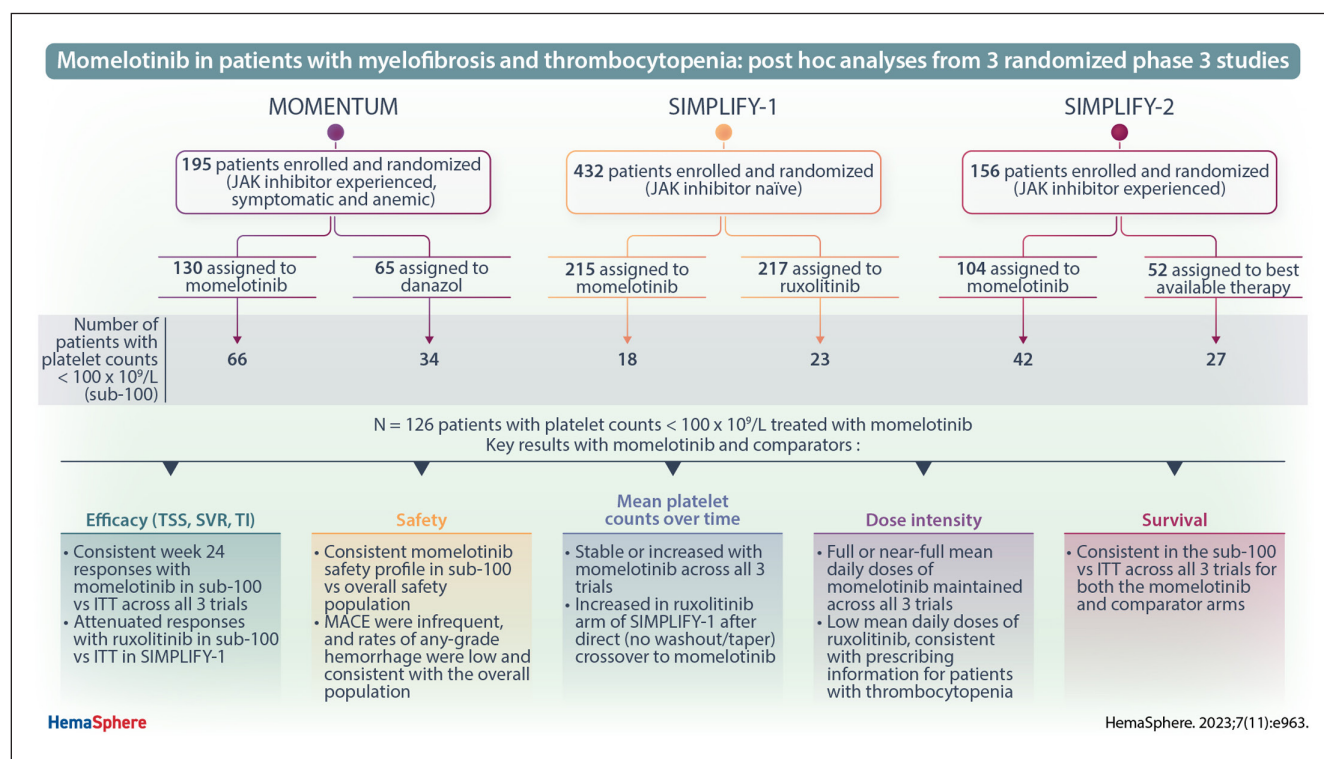**Article**
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Momelotinib in Myelofibrosis Patients With Thrombocytopenia: Post Hoc Analysis From Three Randomized Phase 3 Trials

Jean-Jacques Kiladjian[1] ⓘ, Alessandro M. Vannucchi[2], Aaron T. Gerds[3], Vikas Gupta[4], Srdan Verstovsek[5], Miklos Egyed[6], Uwe Platzbecker[7], Jiří Mayer[8,9], Sebastian Grosicki[10], Árpád Illés[11], Tomasz Woźny[12], Stephen T. Oh[13], Donal McLornan[14], Ilya Kirgner[15,16], Sung-Soo Yoon[17,18,19], Claire N. Harrison[20], Barbara Klencke[21], Mei Huang[21], Jun Kawashima[21], Ruben Mesa[22]

GRAPHICAL ABSTRACT

HemaSphere. 2023;7(11):e963.

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ABSTRACT

The oral activin A receptor type I, Janus kinase 1 (JAK1), and JAK2 inhibitor momelotinib demonstrated symptom, spleen, and anemia benefits in intermediate- and high-risk myelofibrosis (MF). Post hoc analyses herein evaluated the efficacy and safety of momelotinib in patients with MF and thrombocytopenia (platelet counts $<100 \times 10^9$/L) from randomized phase 3 studies: MOMENTUM (momelotinib versus danazol; JAK inhibitor experienced); SIMPLIFY-1 (momelotinib versus ruxolitinib; JAK inhibitor naïve); and SIMPLIFY-2 (momelotinib versus best available therapy; JAK inhibitor experienced); these studies were not statistically powered to assess differences in thrombocytopenic subgroups, and these analyses are descriptive. The treatment effect of momelotinib versus ruxolitinib on week 24 response rates (spleen volume reduction ≥35%/Total Symptom Score reduction ≥50%/transfusion independence) was numerically comparable or better in thrombocytopenic patients versus the overall JAK inhibitor naive population; rates were preserved with momelotinib in thrombocytopenic patients but attenuated with ruxolitinib (momelotinib: 27%/28%/67% overall versus 39%/35%/61% in thrombocytopenic group; ruxolitinib: 29%/42%/49% overall versus 0%/22%/39% in thrombocytopenic group, respectively). In contrast to ruxolitinib, momelotinib maintained high dose intensity throughout the treatment. In the JAK inhibitor experienced population, thrombocytopenic patients had the following: (1) numerically higher symptom and transfusion independence response rates with momelotinib than in control arms; and (2) preserved spleen, symptom, and transfusion independence response rates with momelotinib relative to the overall study populations. The safety profile of momelotinib in thrombocytopenic patients was also consistent with the overall study population. In summary, momelotinib represents a safe and effective treatment option for patients with MF and moderate-to-severe thrombocytopenia.

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INTRODUCTION

Myelofibrosis (MF) is a clonal myeloproliferative neoplasm characterized by splenomegaly, constitutional symptoms, and cytopenias.[1] Despite advances in treating MF-associated splenomegaly and symptoms with the approval of Janus kinase (JAK) inhibitors, disease- and treatment-associated cytopenias remain challenging.[2] Thrombocytopenia (platelet counts <100×10⁹/L), commonly associated with anemia and transfusion dependence in MF, occurs in ≈21%–25% of patients at diagnosis and in up to 70% of patients at any time during the disease course and is an adverse prognostic factor for leukemia-free survival (LFS) and overall survival (OS).[3–7]

Ruxolitinib, a JAK1 and JAK2 inhibitor, was the first JAK inhibitor approved for adults with intermediate- or high-risk MF. It reduced spleen size and symptoms but grade ≥3 cytopenias occurred frequently (anemia: 42%–45%; thrombocytopenia: 8%–13%).[8–10] Although ruxolitinib remains the most widely prescribed JAK inhibitor for the treatment of MF, reduced starting doses are required for patients with baseline platelet counts <200×10⁹/L, and dose-limiting myelosuppression is common.[8] Worsening thrombocytopenia commonly results in dose reductions to as little as 25% of the standard dose.[11] In the real world, approximately one-third of patients initiate ruxolitinib at a lower dose than recommended[12–14] and an estimated 41%–64% of patients discontinue ruxolitinib within 3 years,[14,15] most often due to treatment-related cytopenias.[12,15] Rapid increases in spleen size and symptoms have been observed with ruxolitinib dose reductions,[16] and ruxolitinib discontinuation is associated with poor survival, particularly for patients with thrombocytopenia.[12] Grade ≥3 cytopenias were also common with fedratinib (anemia: 38%–43%; thrombocytopenia: 17%–22%), a JAK2 and FMS-like tyrosine kinase 3 inhibitor.[17–19] Fedratinib approval came with a boxed warning on the risk of serious and fatal encephalopathy including Wernicke.[19] The JAK2 inhibitor pacritinib is the only JAK inhibitor approved by the US Food and Drug Administration (FDA) for use in patients with MF with platelets <50×10⁹/L, based on spleen volume reduction ≥35% (SVR35) in 31 patients in PERSIST-2; a confirmatory trial is ongoing.[20–22] The most common grade 3/4 adverse events (AEs) with pacritinib were thrombocytopenia (32%) and anemia (22%).[22]

