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Momelotinib long-term safety and survival in myelofibrosis: integrated analysis of phase 3 randomized controlled trials

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Key Points

- AEs with momelotinib were mostly grade 1/2, noncumulative, and associated with low rates of discontinuation.
- In this large, heterogeneous MF data set evaluating a JAK inhibitor, 12% of patients received momelotinib for ≥5 years.

Momelotinib is the first inhibitor of Janus kinase 1 (JAK1) and JAK2 shown to also inhibit activin A receptor type 1 (ACVR1), a key regulator of iron homeostasis, and has demonstrated improvements in splenomegaly, constitutional symptoms, and anemia in myelofibrosis (MF). This long-term analysis pooled data from 3 randomized phase 3 studies of momelotinib (MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2), representing MF disease from early (JAK inhibitor–naive) to late (JAK inhibitor–experienced) stages. Patients in the control arms (danazol in MOMENTUM, ruxolitinib in SIMPLIFY-1, and best available therapy in SIMPLIFY-2) could cross over to receive momelotinib at the end of the 24-week randomized period, and all patients could continue momelotinib treatment after the completion of these studies via an extended access protocol (XAP). Across these studies, 725 patients with MF received momelotinib; 12% remained on therapy for ≥5 years, with a median treatment exposure of 11.3 months (range, 0.1-90.4 months). The most common nonhematologic treatment-emergent adverse event (AE) occurring in ≥20% of patients was diarrhea (any grade, 27% and grade ≥3, 3%). Any-grade thrombocytopenia, anemia, and neutropenia occurred in 25%, 23%, and 7% of patients, respectively. The most common reason for momelotinib discontinuation was thrombocytopenia (4% discontinuation rate). The incidence of AEs of

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The full-text version of this article contains a data supplement.

clinical importance (eg, infections, malignant transformation, peripheral neuropathy, and hemorrhage) did not increase over time. This analysis of one of the largest randomized trial databases for a JAK inhibitor to date in MF demonstrated a consistent safety profile of momelotinib without long-term or cumulative toxicity. These trials were registered at www.clinicaltrials.gov as: MOMENTUM (#NCT04173494), SIMPLIFY-1 (#NCT01969838), SIMPLIFY-2 (#NCT02101268), and XAP (#NCT03441113).

Introduction

Myelofibrosis (MF) is a Philadelphia chromosome–negative myeloproliferative neoplasm characterized by splenomegaly, progressively worsening anemia and thrombocytopenia, and symptoms (eg, fatigue, cachexia, fever, night sweats, and bone pain) that negatively affect the quality of life.[1-4] Dysregulation of the Janus kinase (JAK)–mediated signaling pathway leads to abnormal myeloproliferation and overproduction of inflammatory cytokines, playing a key role in the pathogenesis of MF.[2,5,6] Two JAK inhibitors, ruxolitinib and fedratinib, are currently approved in many regions globally for MF; the JAK inhibitor pacritinib is also currently approved for MF only by the US Food and Drug Administration.[7-9]

Although ruxolitinib, fedratinib, and pacritinib have clinical benefits,[10-12] several limitations exist. Ruxolitinib frequently worsens anemia and thrombocytopenia, which often leads to dose reductions and treatment interruptions, potentially limiting treatment efficacy.[7,13,14] Furthermore, ruxolitinib dosing is based on patient characteristics such as platelet counts, which require close monitoring.[7] Fedratinib frequently causes gastrointestinal toxicities, can worsen anemia and thrombocytopenia, and has also been associated with the risk of Wernicke encephalopathy.[8] Although pacritinib does not have a myelosuppressive profile, it is associated with safety concerns of gastrointestinal toxicities, bleeding, and cardiovascular events, and is currently only approved for patients with MF with severe thrombocytopenia (platelet count $<50 \times 10^9$/L).[9,11,15,16] Safe and effective treatment is needed for patients with MF who are anemic or are no longer candidates for receiving currently approved JAK inhibitors.[13,17]

Momelotinib is a first-in-class oral inhibitor of activin A receptor type 1 (ACVR1), JAK1, and JAK2 that has been evaluated in both JAK inhibitor–naive and previously treated patients with intermediate- and high-risk MF in several clinical trials, including 3 randomized phase 3 trials (MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2),[18-20] and has demonstrated clinical activity against hallmark features of MF, such as anemia, symptoms, and splenomegaly.[18-22] Patients in these 3 studies were able to continue treatment (often for several years) in a long-term, extended access protocol (XAP) study. Momelotinib has shown demonstrable activity against anemia, with results from a phase 2 translational study linking these anemia benefits to its inhibition of ACVR1, which thereby reduces levels of circulating hepcidin (a key regulator of iron homeostasis), resulting in increased iron availability for erythropoiesis.[23,24]

To further characterize the safety and tolerability of momelotinib established in these trials,[18-20] we report the results of a long-term safety analysis of one of the largest data sets of patients with MF treated with a JAK inhibitor, pooling data from the MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 studies.

