hb levels were consistently higher in the momelotinib group than in the ruxolitinib group for the duration of double-blind treatment. The mean (SD) maximum percent increase in Hb from baseline during treatment was 15.0% (14.86%) for the momelotinib group and 7.5% (13.82%) for the ruxolitinib group. At week 24 (end of treatment), the mean (SD) percent change from baseline in Hb was 6.9% (16.00%) for the momelotinib group and -6.5% (14.74%) for the ruxolitinib group.

Serum iron and transferrin saturation at week 24 are shown in Appendix Table A1 (online only). Compared with patients treated with momelotinib, those treated with ruxolitinib tended to have higher serum iron and transferrin saturation at week 24. There were 9% and 23% of patients with transferrin saturation > 50% at week 24 in the momelotinib and ruxolitinib groups, respectively.

Table A1. Iron and Transferrin Saturation at Week 24

Median (Q1, Q3)	Momelotinib (n = 170)	Ruxolitinib (n = 193)
Iron, $\mu\text{g/dL}$	74.0 (47.0-103.0)	102.0 (78.0-139.0)
Transferrin saturation, %	27.0 (17.0-36.0)	37.0 (26.0-47.0)
Abbreviation: Q, quartile.		

Momelotinib v Ruxolitinib in JAK Inhibitor-Naïve Myelofibrosis

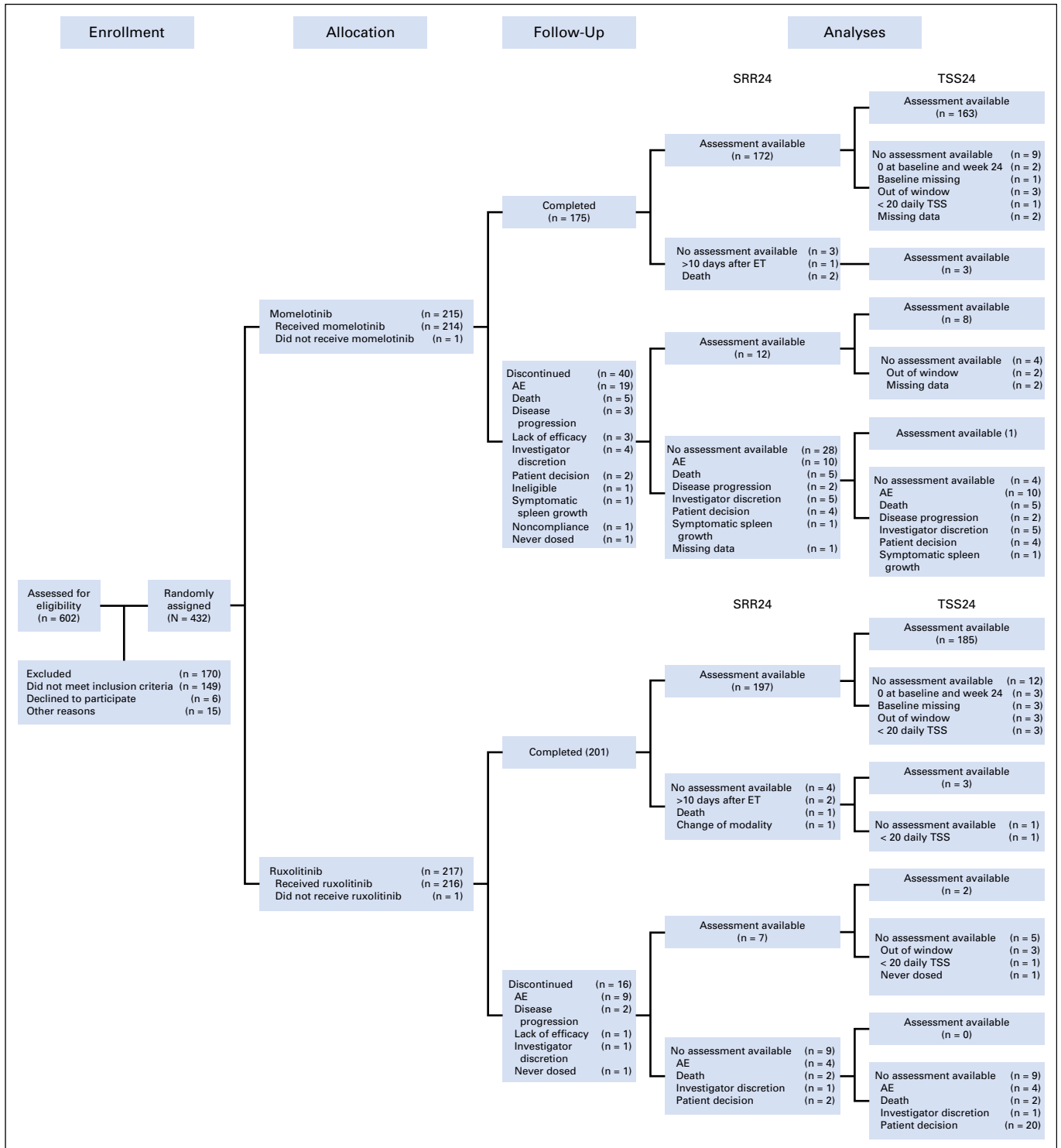


Fig A1. Patient disposition and availability for assessments. AE, adverse effect; ET, essential thrombocythemia; SSR24, spleen response rate at 24 weeks; TSS24, Total Symptom Score at 24 weeks.