Treatment of patients with MF and cytopenias remains a high medical need.[2,3,5] Momelotinib is the first JAK1 and JAK2 inhibitor demonstrated to also inhibit activin A receptor type I (ACVR1), which downregulates the expression of hepcidin, a key regulator of iron homeostasis.[23] Hepcidin is frequently elevated in MF and is associated with poor prognosis.[24] Momelotinib suppresses hepcidin production, which leads to increased iron availability and stimulates erythropoiesis, resulting in anemia benefits, in addition to the spleen and symptom benefits provided by JAK inhibition, for patients with MF.[23,25] Momelotinib starting dose is fixed for all patients, irrespective of baseline platelet count, and platelet levels are generally maintained on momelotinib therapy without the need for dose adjustments.[26] The tolerability and clinical efficacy of momelotinib in improving anemia, symptoms, and splenomegaly were demonstrated in phase 3 trials of patients with MF who were JAK inhibitor naïve (SIMPLIFY-1) and previously exposed to ruxolitinib (SIMPLIFY-2) or any approved JAK inhibitor (MOMENTUM).[27–29] In MOMENTUM, which required baseline platelet counts of ≥25×10⁹/L, momelotinib showed superior week 24 symptom response and SVR35 rates, and a noninferior transfusion independence rate, when compared with danazol in the overall study population and in patients with baseline platelet counts <100×10⁹/L and <50×10⁹/L.[29] In SIMPLIFY-1, which required baseline platelet counts of ≥50×10⁹/L, and in SIMPLIFY-2, which had no restrictions on baseline platelet counts, more patients overall achieved week 24 transfusion independence response with momelotinib than controls (ruxolitinib

in SIMPLIFY-1; best available therapy [BAT; 88.5% ruxolitinib] in SIMPLIFY-2).[27,28] A systematic review and network meta-analysis of JAK inhibitors in MF reported that momelotinib offered similar SVR35 benefits but was associated with significantly less grade 3/4 anemia compared with ruxolitinib.[30]

The tolerability of momelotinib and its lower myelosuppressive activity compared with ruxolitinib may enable more prolonged, adequate dose treatment in thrombocytopenic patients.[28] This post hoc analysis from MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 evaluates the efficacy and safety of momelotinib in MF patients with thrombocytopenia.

MATERIALS AND METHODS

Study design and patients

Detailed study designs for MOMENTUM (NCT04173494),[29] SIMPLIFY-1 (NCT01969838),[28] and SIMPLIFY-2 (NCT02101268)[27] have been published. The phase 3 MOMENTUM study included patients with symptomatic (Myelofibrosis Symptom Assessment Form Total Symptom Score [TSS] ≥10) and anemic (hemoglobin <100 g/L) primary MF (PMF), post-polycythemia vera (post-PV) MF, or post-essential thrombocythemia (post-ET) MF previously treated with JAK inhibitor therapy. Baseline platelet counts ≥25×10⁹/L were required for eligibility. Patients (N = 195) were randomized (2:1) to receive momelotinib 200 mg once daily plus danazol placebo or danazol 300 mg twice daily plus momelotinib placebo. Previous JAK inhibitors included ruxolitinib (100%) and fedratinib (5%). For patients with baseline platelet counts ≥100×10⁹/L, study treatment doses were reduced if platelet counts fell below 50×10⁹/L; if counts fell below 20×10⁹/L, treatment was tapered if appropriate, interrupted, and resumed with reduction by 1 dose level if counts recovered to ≥50×10⁹/L. For patients with baseline platelet counts <100×10⁹/L that fell to <20×10⁹/L, treatment was tapered if appropriate, interrupted, and could resume with reduction by 1 dose level if counts recovered to ≥50% of baseline; for those with baseline platelet counts <50×10⁹/L, the same protocol was followed with resumption of treatment if counts recovered to ≥25×10⁹/L.

SIMPLIFY-1 was a phase 3 noninferiority study of JAK inhibitor-naïve patients with intermediate- or high-risk PMF, post-PV MF, or post-ET MF with baseline platelet counts ≥50×10⁹/L. Patients (N = 432) were randomized 1:1 to momelotinib 200 mg once daily plus ruxolitinib placebo or ruxolitinib twice daily plus momelotinib placebo with the ruxolitinib starting dose dependent on baseline platelet counts and other laboratory values (Suppl. Table S1). Doses of momelotinib/momelotinib placebo on study were reduced if platelet counts fell below 50×10⁹/L from ≥100×10⁹/L at baseline and interrupted if they fell below 25×10⁹/L regardless of baseline platelet counts. Ruxolitinib/ruxolitinib placebo dose was reduced to a level dependent on the previous dose if platelet counts fell below 125×10⁹/L and with every additional drop of 25×10⁹/L, and interrupted if platelet counts fell below 25×10⁹/L.

SIMPLIFY-2 was a phase 3 superiority study of patients with intermediate- or high-risk PMF, post-PV MF, or post-ET MF and who experienced hematologic toxicity when previously treated with ruxolitinib. No minimum baseline platelet count was required, and there was no washout period from prior ruxolitinib treatment. Patients (N = 156) were randomized (2:1) to receive momelotinib 200 mg once daily or BAT. BAT included ruxolitinib (88.5%), other standard treatments alone or in combination at a schedule and dose in accordance with the standard of care per investigator, or no treatment. Dose modifications for momelotinib were as described for SIMPLIFY-1. Dose modifications for BAT were as determined by the investigator in accordance with standard of care. One option in the BAT arm of SIMPLIFY-2 was no treatment, and switching and pausing of control arm therapy were permitted per investigator discretion.

Risk assessment categories for SIMPLIFY-1 were based on the International Prognostic Scoring System criteria[31] and for SIMPLIFY-2 and MOMENTUM were based on Dynamic International Prognostic Scoring System criteria.[32]

In all 3 studies, patients received randomized treatment for 24 weeks; thereafter, patients randomized to momelotinib could continue receiving momelotinib for an extended treatment period, whereas patients randomized to control arms could cross over to momelotinib without any washout period. Patients receiving momelotinib at study completion were eligible to roll over to an extended access protocol (NCT03441113) if they were tolerating momelotinib therapy and had not experienced disease progression. Data captured during this extension protocol were included in the OS analyses.

End points and statistical analyses

In MOMENTUM, the primary end point was ≥50% reduction in TSS response rate at week 24.[29] Key secondary end points were 24-week rates of SVR25, SVR35, transfusion independence, zero transfusions, and change from baseline in mean TSS. Additional secondary end points included OS and anemia-related end points. In SIMPLIFY-1 and SIMPLIFY-2, the primary end point was SVR35 rate at 24 weeks.[27,28] Secondary end points included mean TSS response rate and red blood cell (RBC) transfusion independence rate at 24 weeks; exploratory end points included OS and LFS.

Primary efficacy analyses for all 3 studies have been previously reported.[27–29] Patients with platelet counts $<100 \times 10^9/L$ at baseline (referred to hereafter as sub-100 group) from MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 were included in the present post hoc, exploratory, efficacy and safety analyses. Patients were further subdivided into those with baseline platelet counts 50 to $<100 \times 10^9/L$ (moderate thrombocytopenia; all 3 studies) and $<50 \times 10^9/L$ (severe thrombocytopenia [sub-50 group]; 31 patients from MOMENTUM only). Zero patients from SIMPLIFY-1 and 16 patients [9 momelotinib and 7 BAT] from SIMPLIFY-2 had platelet counts $<50 \times 10^9/L$ and were not evaluated separately. Efficacy and safety were also evaluated in patients with platelet counts $\leq150 \times 10^9/L$. Data reported are descriptive and P values were not calculated due to the exploratory nature of this analysis. Major adverse cardiovascular events (MACE) were defined according to the FDA guideline on composite end point determination for cardiovascular and stroke studies.[33]

All studies were approved by the Institutional Review Boards or independent ethics committees, and all participants provided written informed consent. The present analysis was not prespecified.

Data availability

Sierra Oncology, a GSK company, 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 United States and the EU. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after the US FDA 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 provide 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.

RESULTS

Patients

In total, 210 of 783 patients (27%) randomized in MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 had baseline platelet counts $<100 \times 10^9/L$ (sub-100 group) and 47 patients (6%) had baseline platelet counts $<50 \times 10^9/L$ (sub-50 group) including 31 from MOMENTUM (Suppl. Figure S1). Of the 210 patients in the sub-100 group, 126 received momelotinib in the 24-week randomized treatment period (MOMENTUM, n = 66; SIMPLIFY-1, n = 18; and SIMPLIFY-2, n = 42) and 84 received therapy in the control arms (danazol, n = 34; ruxolitinib, n = 23; BAT, n = 27; respectively). Overall, 62 patients crossed over to open-label momelotinib from the control arms after the 24-week randomized treatment period (23/34 patients [68%] from danazol; 17/23 patients [74%] from ruxolitinib; and 22/27 patients [81%] from BAT). In MOMENTUM and SIMPLIFY-2, baseline characteristics were generally comparable between treatment arms (Table 1). In SIMPLIFY-1, baseline demographics were generally comparable between arms except that more patients randomized to momelotinib were older (aged ≥65 years; 61% versus 48%), male (67% versus 48%), and had anemia (hemoglobin levels <100 g/L, 72% versus 57%) compared with those randomized to ruxolitinib.