Methods

Data sources

Safety data were pooled from patients with intermediate- and high-risk MF who received ≥1 dose of momelotinib in MOMENTUM (NCT04173494), SIMPLIFY-1 (NCT01969838), and SIMPLIFY-2 (NCT02101268) (all phase 3 studies with enrollment dates from 2013 to 2021) and from patients who rolled over to the XAP study (NCT03441113; ongoing; supplemental Figure). The detailed study designs and protocols of MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 have been reported.[18-20]

In MOMENTUM, a randomized, double-blind, multicenter, phase 3 study of symptomatic and anemic patients with MF previously treated with a JAK inhibitor, patients were randomized (2:1) to receive momelotinib 200 mg once a day plus placebo or danazol 300 mg twice a day plus placebo. After 24 weeks of double-blind treatment, patients who continued receiving study treatment in the danazol arm were eligible to cross over to momelotinib therapy.[18]

In SIMPLIFY-1, a randomized, double-blind, multicenter, phase 3 study of patients with MF who had not received prior JAK inhibitor treatment, patients were randomized (1:1) to momelotinib 200 mg once a day plus placebo or ruxolitinib 20 mg twice a day (or dose adjusted per label)[7] plus placebo. After 24 weeks of double-blind treatment, patients who remained on study treatment in the ruxolitinib arm crossed over to momelotinib[20]; these patients were considered JAK inhibitor naive for this analysis.

In SIMPLIFY-2, a randomized, open-label, multicenter, phase 3 study of patients with MF who had been previously treated with ruxolitinib, patients were randomized (2:1) to momelotinib 200 mg once a day or best available therapy (BAT; 88.5% receiving ruxolitinib at the investigator's choice of dose, alone or in combination). After 24 weeks of randomized open-label treatment, patients who remained on study treatment in the BAT arm crossed over to momelotinib.[19]

The study protocols were reviewed and approved by each participating site's institutional review board or independent ethics committees, and the studies were conducted in accordance with good clinical practice guidelines and local country regulations. All patients provided written informed consent. Data analyses were performed by Sierra Oncology, and all authors had access to the final clinical study reports.

Assessments

AEs. Adverse events (AEs) were defined as those that started or worsened after the first dose of momelotinib and started ≤30 days after the last dose of momelotinib. For consistency across studies, AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. AEs were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 for SIMPLIFY-1 and SIMPLIFY-2, and version 5.0 for MOMENTUM; version differences did not affect the analysis. Unless otherwise specified, occurrences were described as a percentage of the total pooled analysis population (N = 725).

AEs of clinical importance were identified as all infections, including opportunistic infections; malignancies, including acute myeloid leukemia (AML) and nonmelanoma skin cancer; major adverse cardiovascular events (MACEs); anemia; neutropenia; thrombocytopenia; peripheral neuropathy; thromboembolism; and hemorrhage. The detailed search criteria for the categories of AEs of clinical importance are listed in the supplemental Methods. In addition, the incidence of AEs of clinical importance was analyzed using 24- and 48-week momelotinib treatment time windows. AEs of clinical importance were based on individual findings reported in momelotinib clinical studies as well as publications and prescribing information regarding the safety of approved JAK inhibitors.[7-9,11,19,20,25-27]

Because of the substantial variation in treatment duration, the exposure-adjusted AE rates were also calculated. Exposure-adjusted event rates in 100 person-years were calculated as 100 times the number of AEs, divided by the total person-time follow-up (in years). The number of AEs in the numerator included all new or existing AEs that started after momelotinib treatment within the specified follow-up period. The follow-up time in years was calculated as follows: (earlier date of treatment phase discontinuation date and 30 days after the last dosing date in the treatment phase − the first dosing date in the treatment phase + 1) ÷ 365.25.

Clinical laboratory tests. Hematology tests were summarized using actual values for each predefined analysis visit and were limited to MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 because the XAP study did not collect clinical laboratory results. The analyzed values are based on samples collected by central study laboratories. The mean hemoglobin levels and platelet counts over time for individual studies at various time points have been previously reported.[18,19,21]

Results

Patient demographics and disposition

The integrated safety analysis of MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 included 725 patients with MF (supplemental Figure). Of those who received momelotinib in any treatment phase of the 3 studies, 151 continued momelotinib in the XAP. The total follow-up time was 1261 person-years. Patient characteristics for this heterogeneous patient population, which encompassed the spectrum of MF disease with intermediate-1 or high-risk prognostic scores and overlapping severities of disease characteristics and anemia, are shown in supplemental Table 1.

