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## A phase 2 study of momelotinib, a potent JAK1 and JAK2 inhibitor, in patients with polycythemia vera or essential thrombocythemia

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### Abstract

Momelotinib is a potent inhibitor of JAK1 and JAK2 that demonstrated efficacy in patients with primary and secondary myelofibrosis. This phase 2, open-label, randomized study evaluated the efficacy and safety of oral once-daily momelotinib (100 mg and 200 mg) for the treatment of polycythemia vera (PV) and essential thrombocythemia (ET). The primary endpoint for PV was overall response rate (ORR), defined as the proportion of patients with hematocrit < 45%, white blood cell count <  $10 \times 10^9/L$ , platelet count <  $400 \times 10^9/L$ , and resolution of palpable splenomegaly, each lasting  $\geq 4$  weeks. The definition of ORR for ET excluded the hematocrit component. A total of 39 patients (28 PV, 11 ET) were enrolled, with 28 patients receiving  $\geq 12$  weeks of treatment. The study was terminated due to limited efficacy. Two patients (ORR 5.1%) met the primary efficacy endpoint (both PV 200 mg). Predose plasma levels of momelotinib were stable over time. A total of 31 (79.5%) patients experienced momelotinib-related adverse events (AEs), the most frequent being headache (23.1%), dizziness (18.0%), somnolence (15.4%), nausea (15.4%), and fatigue (15.4%). Three patients experienced serious AEs (7.7%), with 1 considered

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Author contributions

SV and RM designed the study and SV, SC, MG, RM, JK, DH, AB contributed to the conduct of the study. SV, RM, CBB, JK, JM, LS, and YX analyzed or interpreted the results and SV, RM, CBB, JK, and JM drafted the manuscript. All authors revised and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.leukres.2017.05.002>.

related to momelotinib (dyspnea). Peripheral neuropathy occurred in 7 (17.9%) patients (4 PV, 3 ET).

## Keywords

Momelotinib; Polycythemia vera; Essential thrombocythemia; Phase 2 study

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## 1. Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (MF) belong to a group of *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs) [1], characterized by excessive clonal myeloproliferation, resulting, characteristically, in erythrocytosis in PV and thrombocytosis in ET [1,2]. Other disease characteristics may include leukocytosis, splenomegaly, thrombosis, bleeding, microcirculatory symptoms, and several constitutional symptoms (headache, fatigue, dizziness, pruritus, and sweating) [2,3]. Standard therapies for PV and ET are ineffective or intolerable in some patients [4,5]. Therefore, there is a need for improved, biologically targeted therapies.

A single acquired substitution of valine for phenylalanine in codon 617 in the Janus kinase (JAK) 2 gene (*JAK2*<sup>V617F</sup>) is frequently present in patients with PV (about 97%) or ET (about 57%) [6–9]. This mutation renders JAK2 kinase constitutively active, disrupts Signal Transducer and Activator of Transcription (STAT) signaling, and leads to cell transformation [7,9,10]. Higher burden of *JAK2*<sup>V617F</sup> is associated with pruritus and an increased risk of fibrotic transformation in PV [11] and arterial and venous thrombosis in ET [12]. Less common MPN-associated mutations include *JAK2* exon 12 mutation (seen in PV), and calreticulin or myeloproliferative leukemia virus oncogene mutations (seen in ET) [2,13]. All of these mutations activate the JAK-STAT pathway in hematopoietic cells. A hyperactive JAK-STAT pathway, therefore, is a unifying biological abnormality in MPNs and is a target for new drug development (ie, JAK inhibitors).

Several small-molecule compounds developed to inhibit activity of JAK2 have demonstrated efficacy in patients with MF, PV, and ET [14–20], but many had further development stalled due to their toxicity (eg, neurological side effects) and/or limited efficacy [21]. One of the newer compounds, momelotinib (formerly CYT387), is an aminopyrimidine derivative that inhibits activity of JAK1 and JAK2 [22,23], and demonstrates activity in a mouse model of *JAK2*<sup>V617F</sup>-driven PV-like MPN [24] and in patients with primary and secondary MF [25,26].

This paper presents results of an open-label phase 2 study of momelotinib in patients with PV and ET. The study was terminated early due to limited efficacy. This paper discusses possible explanations for why momelotinib is efficacious in MF, but did not benefit patients with PV or ET.

## 2. Methods

### 2.1. Patients

Male or nonpregnant, nonlactating females, 18 years old diagnosed with either PV or ET, as defined by the 2008 WHO Diagnostic Criteria, requiring treatment, were eligible for this study [1]. Patients were required to have direct bilirubin  $\leq 2$  x upper limit of normal (ULN); liver transaminases  $\leq 3$  x ULN; calculated creatinine clearance of  $\geq 45$  mL/min; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; and a life expectancy  $> 24$  weeks. Key exclusion criteria included prior splenectomy, major surgery within 28 days of first dose of study drug, myeloproliferative neoplasm-directed therapy (other than aspirin, hydroxyurea, anagrelide, and/or phlebotomy) within 21 days of first dose of study drug, use of strong cytochrome P450 3A4 inhibitors or inducers within 1 week of the first dose of study drug, prior use of a JAK1 or JAK2 inhibitor, hepatitis B or C infection, human immunodeficiency virus-positive, unresolved (grade  $> 1$ ) non-hematologic toxicities from prior therapies, or the presence of peripheral neuropathy grade  $\geq 2$ . All patients provided signed informed consent.