Efficacy

The SVR35 rate at week 24 was numerically comparable or higher in the sub-100 groups with momelotinib than in the overall study populations in MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 (Figure 1A). In the control arms, the SVR35 rate at week 24 in the sub-100 group was numerically comparable to that in the overall study populations for danazol (MOMENTUM) and BAT (SIMPLIFY-2), but not for ruxolitinib (SIMPLIFY-1), with no patients achieving an SVR35 with ruxolitinib.

Transfusion independence rates in the sub-100 group with momelotinib were numerically comparable to the overall study populations across all 3 studies, including when looking specifically in patients with moderate thrombocytopenia (platelet counts $50–100 \times 10^9/L$; Figure 1B). The proportion of sub-100 group patients with transfusion independence increased numerically from baseline to week 24 in the momelotinib arms in each study (14% to 27% in MOMENTUM; 28% to 61% in SIMPLIFY-1; and 38% to 48% in SIMPLIFY-2), whereas the rate decreased numerically in the control arms of SIMPLIFY-1 and -2 (47% to 39% and 37% to 30%, respectively). Among patients in the sub-100 group treated with momelotinib, RBC transfusion requirements (median units transfused) during randomized treatment were numerically comparable (MOMENTUM, 5 units; SIMPLIFY-1, 2 units; and SIMPLIFY-2, 1 units) to those observed in the overall momelotinib-treated population of each study.

TSS response rate at week 24 was numerically comparable or higher in the sub-100 groups than the overall study populations with momelotinib in all 3 studies and remained steady in the BAT arm in SIMPLIFY-2 (Figure 1C). In contrast, the TSS response rate in the ruxolitinib arm in the sub-100 group was approximately half the rate observed in ruxolitinib arm of the overall SIMPLIFY-1 population (22% and 42%, respectively).

Table 1

Baseline Demographics and Characteristics for Patients With Baseline Platelet Count <100 × 10⁹/L in MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2

Arm	MOMENTUM		SIMPLIFY-1		SIMPLIFY-2	
	Momelotinib	Danazol	Momelotinib	Ruxolitinib	Momelotinib	BAT
	(n = 66)	(n = 34)	(n = 18)	(n = 23)	(n = 42)	(n = 27)
Age						
Mean (SD), y	70.0 (7.6)	70.6 (6.9)	68.8 (8.6)	64.0 (7.9)	66.7 (7.2)	69.7 (7.7)
≥65 y, n (%)	54 (82)	27 (79)	11 (61)	11 (48)	25 (60)	19 (70)
Male, n (%)	40 (61)	23 (68)	12 (67)	11 (48)	26 (62)	14 (52)
Mean BMI (SD), kg/m²	25.6 (4.1)	24.9 (3.6)	24.4 (3.5)	24.1 (3.9)	27.6 (4.7)	27.0 (3.6)
Race, n (%)						
Asian	6 (9)	3 (9)	0	2 (9)	0	0
Black	2 (3)	2 (6)	0	1 (4)	1 (2)	0
Missing[a]	1 (2)	1 (3)	2 (11)	5 (22)	4 (10)	6 (22)
White	53 (80)	25 (74)	16 (89)	15 (65)	37 (88)	21 (78)
Ethnicity, n (%)						
Hispanic or Latino	2 (3)	2 (6)	0	1 (4)	2 (5)	1 (4)
Not Hispanic or Latino	58 (88)	29 (85)	15 (83)	17 (74)	35 (83)	20 (74)
Unknown[b]	6 (9)	3 (9)	3 (17)	5 (22)	5 (12)	6 (22)
Myelofibrosis subtype, n (%)						
Primary	40 (61)	24 (71)	13 (72)	14 (61)	29 (69)	17 (63)
Post-PV	19 (29)	6 (18)	1 (6)	6 (26)	6 (14)	6 (22)
Post-ET	7 (11)	4 (12)	4 (22)	3 (13)	7 (17)	4 (15)
IPSS or DIPSS risk category, n (%)[c]						
Intermediate-1	3 (5)	1 (3)	2 (11)	2 (9)	9 (21)	10 (37)
Intermediate-2	39 (59)	21 (62)	6 (33)	11 (48)	26 (62)	15 (56)
High	24 (36)	11 (32)	10 (56)	10 (43)	7 (17)	2 (7)
Missing	0	1 (3)	0	0	0	0
JAK2V617F mutation, n (%)						
Positive	56 (85)	26 (76)	11 (61)	17 (74)	31 (74)	18 (67)
Negative	10 (15)	8 (24)	5 (28)	5 (22)	10 (24)	8 (30)
Unknown	0	0	0	0	0	0
Not previously tested	0	0	2 (11)	1 (4)	1 (2)	1 (4)
TSS, mean (SD)[d]	27.7 (13.9)	24.9 (13.4)	19.2 (13.8)	21.1 (10.6)	18.9 (12.3)	14.4 (13.0)
ECOG PS, n (%)						
0	9 (14)	7 (21)	5 (28)	4 (17)	9 (21)	9 (33)
1	37 (56)	18 (53)	11 (61)	15 (65)	32 (76)	13 (48)
2	20 (30)	9 (26)	2 (11)	4 (17)	1 (2)	5 (19)
Hb						
Mean (SD), g/L	81 (10.5)	78 (9.1)	93 (19.2)	101 (29.6)	94 (18.5)	94 (15.6)
<100 g/L, n (%)	64 (97)[e]	34 (100)	13 (72)	13 (57)	25 (60)	20 (74)
<80 g/L, n (%)	34 (52)	17 (50)	6 (33)	5 (22)	9 (21)	2 (7)
RBC transfusion dependent, n (%)[f]						
Yes	32 (48)	19 (56)	10 (56)	11 (48)	19 (45)	15 (56)
No	34 (52)	15 (44)	8 (44)	12 (52)	23 (55)	12 (44)
RBC transfusion independent, n (%)[g]						
Yes	9 (14)	5 (15)	5 (28)	11 (48)	16 (38)	10 (37)
No	57 (86)	29 (85)	13 (72)	12 (52)	26 (62)	17 (63)
Platelet count						
Mean (SD) × 10⁹/L	62.0 (20.5)	58.6 (21.0)	76.5 (12.0)	74.4 (11.6)	62.7 (18.2)	62.3 (18.9)
<50 × 10⁹/L, n (%)	18 (27)	13 (38)	0	0	9 (21)	7 (26)
<25 × 10⁹/L, n (%)	1 (2)	0	0	0	2 (5)	0
Mean ANC × 10⁹/L (SD)	7.9 (10.4)	8.0 (10.6)	7.9 (9.4)	9.3 (8.2)	10.2 (14.3)	5.8 (7.5)
Mean spleen volume, cm³ (SD)	2457 (1139)[h]	2327 (1192)[h]	1873 (1114)	2686 (1480)	2726 (1584)	2254 (1056)

[a]Missing or not permitted to be reported. Additionally, in the MOMENTUM study, 4 patients (6%) in the momelotinib arm and 3 patients (9%) in the danazol arm reported Other as their race.

[b]Unknown, missing, or not permitted to be reported.

[c]IPSS risk categories based on Cervantes and collaborators (2009) reported in SIMPLIFY-1.[31] DIPSS risk categories based on Passamonti and collaborators (2010) reported for the SIMPLIFY-1 and MOMENTUM studies.[32]

[d]Available in 17 patients in the momelotinib arm and 23 patients in the ruxolitinib arm in SIMPLIFY-1.

[e]Per protocol, patients in MOMENTUM must have had Hb <100 g/L at screening. However, Hb levels increased to >100 g/L without red blood cell transfusions between screening and baseline in 2 patients who were randomized to the momelotinib arm: 1 patient had Hb of 90.7 g/L at screening (study day −30) and 107 g/L at baseline (study day −9), and 1 patient had Hb of 89 g/L at screening (study day −32) and 105 g/L at baseline (study day −7).

[f]Transfusion dependence at baseline was defined as requiring ≥4 red blood cell/whole blood transfusion units in the 8 wks before the first dose, each associated with hemoglobin levels ≤9.5 g/dL (MOMENTUM), or requiring ≥4 red blood cell/whole blood transfusion units, or a hemoglobin level <8 g/dL, in the 8 wks before the first dose (SIMPLIFY-1 and SIMPLIFY-2).

[g]Transfusion independence at baseline was defined in all 3 trials as no red blood cell/whole blood units transfused, with all hemoglobin levels ≥8 g/dL, in the 12 wks before the first dose.