The median duration of momelotinib exposure was 11.3 months (range, 0.1-90.4 months; Table 1). As of the data cutoff (3 December 2021), 12.1% of patients were treated for ≥5 years, including 75% of patients (88/118) who continued momelotinib in the XAP; overall, 50.6% of patients had ≥48 weeks of treatment. The median relative momelotinib dose intensity in the total analysis population was 97.3% (195 mg/day), with median relative dose intensities of 100% (200 mg/day) during randomized treatment and 97.2% (194 mg/day) during open-label treatment. As of the data cutoff, 176 patients (24.3%) were still receiving momelotinib. Most discontinuations were associated with MF progression (n = 100; 13.8%) and common MF-related complications, such as infections (n = 29; 4.0%) and thrombocytopenia (n = 27; 3.7%).

Common AEs

Any-grade and grade ≥3 AEs by preferred term, occurring in ≥10% of patients for any-grade events, are listed in Table 2. The most common any-grade nonhematologic AE was diarrhea (n = 194; 26.8%), followed by nausea (n = 141; 19.4%), fatigue (n = 127; 17.5%), and cough (n = 126; 17.4%). Most gastrointestinal AEs were grade 1 or 2. Peripheral sensory neuropathy was reported in 89 patients (12.3%), with grade ≥3 events in 5 (0.7%). The most common grade ≥3 nonhematologic AE was pneumonia (n = 61; 8.4%). Hematologic AEs included thrombocytopenia (any grade, n = 181 [25.0%] and grade ≥3, n = 119 [16.4%]), anemia (any grade, n = 170 [23.4%] and grade ≥3, n = 107 [14.8%]), and neutropenia (any grade, n = 49 [6.8%] and grade ≥3, n = 38 [5.2%]). Serious hematologic AEs occurred in <5% of patients (anemia, 4.6% and thrombocytopenia, 1.0%).

AEs of clinical importance

Prespecified AEs of clinical importance, including incidence during specific time windows, were evaluated to better understand the potential AEs associated with momelotinib (Table 2). Overall, patients did not experience new AEs over time while receiving momelotinib, with most AEs occurring during the first 24 weeks, corresponding to the randomized phase of treatment during the trials (Table 3).

Infections. Infections were defined by the system organ class (SOC) of infections and infestations of any severity and were the most common AEs of clinical importance evaluated (n = 402; 55.4%; Table 2). Most events were grade 1 or 2 (n = 248; 34.2% of the total analysis population and 61.7% of patients with infections) and not serious (n = 254; 35.0% of the total analysis population and 63.2% of patients with infections). After adjusting for exposure, event rates decreased from the randomized phase to the open-label/extended treatment phase (from 155.3 to 74.0 events per 100 person-years). The incidence of infections did not increase over time (Table 3).

Opportunistic infections. Opportunistic infections, such as herpes zoster, fungal infections, and atypical bacteria, occurred in 40 patients (5.5%; Table 2), and the incidence over time was stable (Table 3). Serious opportunistic infections were uncommon (n = 6; 0.8% of the total analysis population), and none were fatal. Exposure-adjusted event rates decreased from 9.2 to 3.8 events per 100 person-years from the randomized phase to the open-label/extended treatment phase.

Malignancies. The frequency of malignancies (based on a clinical review of the SOC Neoplasm Benign, Malignant, and Unspecified

Table 1. Treatment exposure, dose intensity, dose adjustment, and study drug discontinuation

Dosing and exposure	Momelotinib overall (N = 725)	Momelotinib-randomized treatment phase (n = 448)	Momelotinib open-label phase (n = 604)
Median duration of exposure (range), mo	11.3 (0.1-90.4)	5.5 (0.1-6.1)	11.0 (0.0-85.0)
Duration of exposure, n (%)			
≥4 wk	684 (94.3)	425 (94.9)	565 (93.5)
≥8 wk	637 (87.9)	402 (89.7)	515 (85.3)
≥12 wk	602 (83.0)	385 (85.9)	486 (80.5)
≥24 wk	513 (70.8)	207 (46.2)	406 (67.2)
≥48 wk	367 (50.6)	–	302 (50.0)
≥96 wk	213 (29.4)	–	193 (32.0)
≥36 mo	134 (18.5)	–	122 (20.2)
≥48 mo	103 (14.2)	–	98 (16.2)
≥60 mo	88 (12.1)	–	84 (13.9)
Average daily dose, median (range), mg	194.6 (0-494)	200.0 (0-229)	194.3 (0-775)
Relative dose intensity, median (range), %	97.3 (0-247)	100 (0-114)	97.2 (0-387)

Discontinuations	Momelotinib overall (N = 725)
Momelotinib discontinuation, n (%)	537 (74.1)
Primary reason for momelotinib discontinuation	
AE	183 (25.2)
Disease progression	100 (13.8)
Insufficient treatment efficacy	63 (8.7)
Patient decision	61 (8.4)
Death	55 (7.6)
Investigator discretion	47 (6.5)
Study terminated by sponsor	18 (2.5)

Data cutoff: 3 December 2021.