[h]Centrally assessed.

ANC = absolute neutrophil count; BAT = best available therapy; BMI = body mass index; DIPSS = Dynamic International Prognostic Scoring System; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; IPSS = International Prognostic Scoring System; MMB = momelotinib; N/A, not available; Post-ET = post-essential thrombocythemia; Post-PV = post-polycythemia vera; PS = performance status; RBC = red blood cell; RUX = ruxolitinib; TSS = Total Symptom Score.
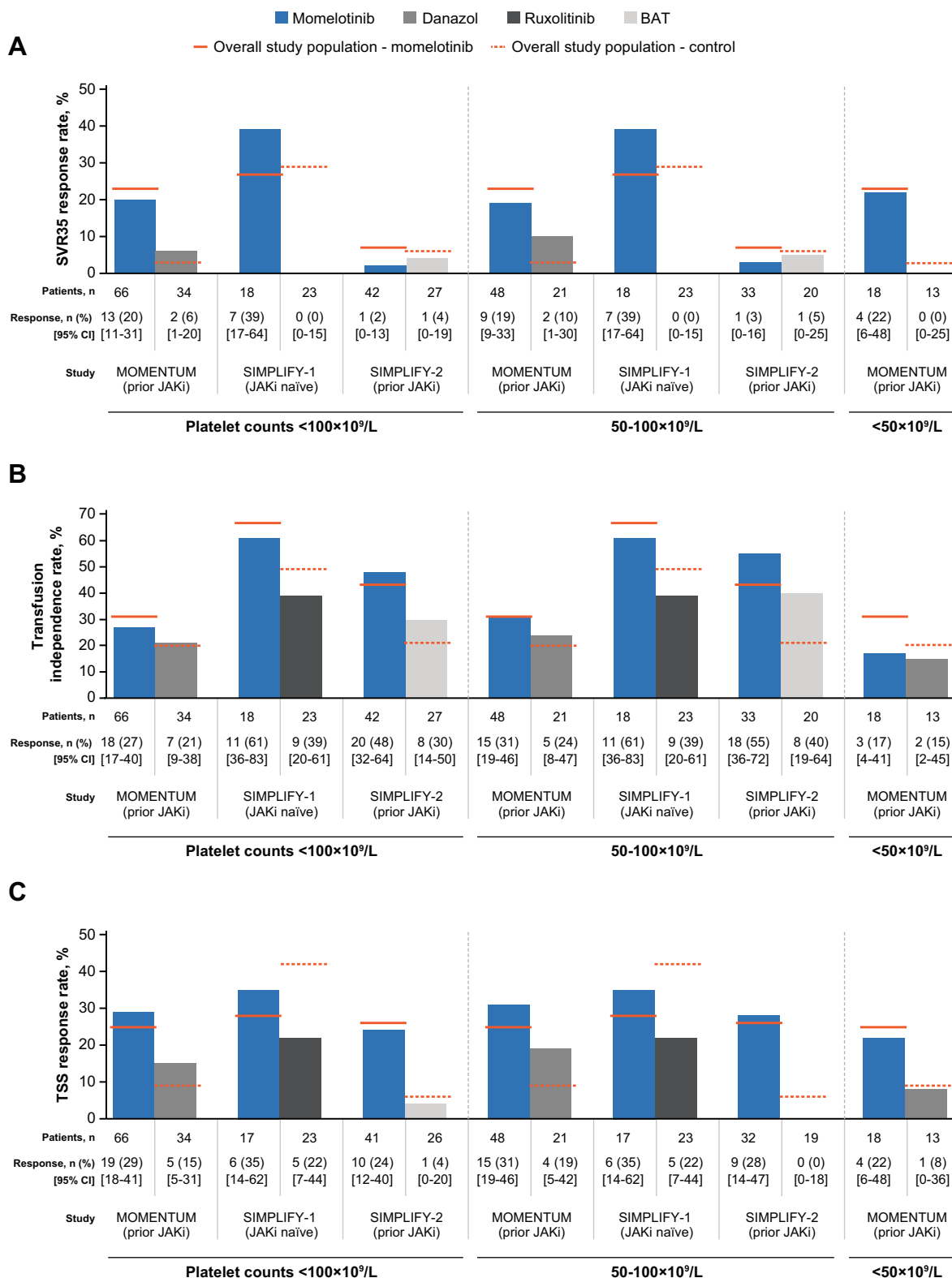
Figure 1. Week 24 response rates by treatment arm among patients with baseline platelet counts <100 × 10⁹/L, 50–100 × 10⁹/L, and <50 × 10⁹/L in MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2. (A) SVR35 response rate, (B) red blood cell transfusion independence rate, and (C) TSS response rate. Horizontal lines indicate response rates achieved in the overall study population with momelotinib (solid line) and controls (dotted line). BAT = best available therapy; JAKi = JAK inhibitor; SVR35, spleen volume reduction of ≥35% from baseline; TSS = Total Symptom Score ≥50%.

Efficacy results were generally consistent when evaluating patients in the sub-50 group (Figure 1A–1C) and all patients with platelet counts ≤150 × 10⁹/L, which included patients with mild thrombocytopenia (Suppl. Figure S2).

All patients from MOMENTUM in the sub-100 group were at least moderately anemic (hemoglobin <100 g/L) at screening, per inclusion criteria, and most patients in SIMPLIFY-1 and SIMPLIFY-2 were at least mildly anemic at baseline (Table 1).

Among sub-100 group patients with anemia, SVR35, transfusion independence, and TSS response rates were generally numerically higher with momelotinib than controls across all 3 studies with the exception of TSS response in SIMPLIFY-1 (Suppl. Figure S3).

Survival

OS rates were generally comparable for both the momelotinib and the control arms in the sub-100 groups versus the overall study populations in all 3 studies (Table 2). In the MOMENTUM sub-100 group (median follow-up, momelotinib, 9 months; danazol, 10 months), median OS was not reached in either arm with a hazard ratio (HR; momelotinib versus danazol) of 0.659 (95% confidence interval [CI], 0.268-1.622) when analyzed over the entire follow-up period and 0.616 (95% CI, 0.211-1.802) when assessed over the 24-week randomized treatment period alone (Figure 2A). In the SIMPLIFY-1 sub-100 group (median follow-up, momelotinib, 3.0 years; ruxolitinib, 3.7 years), the estimated 3-year OS rate was 56.7% (95% CI, 29.2-77.0) and 53.3% (95% CI, 28.9-72.7), respectively (HR, 0.848 [95% CI, 0.341-2.2113]) (Figure 2B). In the SIMPLIFY-2 sub-100 group (median follow-up, momelotinib, 3.4 years; BAT, 3.5 years), the estimated 3-year OS rate was 59.8% (95% CI, 41.5-74.0) and 65.5% (95% CI, 44.0-80.4), respectively (HR, 0.984 [95% CI, 0.451-2.147]) (Figure 2C).

Mean platelet counts over time

In all 3 studies, mean platelet counts either increased or were maintained from baseline levels over the initial 24-week treatment period in sub-100 group patients in the momelotinib arm. In MOMENTUM, mean platelet counts at baseline were $\approx 60 \times 10^9$/L in both treatment arms. In patients who received momelotinib, mean platelet counts increased to $\approx 75 \times 10^9$/L by week 12 of therapy and remained relatively stable between 75×10^9/L and 100×10^9/L through week 48 (Figure 3A). In patients who received danazol, platelet counts increased during the 24-week randomized treatment period up to 140×10^9/L, which is consistent with previous reports,[34] and remained in the 100×10^9/L range with some fluctuations following crossover to momelotinib (Figure 3A). In SIMPLIFY-1, mean platelet levels increased within the first 2 weeks of therapy and were maintained above 100×10^9/L throughout the duration of therapy with momelotinib (Figure 3B). In contrast, in the ruxolitinib arm, mean platelet counts remained low at $\approx 75 \times 10^9$/L throughout the 24-week randomized period (Figure 3B). Crossover to momelotinib at week 24 led to a mean platelet count rebound by week 48 of the open-label period. In SIMPLIFY-2, baseline platelet counts were $\approx 60 \times 10^9$/L in both treatment arms and increased above 100×10^9/L by the end of the 24-week treatment period in the momelotinib arm, with levels generally maintained in the extended phase (Figure 3C). In the BAT arm, mean platelet counts increased up to 8 weeks of therapy, and then decreased and fluctuated around 75×10^9/L for the remainder of both the randomized and extension period up to week 48 (Figure 3C).

Dose intensity

In the sub-100 group in MOMENTUM, the mean (SD) daily dose of momelotinib at week 24 was 183.70 mg (31.7), which is near the full recommended dose (200 mg daily), and remained high throughout the 48-week treatment period (Figure 4A). Similarly, 70% or more of patients who crossed over to momelotinib from danazol at week 24 had a mean daily dose intensity at full or near-full dose through week 48 (Figure 4B). Daily doses of momelotinib in the sub-100 group remained high throughout the 48-week treatment period, with more than half of the patients receiving full or near-full doses of momelotinib in SIMPLIFY-1 (mean [SD] daily dose, 163.4 mg [55.3]) and >80% of patients doing so in SIMPLIFY-2 (mean [SD] daily dose, 188.5 mg [40.8]) (Figure 4C and 4E). In contrast, mean daily doses of ruxolitinib were low over the 24-week randomized treatment period in the sub-100 group in SIMPLIFY-1 (mean [SD] daily dose, 11.8 mg [3.9]), with at least 90% of patients receiving 10 mg or less daily of ruxolitinib for most of the 24-week treatment period, which is $\approx 25\%$ of the full recommended (40 mg daily) dose (Figure 4D). In the ruxolitinib-exposed sub-100 group in SIMPLIFY-2, mean daily doses of
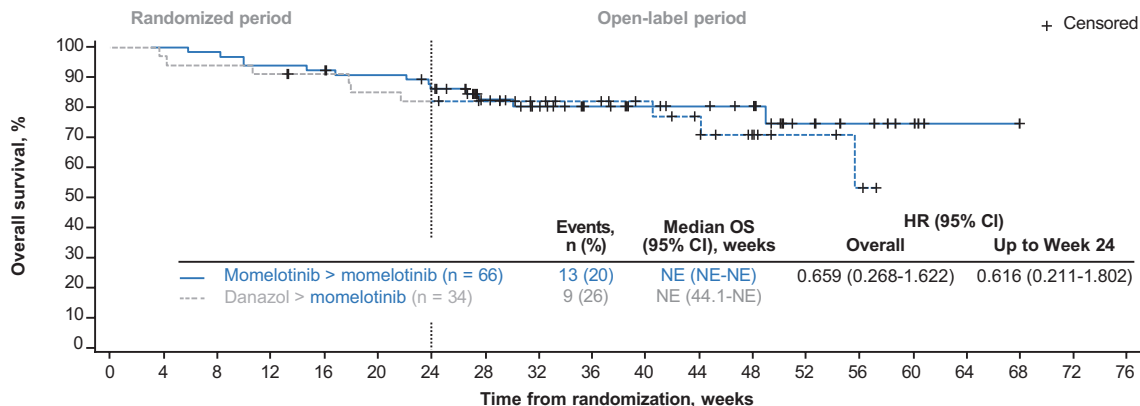

Table 2

Overall Survival in Patients With Thrombocytopenia and in the Overall Populations in MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2

	SIMPLIFY-1 (JAK Inhibitor Naïve)[a]				SIMPLIFY-2 (Prior JAK Inhibitor)[a]			
	Momelotinib > Momelotinib		Ruxolitinib > Momelotinib		Momelotinib > Momelotinib		BAT > Momelotinib	
	Sub-100	Overall	Sub-100	Overall	Sub-100	Overall	Sub-100	Overall
	(n = 18)	(N = 215)	(n = 23)	(N = 217)	(n = 42)	(N = 104)	(n = 27)	(N = 52)
OS rate, %								
2 y	71.3	81.6	65.1	80.6	78.1	65.8	73.4	61.2
3 y	56.7	71.1	53.3	71.7	59.8	49.9	65.5	53.9
4 y	56.7	62.9	53.3	64.4	59.8	49.9	54.6	46.7
6 y	37.8	54.3	26.6	53.3	59.8	42.8	54.6	46.7
Median follow-up, y	3.0	3.4	3.7	3.5	3.4	3.1	3.5	3.1

	MOMENTUM (Prior JAK Inhibitor, Anemic)[a]					
	Momelotinib > Momelotinib			Danazol > Momelotinib		
	Sub-50	Sub-100	Overall	Sub-50	Sub-100	Overall
	(n = 18)	(n = 66)	(N = 130)	(n = 13)	(n = 34)	(N = 65)
OS rate, %						
6 mo	94.4	86.2	88.1	59.8	82.1	79.9
9 mo	94.4	80.5	83.2	59.8	82.1	79.9
12 mo	75.6	74.7	74.0	47.9	71.0	73.6
Median follow-up, mo	7.5	8.9	9.0	10.2	10.1	9.7

[a]Treatment arms expressed as therapy 1 > therapy 2, where therapy 1 is the therapy received in 24-wk randomized period and therapy 2 received in the extended treatment period after crossover (>).

> = crossover; ITT = intention-to-treat population; JAK = Janus kinase; Sub-50 = platelet counts <50 × 10⁹/L; Sub-100 = platelet counts <100 × 10⁹/L.
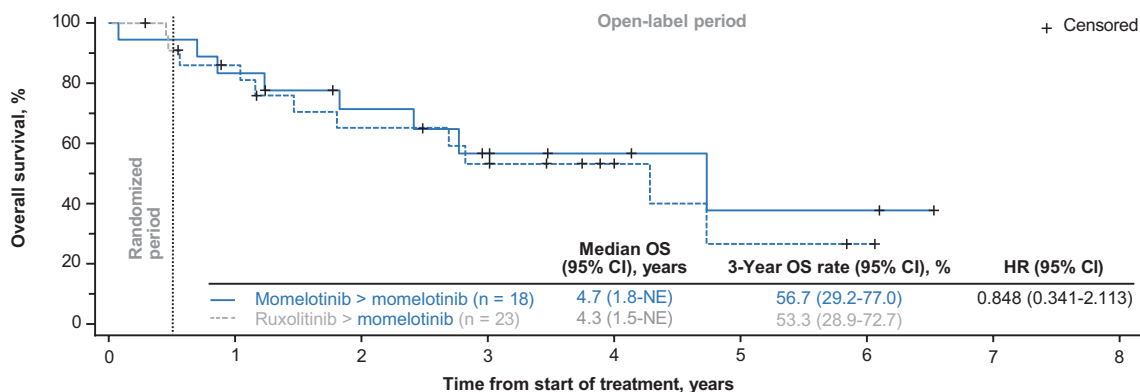
A

B

C

Figure 2. Kaplan-Meier estimates of overall survival. Shown is overall survival by treatment arm in patients with baseline platelet counts <100 × 109/L in (A) MOMENTUM, (B) SIMPLIFY-1, and (C) SIMPLIFY-2. Vertical dashed line indicates the end of the randomized period and the beginning of the open-label period, when patients randomized to the control arms were allowed to cross over to momelotinib therapy. BAT = best available therapy; HR = hazard ratio; NE = not estimable; OS = overall survival.
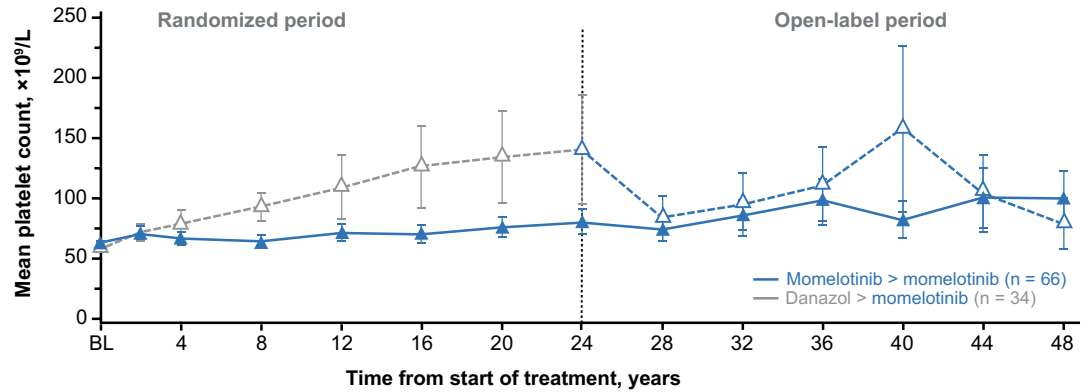
ruxolitinib were low at the start of the study and remained low through the 24-week treatment period (mean [SD] daily dose, 18.4 mg [9.6]) (Figure 4F). Most patients who crossed over to momelotinib at week 24 in both SIMPLIFY trials received full dose momelotinib (200 mg once daily) throughout the extended treatment period and into the extended access protocol.