[Including Cysts and Polyps]; any grade, n = 97 [13.4%] and grade ≥3, n = 53 [7.3%]) was within the expected range for the patient age group (Table 2); the overall incidence of malignancies did not increase over time (Table 3). Exposure-adjusted event rates decreased from 18.9 to 13.0 events per 100 person-years from the randomized phase to the open-label/extended treatment phase.

Nonmelanoma skin cancer was reported in 35 patients (4.8%; Table 2). Most events were grade 2, and none were fatal or led to momelotinib discontinuation; incidence remained stable over time (Table 3). Exposure-adjusted event rates decreased from 8.1 to 7.7 events per 100 person-years from the randomized phase to the open-label/extended treatment phase.

AML (leukemic transformation). AML (leukemic transformation) occurred in 22 patients (3.0%; Table 2). Most events occurred in the first 24 weeks of treatment (Table 3), and exposure-adjusted event rates decreased from 4.3 to 1.4 events per 100 person-years from the randomized phase to the open-label/extended treatment phase, suggesting no increase in incidence with continued momelotinib exposure.

MACE. MACE, defined in accordance with the US Food and Drug Administration guideline on composite end point determination for cardiovascular and stroke studies,[28] occurred in 57 patients (7.9%), including 48 (6.6%) with grade ≥3 events (Table 2); 11 events (1.5%) were fatal. Momelotinib was associated with MACE incidence rates ranging from 0.9% to 4.9% during different time windows, but there was no consistent trend toward increased incidence over time (Table 3). Exposure-adjusted event rates decreased from 9.2 to 5.6 events per 100 person-years from the randomized phase to the open-label/extended treatment phase.

Thromboembolism. Thromboembolism was reported in 64 patients (8.8%), including 39 (5.4%) with grade ≥3 events (Table 2); however, the incidence did not increase over time (Table 3). Exposure-adjusted event rates decreased from 11.9 to 6.5 events per 100 person-years from the randomized phase to the open-label/extended treatment phase.

Hemorrhage. Hemorrhage (standardized MedDRA query search) occurred in 207 patients (28.6%); most patients (n = 158, 21.8% of the total analysis population and 76.3% of patients with hemorrhage) had events of grade 1 or 2 (Table 2). Among patients with baseline platelet counts $<150 \times 10^9$/L (n = 292), hemorrhage occurred in 32.2% (n = 94), representing 45.4% of hemorrhage events. A total of 118 patients (57.0% of patients with hemorrhage) had a last recorded platelet count $<150 \times 10^9$/L before a hemorrhage AE. Incidence was 19.4% from 0 to 24 weeks after the start of momelotinib therapy, 10.0% from 25 to 48 weeks, and subsequently decreased to 2.8%. Exposure-adjusted event rates

Table 2. Common treatment-emergent AEs

AE	Momelotinib (N = 725), n (%)	
	Any-grade AE	Grade ≥3 AE
Most common nonhematologic AEs (occurring in ≥10% of patients) by PT		
Diarrhea	194 (26.8)	19 (2.6)
Nausea	141 (19.4)	8 (1.1)
Fatigue	127 (17.5)	18 (2.5)
Cough	126 (17.4)	5 (0.7)
Dizziness	112 (15.4)	4 (0.6)
Abdominal pain	102 (14.1)	13 (1.8)
Pyrexia	102 (14.1)	9 (1.2)
Headache	101 (13.9)	6 (0.8)
Asthenia	96 (13.2)	8 (1.1)
Pruritus	90 (12.4)	5 (0.7)
Dyspnea	89 (12.3)	15 (2.1)
Peripheral sensory neuropathy	89 (12.3)	5 (0.7)
Urinary tract infection	88 (12.1)	18 (2.5)
Pneumonia	83 (11.4)	61 (8.4)
Constipation	81 (11.2)	1 (0.1)
Peripheral edema	75 (10.3)	5 (0.7)
Arthralgia	73 (10.1)	2 (0.3)
Upper respiratory tract infection	73 (10.1)	3 (0.4)
AEs of clinical importance*		
Infections (SOC)	402 (55.4)	154 (21.2)
Opportunistic infections (similar PTs)	40 (5.5)	11 (1.5)
Malignancies (similar PTs)	97 (13.4)	53 (7.3)
AML/malignant transformation (similar PTs)	22 (3.0)	22 (3.0)
Nonmelanoma skin cancer (similar PTs)	35 (4.8)	4 (0.6)
MACE (similar PTs)	57 (7.9)	48 (6.6)
Thrombocytopenia (similar PTs)	181 (25.0)	119 (16.4)
Neutropenia (similar PTs)	49 (6.8)	38 (5.2)
Anemia (similar PTs)	170 (23.4)	107 (14.8)
Thromboembolism (SMQ)	64 (8.8)	39 (5.4)
Hemorrhage (SMQ)	207 (28.6)	49 (6.8)
Peripheral neuropathy (SMQ)	107 (14.8)	9 (1.2)