Safety

The most common (occurring in ≥10% of patients) treatment-emergent AEs (TEAEs) in sub-100 groups during the 24-week randomized treatment period are reported in Table 3 and were generally consistent with those reported in the overall population of each study. In addition, MACE were infrequent
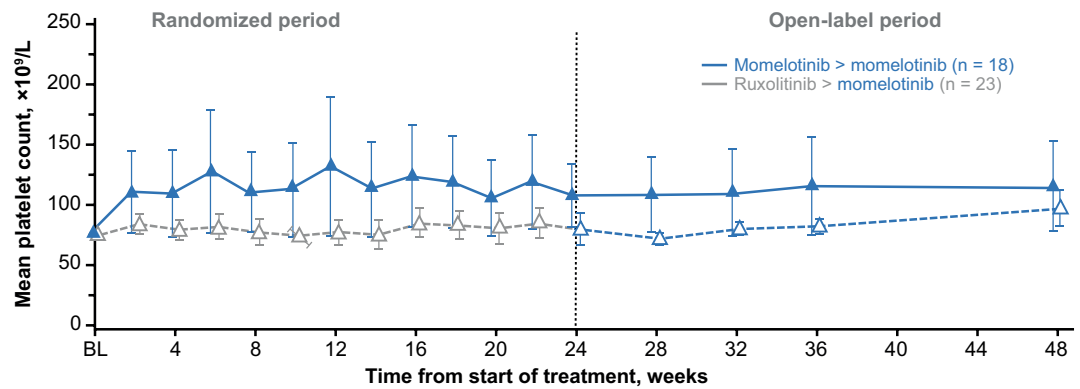
Figure 3. Mean platelet counts in phase 3 studies of momelotinib (up to week 48) in patients with baseline platelet counts <100 × 10⁹/L. (A) Mean platelet counts in the randomized and open-label phases of (A) MOMENTUM (anemic patients with prior JAKi exposure), (B) SIMPLIFY-1 (patients naïve to previous JAKi therapy), and (C) SIMPLIFY-2 (patients with prior JAKi exposure). Vertical dashed line indicates the end of the randomized period and the beginning of the open-label period, when patients randomized to the control arms were allowed to cross over to momelotinib therapy. BAT = best available therapy; JAKi = Janus kinase inhibitor.
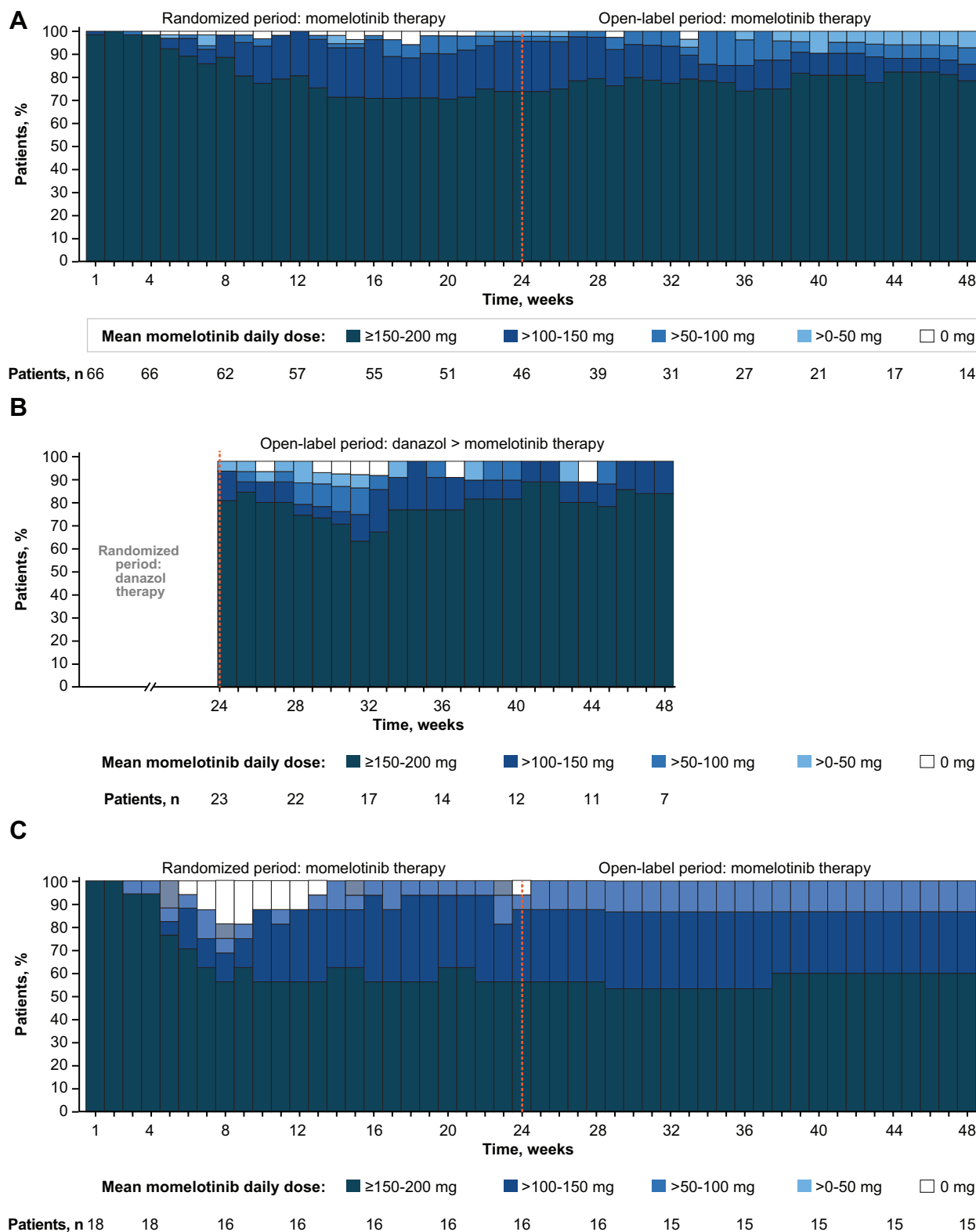
Figure 4. **(Continued on next page) Dose intensity over time among patients with baseline platelet count <100 × 10⁹/L.** Mean daily dose intensity in (A) the momelotinib arm of MOMENTUM, (B) the danazol to momelotinib crossover arm of MOMENTUM (weeks 24–48 of therapy), (C) the momelotinib arm of SIMPLIFY-1, (D) the ruxolitinib to momelotinib crossover arm of SIMPLIFY-1, (E) the momelotinib arm of SIMPLIFY-2, and (F) the BAT to momelotinib crossover arm of SIMPLIFY-2. Vertical dashed line indicates the end of the randomized period and the beginning of the open-label period, when patients randomized to the control arms were allowed to cross over to momelotinib therapy. BAT = best available therapy.
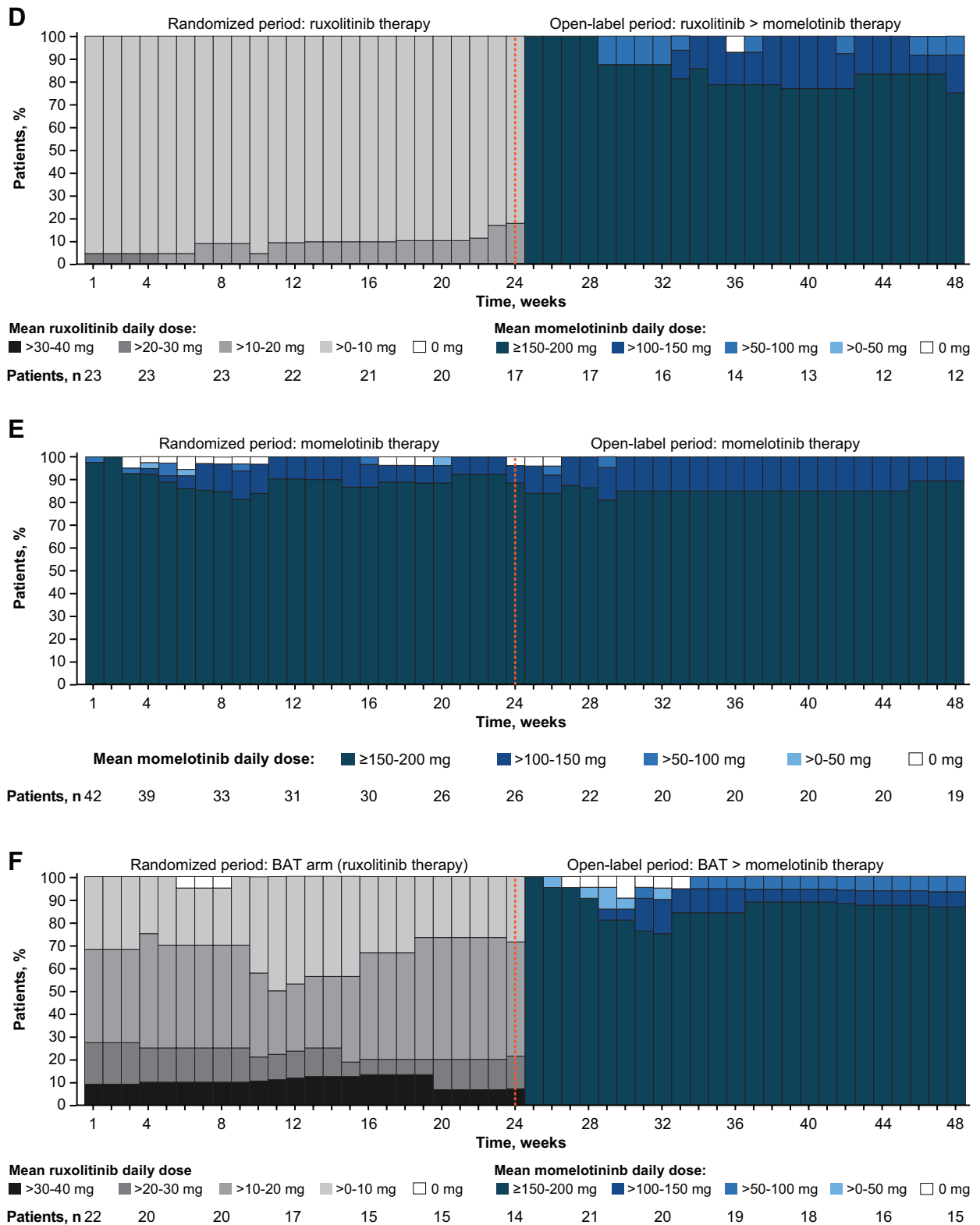
Figure 4. Continued