Data cutoff: 3 December 2021.
Includes AEs reported between the first momelotinib dose date and 30 days after the last momelotinib dose date.
PT, preferred term; SMQ, standardized MedDRA query.
*Detailed search criteria for the categories of AEs of clinical importance are listed in the supplemental Methods.

decreased from 84.1 to 20.7 events per 100 person-years from the randomized phase to the open-label/extended treatment phase.

Peripheral neuropathy. Of the 107 patients (14.8%) who developed peripheral neuropathy, 89 (12.3%) had peripheral sensory neuropathy, 5 (0.7%) had peripheral sensorimotor neuropathy, and 4 (0.6%) had peripheral motor neuropathy. Nine patients (1.2%) experienced grade ≥3 events (Table 2); 2 events were considered serious, and none were fatal. The incidence was 7.6% during the 0 to 24-week window and decreased over time. Exposure-adjusted event rates decreased from 31.3 to 8.9 events per 100 person-years from the randomized phase to the open-label/extended treatment phase.

AEs leading to dose adjustments and discontinuation

Of the 725 patients in the pooled analysis, 262 (36.1%) had ≥1 AE (preferred term, unless otherwise specified), leading to dose adjustments (dose reduction/interruption) of momelotinib (Table 4). The most common AE leading to dose adjustment was thrombocytopenia (n = 76; 10.5%); infections and infestations (SOC), including pneumonia, led to dose adjustment in 51 patients (7.0%). Nausea and diarrhea led to momelotinib dose adjustments in 15 (2.1%) and 14 (1.9%) patients, respectively.

A total of 229 patients (31.6%) had ≥1 AE leading to momelotinib discontinuation, most commonly infections and infestations (SOC; n = 29; 4.0%) and thrombocytopenia (n = 27; 3.7%; Table 4). Diarrhea led to momelotinib discontinuation in 8 patients (1.1%). A complete list of AEs that led to discontinuation is shown in supplemental Table 2. Exposure-adjusted event rates for any AE leading to study drug discontinuation decreased over time from the randomized phase to the open-label/extended treatment phase (from 48.0 to 19.4 events per 100 person-years), including thrombocytopenia (from 5.4 to 1.6) and AML (from 2.2 to 0.7). Fatal AEs were reported in 102 patients (14.1%), with pneumonia being the most common (n = 9; 1.2%), followed by AML (n = 6; 0.8%) and sepsis (n = 5; 0.7%).

OS

With a median survival follow-up of 3.0 years in the pooled momelotinib-treated population, the survival probabilities were 76.5%, 59.6%, and 51.1% at years 2, 4, and 6, respectively; the median overall survival (OS) was not reached (95% confidence interval [95% CI], 5.01 years to not evaluable). In SIMPLIFY-1, the 2-, 4-, and 6-year OS rates were 81.6%, 62.9%, and 56.5% in momelotinib-randomized patients and 80.6%, 64.4%, and 52.7% in ruxolitinib-randomized patients who all crossed over to momelotinib, and the median follow-up durations were 3.4 and 3.5 years in the respective arms. In SIMPLIFY-2, the 2-year OS rate was 65.8% in momelotinib-randomized patients and 61.2% in BAT/ruxolitinib-randomized patients who all crossed over to momelotinib, and the median follow-up durations were 3.1 and 3.2 years in the respective arms.[29] In MOMENTUM, a trend toward improved OS over the entire study period was observed in the momelotinib group compared with the danazol group (hazard ratio [HR], 0.73; 95% CI, 0.38-1.41), and the median follow-up durations were 275 and 295 days in the respective arms. This trend was also observed during the first 24 weeks of treatment (randomized phase only; HR, 0.51; 95% CI, 0.24-1.08).[18]