in the sub-100 group with momelotinib, occurring in 1 patient (2%) in MOMENTUM, 2 patients (11%) in SIMPLIFY-1, and no patients in SIMPLIFY-2, and were not reported in control arms in any of the 3 studies. These results were generally consistent with those from the overall patient populations (MOMENTUM: momelotinib, 2 patients [2%]; danazol, 4 patients [6%]); SIMPLIFY-1: momelotinib, 8 patients [4%]; ruxolitinib, 5 patients [2%]); and SIMPLIFY-2: momelotinib, 4 patients [4%]; BAT, 2 patients [4%]).

Rates of any-grade hemorrhage were comparable in the overall population and sub-100 group of each trial; while rates of any-grade hemorrhage were numerically higher in the sub-50

Table 3

Most Common Treatment-emergent Adverse Events of Any Grade Occurring in at Least 10% of Patients With Baseline Platelet Counts <100×10⁹/L in Either Treatment Arm During the 24-wk Randomized Treatment Phases of SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM

	MOMENTUM		SIMPLIFY-1		SIMPLIFY-2	
	Momelotinib	Danazol	Momelotinib	Ruxolitinib	Momelotinib	BAT
Any-grade TEAE, n (%)ᵃ	(n = 66)	(n = 34)	(n = 18)	(n = 23)	(n = 42)	(n = 27)
Overall	61 (92)	32 (94)	18 (100)	22 (96)	41 (98)	25 (93)
Diarrhea	16 (24)	4 (12)	2 (11)	8 (35)	17 (40)	7 (26)
Thrombocytopenia	16 (24)	6 (18)	3 (17)	5 (22)	10 (24)	3 (11)
Anemia	10 (15)	5 (15)	3 (17)	2 (9)	7 (17)	6 (22)
Asthenia	10 (15)	2 (6)	0	4 (17)	6 (14)	6 (22)
Nausea	10 (15)	3 (9)	4 (22)	1 (4)	10 (24)	2 (7)
Weight decreased	8 (12)	3 (9)	0	1 (4)	5 (12)	2 (7)
Blood alkaline phosphatase increase	7 (11)	0	0	0	2 (5)	0
Pruritis	7 (11)	3 (9)	1 (6)	2 (9)	6 (14)	4 (15)
Pyrexia	7 (11)	1 (3)	2 (11)	1 (4)	2 (5)	3 (11)
Blood creatinine increase	6 (9)	5 (15)	1 (6)	0	3 (7)	0
Cough	6 (9)	2 (6)	4 (22)	2 (9)	9 (21)	2 (7)
ALT increase	5 (8)	1 (3)	2 (11)	0	1 (2)	0
Back pain	5 (8)	1 (3)	2 (11)	0	1 (2)	3 (11)
Decreased appetite	5 (8)	2 (6)	2 (11)	2 (9)	3 (7)	1 (4)
Dizziness	5 (8)	0	5 (28)	1 (4)	7 (17)	2 (7)
UTI	5 (8)	1 (3)	2 (11)	1 (4)	6 (14)	2 (7)
Arthralgia	4 (6)	1 (3)	3 (17)	4 (17)	5 (12)	4 (15)
Contusion	4 (6)	0	3 (17)	1 (4)	3 (7)	2 (7)
Epistaxis	4 (6)	3 (9)	1 (6)	1 (4)	3 (7)	5 (19)
Fatigue	4 (6)	3 (9)	4 (22)	3 (13)	9 (21)	7 (26)
Hypotension	4 (6)	1 (3)	2 (11)	0	2 (5)	0
Paresthesia	4 (6)	1 (3)	3 (17)	1 (4)	0	1 (4)
Peripheral edema	4 (6)	5 (15)	1 (6)	3 (13)	3 (7)	4 (15)
Dyspnea	3 (5)	3 (9)	1 (6)	1 (4)	6 (14)	5 (19)
Hyperkalemia	3 (5)	2 (6)	2 (11)	1 (4)	2 (5)	0
Abdominal pain	2 (3)	5 (15)	3 (17)	5 (22)	7 (17)	4 (15)
Abdominal pain upper	2 (3)	4 (12)	0	0	0	0
Acute kidney injury	2 (3)	4 (12)	0	1 (4)	1 (2)	0
Bone pain	2 (3)	2 (6)	0	5 (22)	2 (5)	2 (7)
Chronic obstructive pulmonary disease	2 (3)	0	2 (11)	0	0	0
Dyspepsia	2 (3)	1 (3)	0	2 (9)	5 (12)	0
Insomnia	2 (3)	2 (6)	0	2 (9)	2 (5)	3 (11)
Headache	2 (3)	0	3 (17)	8 (35)	5 (12)	1 (4)
General physical deterioration	2 (3)	1 (3)	0	0	1 (2)	3 (11)
Vomiting	2 (3)	0	1 (6)	1 (4)	5 (12)	0
Cystitis	1 (2)	0	2 (11)	0	1 (2)	0
Early satiety	1 (2)	2 (6)	0	0	2 (5)	3 (11)
Hyperhidrosis	1 (2)	0	0	0	1 (2)	3 (11)
Iron deficiency	1 (2)	0	2 (11)	0	1 (2)	0
Night sweats	1 (2)	0	0	0	6 (14)	3 (11)
Pain in extremity	1 (2)	1 (3)	3 (17)	3 (13)	2 (5)	5 (19)
Presyncope	1 (2)	0	2 (11)	0	2 (5)	0
Skin laceration	1 (2)	0	2 (11)	0	0	0
URTI	1 (2)	1 (3)	2 (11)	1 (4)	4 (10)	0
Anxiety	0	1 (3)	3 (17)	1 (4)	2 (5)	0
Chronic kidney disease	0	1 (3)	2 (11)	0	0	1 (4)
Hypertension	0	4 (12)	2 (11)	2 (9)	2 (5)	2 (7)
Nasopharyngitis	0	0	2 (11)	2 (9)	3 (7)	1 (4)
Skin infection	0	0	2 (11)	0	1 (2)	0

ᵃTEAEs were coded to preferred term using MedDRA, version 23.0.

ALT = alanine aminotransferase; BAT = best available therapy; MMB = momelotinib; RUX = ruxolitinib; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

groups of MOMENTUM and SIMPLIFY-2, only 1 patient in this subgroup from each study had grade ≥3 hemorrhage (Suppl. Table S2). Observations of grade ≥3 thrombocytopenia or hemorrhage in the sub-100 groups during the 24-week randomized period across studies were generally infrequent. In MOMENTUM, grade ≥3 thrombocytopenia and hemorrhage occurred in 22 (33%) and 4 patients (6%) in the momelotinib group and 7 (21%) and 0 patients in the danazol group, respectively (Suppl. Table S2). In SIMPLIFY-1, grade ≥3 thrombocytopenia and hemorrhage occurred in 3 (17%) and 1 patient (6%)

in the momelotinib group and 5 (22%) and 1 patient (4%), in the ruxolitinib group, respectively. In SIMPLIFY-2, grade ≥3 thrombocytopenia and hemorrhage occurred in 8 (19%) and 3 patients (7%) in the momelotinib group and 2 (7%) and 0 patients in the BAT group. The safety profile of momelotinib in patients in the sub-50 group in MOMENTUM remained generally consistent with that in the sub-100 group and the overall study population (Suppl. Table S3). No deaths due to thrombocytopenia were reported in any of the phase 3 studies.