Hematologic laboratory values

Changes in mean hemoglobin level, platelet count, and neutrophil count up to 48 weeks of treatment (24 weeks of randomized treatment, followed by open-label/extended treatment with momelotinib) in patients randomized to the momelotinib and control arms (danazol-treated patients from MOMENTUM, ruxolitinib-treated patients from SIMPLIFY-1, and BAT-treated patients from SIMPLIFY-2) are shown in Figure 1. Patients in MOMENTUM had the lowest baseline mean hemoglobin levels among the 3 studies, given the eligibility criterion of hemoglobin levels <10 g/dL; patients in SIMPLIFY-2 had lower mean hemoglobin levels at baseline than those in SIMPLIFY-1

Table 3. Incidence of select AEs of clinical importance over time

Time window (duration of time window), wk*	0-24 (24) N = 725	25-48 (24) n = 510	49-96 (48) n = 367	97-144 (48) n = 213	145-192 (48) n = 150	193-240 (48) n = 109	241-288 (48) n = 93	≥289 n = 64
n (%)								
Any AE	663 (91.4)	371 (72.7)	280 (76.3)	159 (74.6)	99 (66.0)	60 (55.0)	51 (54.8)	20 (31.3)
All infections (SOC)	263 (36.3)	133 (26.1)	121 (33.0)	64 (30.0)	38 (25.3)	22 (20.2)	20 (21.5)	8 (12.5)
Opportunistic infections (similar PTs)	13 (1.8)	7 (1.4)	9 (2.5)	8 (3.8)	3 (2.0)	0	4 (4.3)	1 (1.6)
Malignancies (similar PTs)	38 (5.2)	21 (4.1)	23 (6.3)	13 (6.1)	12 (8.0)	3 (2.8)	7 (7.5)	3 (4.7)
AML/malignant transformation (similar PTs)	12 (1.7)	1 (0.2)	6 (1.6)	1 (0.5)	2 (1.3)	0	0	0
Nonmelanoma skin cancer (similar PTs)	9 (1.2)	14 (2.7)	10 (2.7)	5 (2.3)	3 (2.0)	1 (0.9)	3 (3.2)	3 (4.7)
MACE (similar PTs)	20 (2.8)	9 (1.8)	18 (4.9)	8 (3.8)	4 (2.7)	1 (0.9)	2 (2.2)	1 (1.6)
Thromboembolism (SMQ)	25 (3.4)	12 (2.4)	19 (5.2)	8 (3.8)	6 (4.0)	2 (1.8)	3 (3.2)	2 (3.1)

Data cutoff: 3 December 2021.
PT, preferred term; SMQ, standardized MedDRA query.
*n in the column heading represents the number of patients who were still receiving treatment at the beginning of each time window and is used as the denominator to calculate percent of patients with AEs. A patient can appear multiple times in this table because it captures the presence of an event during a specific time window. Events included could be of any severity.

Table 4. Treatment-emergent AEs leading to dose interruption/reduction and treatment discontinuation

Preferred term, unless noted otherwise	N = 725 n (%)
AE leading to dose interruption/reduction in ≥1% of patients	
Any AE	262 (36.1)
Thrombocytopenia	76 (10.5)
Infections and infestations (SOC)*	51 (7.0)
Nausea	15 (2.1)
Diarrhea	14 (1.9)
Anemia	12 (1.7)
Neutropenia	12 (1.7)
Asthenia	11 (1.5)
Headache	11 (1.5)
Alanine aminotransferase increased	9 (1.2)
Atrial fibrillation	8 (1.1)
Fatigue	8 (1.1)
Platelet count decreased	8 (1.1)
AE leading to momelotinib discontinuation in ≥1% of patients	
Any AE	229 (31.6)
Infections and infestations (SOC)†	29 (4.0)
Thrombocytopenia	27 (3.7)
Peripheral sensory neuropathy	13 (1.8)
Acute myeloid leukemia	11 (1.5)
Disease progression	11 (1.5)
Diarrhea	8 (1.1)
Anemia	7 (1.0)
Splenomegaly	7 (1.0)

*Includes preferred term pneumonia (n = 15; 2.1%).
†Includes preferred term pneumonia (n = 8,;1.1%).

(Figure 1A). As previously reported, mean hemoglobin levels increased in each momelotinib-treated population, including patients in the control arms who had crossed over to receive momelotinib after week 24, and were maintained over time[18,19,21] Consistent with these improvements in mean hemoglobin levels, the incidence of anemia events (similar preferred terms) did not increase over time with momelotinib. Mean platelet counts (Figure 1B) also varied at baseline, depending on the study, and were lower in SIMPLIFY-2 and MOMENTUM, which enrolled patients who had received prior JAK inhibitor treatment, than in SIMPLIFY-1. However, mean counts comparable to baseline were maintained throughout the duration of momelotinib treatment, as previously reported for individual studies.[18,19] Similarly, mean neutrophil counts fluctuated across studies but did not show any consistent trends over time compared with baseline (Figure 1C). In patients treated with momelotinib, neutropenia was not common, and incidence decreased over time.

Discussion

This integrated analysis characterized the overall safety profile of momelotinib by summarizing AEs and survival across the phase 3 clinical trial program. Most AEs frequently observed with momelotinib were of grade 1/2 and did not worsen with continued

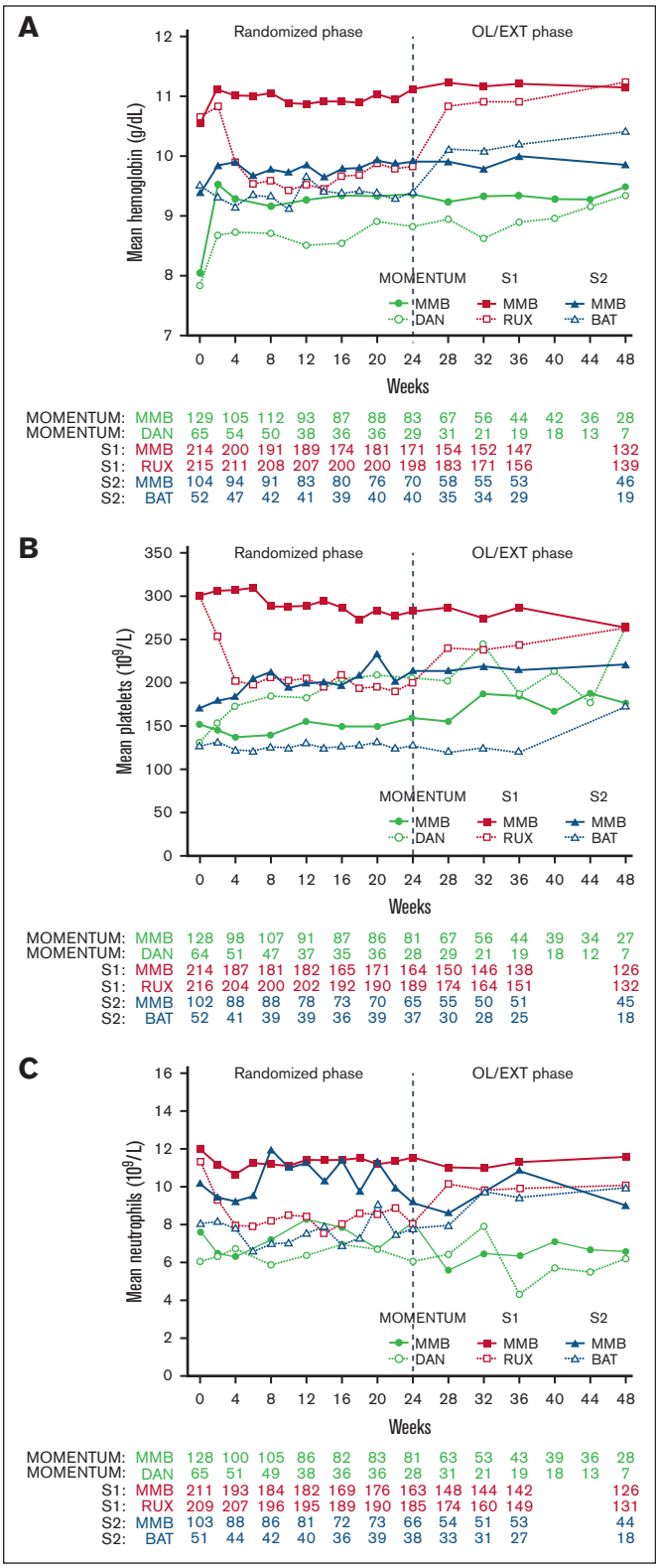

Figure 1. Mean laboratory values over time based on treatment group. (A) Hemoglobin levels. (B) Platelet counts. (C) Neutrophil counts. DAN, danazol; MMB, momelotinib; OL/EXT, open-label/extended treatment; RUX, ruxolitinib; S1, SIMPLIFY-1; S2, SIMPLIFY-2.

treatment. Indeed, there was no time trend suggesting late-onset or cumulative toxicity with exposure through 7 years, aligning with phase 1/2 momelotinib trials, in which some patients have now been receiving treatment for >11 years. Analyses over time showed that the incidence of most toxicities, including infections and hematologic AEs, decreased over time despite continued momelotinib dosing. The dose intensity of momelotinib was maintained throughout the duration of treatment (median relative dose intensity, 97.3%), thereby preserving an effective therapeutic drug exposure.