Dose reductions or interruptions due to thrombocytopenia were infrequent during the 24-week randomized period in the sub-100 groups with momelotinib. In the momelotinib arm of MOMENTUM, thrombocytopenia resulted in dose reductions and treatment discontinuation in 8 patients (12%) and 3 patients (5%), respectively (Suppl. Table S4). In SIMPLIFY-1, thrombocytopenia resulted in dose reductions in 3 patients (17%) in the momelotinib arm. Importantly, patients with baseline platelet counts $<100 \times 10^9$/L in SIMPLIFY-1 must have initiated ruxolitinib at a reduced dose (5 mg twice daily) and ruxolitinib may have been interrupted if platelet counts fell below 50×10^9/L but must have been interrupted if platelet counts fell below 25×10^9/L. Treatment discontinuation due to thrombocytopenia occurred less frequently with momelotinib than ruxolitinib in the sub-100 group in SIMPLIFY-1 (0% versus 13%). In the momelotinib arm of SIMPLIFY-2, thrombocytopenia resulted in dose reductions in 1 patient (2%) and in treatment discontinuation in 4 patients (10%).

DISCUSSION

This analysis of three phase 3 clinical studies supports the safe and effective use of momelotinib in patients with MF and moderate-to-severe thrombocytopenia. Momelotinib demonstrated numerically greater clinical benefit than comparators including ruxolitinib, BAT, and danazol in the thrombocytopenic patient subgroups while maintaining a favorable safety profile. Efficacy results with momelotinib in sub-100 group and sub-50 group patients were consistent with those previously reported in the overall study populations.[26,27–29] Observed improvements in symptom reduction, spleen response, and transfusion independence rates with momelotinib in patients with MF and thrombocytopenia are likely due to momelotinib's high dose intensities, whereas the data from the SIMPLIFY studies suggest that ruxolitinib's efficacy is attenuated in patients with thrombocytopenia as it is frequently administered at lowered doses per the ruxolitinib prescribing information based on platelet levels.

Cytopenias are common in patients with MF, and patients with moderate or severe thrombocytopenia tend to have greater symptom burden, higher rates of anemia and transfusion dependence, and worse prognosis than MF patients with higher platelet counts.[5–7] Thrombocytopenia and anemia events are frequent in patients with MF receiving ruxolitinib and may require treatment dose reductions and discontinuation, which limit efficacy and survival.[13,14,35] Currently, ruxolitinib and fedratinib are not approved for MF patients with severe thrombocytopenia,[8,19] whereas pacritinib approval is limited to patients with platelets $<50 \times 10^9$/L in the United States.[22] Accelerated approval of pacritinib was based on spleen response in a limited number of patients, and no confirmed symptom benefits are depicted in its label.[22] Further, none of the approved JAK inhibitors have shown substantial clinical improvement in anemia in a prospective randomized clinical trial with prespecified anemia end points. Alternative options for the management of thrombocytopenia in patients with MF include platelet transfusions, splenectomy, immunomodulatory drugs with or without corticosteroids, androgens, or hypomethylating agents; however, each of these approaches have shown limited benefit.[36] Thus, effective and safe therapies for patients with anemia and thrombocytopenia are needed. Through inhibition of ACVR1, JAK1,

and JAK2 and demonstrated symptom, spleen, and anemia benefits in patients with MF, momelotinib is uniquely positioned to fill this unmet need in MF.[29]

More than 1000 patients with MF have been treated with momelotinib to date, some of whom have been on therapy for >12 years. The present analyses were conducted using a large dataset of 331 patients with mild-to-severe thrombocytopenia treated in randomized clinical trials, of which 210 had moderate-to-severe thrombocytopenia and 47 had severe thrombocytopenia (MOMENTUM, n = 31; SIMPLIFY-2, n = 16). Although the 16 patients from SIMPLIFY-2 with severe thrombocytopenia were not analyzed separately due to small patient numbers, they were included in the sub-100 group. In SIMPLIFY-1 (JAK inhibitor naïve), treatment effects were more pronounced in favor of momelotinib relative to ruxolitinib in the sub-100 group compared with the overall study population. More specifically, SVR35 and TSS response rates with momelotinib were numerically higher when comparing the sub-100 and overall study populations, whereas SVR35 and TSS response rates with ruxolitinib were attenuated in sub-100 patients when comparing with the overall study population. Further, transfusion independence rates increased from baseline in the momelotinib arm but decreased in the ruxolitinib arm in sub-100 patients. Among sub-100 patients previously exposed to JAK inhibitors in SIMPLIFY-2, transfusion independence and TSS response rates were substantially higher with momelotinib than BAT as was seen in the overall study population, whereas SVR35 was numerically comparable between treatment groups and also consistent with what was reported in the overall study population. In MOMENTUM (JAK inhibitor-exposed, anemic, and symptomatic patients), spleen, symptom, and transfusion independence response rates were numerically higher with momelotinib than danazol in the sub-100 group, and numerically comparable or higher than danazol in the sub-50 group.[29] Further, in patients with anemia and thrombocytopenia from the SIMPLIFY studies, momelotinib demonstrated substantial improvements in transfusion independence and spleen responses in JAK inhibitor-naïve patients (SIMPLIFY-1) and improvements in transfusion independence, spleen, and symptom responses in patients previously exposed to JAK inhibitors (SIMPLIFY-2).

In all 3 studies, rates of TEAEs for patients receiving momelotinib in the 24-week randomized period were numerically comparable between the sub-100 groups and overall study populations; no increased risk of severe bleeding was identified in sub-100 groups.[27–29] Despite thrombocytopenia being the most common grade ≥3 TEAE among sub-100 patients in the phase 3 randomized studies of momelotinib, few patients had dose reductions due to thrombocytopenia with momelotinib. Across all 3 studies, very few sub-100 patients treated with momelotinib discontinued therapy due to thrombocytopenia (7/126 [6%]). Momelotinib dose intensities remained high throughout the treatment period in sub-100 patients in all studies, with most patients receiving full dose momelotinib.

A limitation of the current study is the post hoc, descriptive nature of the analysis. The studies were not prospectively designed to evaluate subgroups based on baseline platelet counts. Due to the exploratory nature of the analysis, no statistical evaluation was performed and all results are descriptive in nature. Additionally, current comparative momelotinib data are restricted to comparison with ruxolitinib (SIMPLIFY-1 and SIMPLIFY-2), precluding any comparative assessment versus other JAK inhibitors.

Some reports suggest that JAK1 inhibition may drive the induction or worsening of thrombocytopenia in patients treated with ruxolitinib.[37] However, it has since been shown that selective JAK1 inhibition contributes to the reduction of disease-related inflammation in patients with MF but is not associated with high degrees of myelosuppression.[38] Results

from the present analyses demonstrating clinical efficacy and less myelosuppression with momelotinib in patients with thrombocytopenia and anemia suggest that non-JAK pathways may be involved in platelet regulation. The exact mechanisms underlying platelet maintenance during momelotinib treatment are not currently understood, and further investigation is needed. Nonetheless, these clinical results provide further evidence that the unique mechanism of action of momelotinib, the first JAK1 and JAK2 inhibitor that also decreases hepcidin through ACVR1 inhibition,[25] may address a critical unmet need particularly in patients with symptomatic MF with anemia and thrombocytopenia.

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

All the investigators and their research teams collected the data. J-JK and JK provided the conception and planning for this work. MH (biostatistician with Sierra Oncology) performed all statistical analyses. J-JK, MH, and JK confirmed the accuracy of the data. All authors had access to the data and contributed to its interpretation, vouch for the accuracy and completeness of the data, provided critical review of the article, and provided final approval for submission for publication.

DISCLOSURES

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. 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. ATG reports consulting fees from AbbVie, Bristol Myers Squibb, Constellation/MorphoSys, CTI Biopharma, Novartis, PharmaEssentia, and Sierra Oncology. 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. 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. JM reports research support from Sierra Oncology. AI reports consulting fees from Celgene, Janssen, Novartis, Pfizer, Roche, and Takeda; and meeting/travel support from Janssen, Novartis, Pfizer, and Roche. TW reports meeting/travel support from Novartis and Roche. 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. DML reports grant support from CPI; speaker fees from AbbVie, Celgene, Jazz, and Novartis. S-SY reports grant support from Roche-Genentech and Yuhan Pharmaceuticals; consulting fees from Amgen and Novartis; honoraria for lectures from Novartis; and participation in data safety monitoring board or advisory board for Hanmi and Pharos iBio. CH reports grant support 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. BK, MH, and JK report employment and stock or stock options at Sierra Oncology, a GSK company. 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, LaJolla, Novartis, and Sierra Oncology. All the other authors have no conflicts of interest to disclose.

SOURCES OF FUNDING

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