Although diarrhea was the most common nonhematologic AE associated with momelotinib, gastrointestinal toxicities were mostly low grade and not the most common AEs leading to dose adjustment or discontinuation. Notably, prophylactic treatment was not protocol-mandated in any of the 3 studies included in this analysis. This contrasts with patients who received fedratinib or pacritinib in clinical trials, in which gastrointestinal AEs were prominent and prophylaxis was administered.[5,11,15,30] Among the AEs of clinical importance that were assessed in this momelotinib analysis, infections occurred as expected in a population with MF[31] but were mostly low grade and did not increase with long-term dosing. Serious opportunistic infections were uncommon and did not lead to death. Nonmelanoma skin cancer was observed with long-term momelotinib treatment (4.8%), consistent with previous reports on other JAK inhibitors.[27,32] Although transformation to AML is a common morbidity for patients and one of the leading causes of death in MF,[31,33] AML and leukemic transformation occurred infrequently with momelotinib, with no evidence of increased risk over time. The AML rate (3.0%) was low and comparable with those of other JAK inhibitors.[16,26,27] Peripheral neuropathy, mostly characterized by grade 1 or 2 numbness and paresthesia, occurred at low rates in the pooled analysis, with only 2 events considered serious. Therefore, this AE does not seem to be a reaction of significant concern in the treated population. Serious hemorrhage and thrombosis events were also uncommon, and the incidence did not increase over time.

Among these AEs of clinical importance, most of the serious AEs reported with momelotinib were consistent with well-described MF complications, including cytopenias, infection, cardiovascular disease, and thrombosis.[6,31] However, these events may also represent potential JAK inhibitor toxicities in malignant and nonmalignant conditions. For example, a systematic review of the literature describes a potential signal for an increased risk of infection, especially herpes zoster, in ruxolitinib-treated patients.[34] Furthermore, cytopenias are a key reason why many patients with MF cannot continue to receive effective doses of ruxolitinib.[13,35] A randomized safety study (ORAL Surveillance) has also shown a signal for MACE and malignancies with the JAK inhibitor tofacitinib, which is used in the treatment of rheumatoid arthritis.[36] Notably, the 3 pooled phase 3 studies of momelotinib in the present analysis represent a much smaller patient sample than that in the ORAL Surveillance study of tofacitinib; however, a review of the safety data suggests that momelotinib does not increase the risk of MACE or malignancies. Overall, analysis of these AEs of clinical importance indicates that they are unlikely to affect the positive benefit-risk balance of momelotinib in patients with MF.

Because of the prevalence of cytopenias in intermediate- and high-risk MF and based on what has been observed with currently available JAK inhibitors, such as ruxolitinib in MF, hematologic AEs were expected to be common in this analysis population.[10,11,27,37,38] In fact, the analysis identified thrombocytopenia as the most common AE resulting in momelotinib dose modification (10.5%); nonetheless, these events less frequently led to momelotinib discontinuation (3.7%). Furthermore, despite ongoing treatment with momelotinib, the incidence of hematologic AEs decreased or remained stable over time. Consistent with the decreasing incidence of hematologic AEs over time, laboratory values, namely mean hemoglobin levels, platelet counts, and neutrophil counts, improved or remained consistent. Although confounded by patients already having low baseline values, especially in MOMENTUM and SIMPLIFY-2, momelotinib improved mean hemoglobin levels and maintained mean platelet and neutrophil counts; this was observed even in patients who had crossed over from the control arms, illustrating the consistent impact of momelotinib on mean laboratory values after receiving another type of therapy. The apparent anemia benefits of momelotinib may be linked to its inhibition of ACVR1 and regulation of hepcidin, which is frequently elevated in MF and is associated with poor prognosis.[39] Inhibition of ACVR1 decreases hepatic hepcidin production, thereby increasing iron availability for erythropoiesis.[23,24] Other currently approved JAK inhibitors that may be associated with hematologic AEs, such as ruxolitinib and fedratinib, do not have demonstrated activity against ACVR1 in conjunction with reduced hepcidin levels.

In summary, this momelotinib analysis describes one of the largest clinical trial safety databases for JAK inhibitors in MF, including patients in both treatment-naive and previously treated settings, with a wide range of disease severity and blood counts. The results from this pooled safety analysis, together with those of previous clinical studies, demonstrate that continuous treatment with momelotinib is tolerated by most patients with MF without cumulative or long-term toxicity, highlighting a positive benefit-risk balance for momelotinib in patients with intermediate- or high-risk MF.

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Authorship

Contribution: M.M. led the integrated analysis design and interpretation; J.K. contributed to the study design, and analysis and interpretation of study data; M.Huang. performed statistical analyses; and all authors had access to the data, contributed to its interpretation, participated in writing and reviewing the manuscript, and provided final approval.

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