### 2.2. Study design

This was an open-label, randomized phase 2 study ([ClinicalTrials.gov # NCT01998828](https://clinicaltrials.gov/ct2/show/study/NCT01998828)). Patients with PV or ET were randomized via interactive voice/web response system 1:1 to receive either 100 or 200 mg of oral momelotinib once daily. Momelotinib 200 mg tablets were chosen for their equivalence to 300-mg capsules (data not shown), which demonstrated effectiveness in MF patients [25,26]. The 100-mg tablet of momelotinib achieved approximately 50% exposure compared with the 200-mg capsule, and was expected to be efficacious based on preliminary dose-response analyses (data not shown). The 100-mg dose was administered in this study to determine whether a lower dose would be sufficient to treat PV or ET compared with the dose needed to treat MF.

All patients were observed for 4 h after the first dose of momelotinib due to possible first-dose hypotension, which was reported within hours after first dose and returned to baseline within 24 h in a previous study on momelotinib in MF patients [26]. In the event of a grade 3 or 4 toxicity considered related to momelotinib, the treatment was interrupted for a maximum of 28 days and was restarted following resolution with dose reduced by 50 mg. If a recurrent grade 3 or 4 toxicity related to momelotinib occurred in patients already taking the 100-mg dose, the treatment was discontinued permanently. The treatment was administered for 24 weeks or until study discontinuation. Following completion of 24 weeks of treatment or study discontinuation, patients were followed for safety and disease status for 30 days. Patients had the option of continuing with maintenance treatment beyond 24 weeks at the clinically beneficial and/or tolerated dose, at investigators' discretion (separate rollover study). This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice.

### 2.3. Study endpoints and assessments

The primary efficacy endpoint was the overall response rate (ORR), defined for the PV cohort as the proportion of patients with hematocrit  $< 45\%$  in the absence of phlebotomy,

white blood cell (WBC) count  $< 10 \times 10^9/L$ , platelet count  $400 \times 10^9/L$ , and resolution of palpable splenomegaly; each lasting for at least 4 weeks. For the ET cohort, ORR was defined as WBC count  $< 10 \times 10^9/L$ , platelet count  $400 \times 10^9/L$ , and resolution of palpable splenomegaly; each criterion met for at least 4 weeks. For patients to be considered responders, all criteria had to be met at some point during the treatment period (not necessarily for the same 4 weeks).

A key secondary endpoint was confirmed ORR for PV or ET, defined as the proportion of responders who maintained the overall response for 12 weeks (all criteria not necessarily met for the same 12 weeks). Other secondary endpoints included proportion of patients with hematocrit  $< 45\%$  in the absence of phlebotomy, WBC  $< 10 \times 10^9/L$ , platelet count  $400 \times 10^9/L$ , and resolution of palpable splenomegaly, all lasting for at least 4 weeks; and proportion of patients with 10-point decrease from baseline in the modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) lasting for at least 12 weeks.

Following screening, patients received an electronic diary to complete the modified MPN-SAF TSS daily through the week 24 or study drug discontinuation visit. Clinical laboratory and disease assessments were performed at the scheduled visits every other week during the first 8 weeks of treatment, and every 4 weeks thereafter.

To monitor the pharmacokinetics of momelotinib and its metabolites, plasma samples were collected prior to dosing at 2, 4, 8, 12, 16, 20, and 24 weeks. Safety was evaluated by characterization of laboratory abnormalities and adverse events (AEs), which were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

*JAK2*<sup>V617F</sup> allele burden was determined in whole blood by allele-specific quantitative real-time polymerase chain reaction (Cancer Genetics Inc., Rutherford, NJ). Relevant plasma markers were analyzed by immunoassay (Myriad MAPv2.0, Austin, TX).

#### 2.4. Statistical analyses

Efficacy was assessed in the intent-to-treat analysis set, which included all randomized patients. The pharmacokinetic analysis set included all patients who received 1 dose of momelotinib and had 1 momelotinib plasma concentration measurement. Safety analyses included all patients who received 1 dose of momelotinib, with study treatment assignment designated according to the actual treatment received.

For each treatment group, ORR and corresponding 90% exact confidence intervals, confirmed ORR, and proportions of patients meeting the criteria of secondary endpoints were calculated using the binomial distribution. Resolution of splenomegaly was defined as 100% reduction in spleen size postbaseline, with baseline spleen size defined as the last spleen size measurement by palpation from the baseline period prior to randomization. Patients who met hematocrit (PV only), WBC, and platelet criteria could be counted as responders if their postbaseline spleen size (0– < 5) remained unchanged.

Baseline and postbaseline MPN-SAF TSS was defined as the average of daily total symptom score (TSS) from the 7-day period. Daily TSS was defined as the sum of 7 individual

symptom scores (each on a 0–10 point scale) collected on the same day. The steady state trough plasma concentrations (at 22–26 h postdose) of momelotinib and its metabolites were summarized by dose and nominal sampling time using descriptive statistics.

### 3. Results

#### 3.1. Patient disposition

From March to October 2014, 39 patients (28 PV, 11 ET) were enrolled. The study was terminated in February 2015 due to limited efficacy. By then, all enrolled patients either completed at least 12 weeks of treatment or withdrew early from the study. All data collected up to week 24 were analyzed.

All patients received at least 1 dose of momelotinib and 15/39 (38.5%) completed the study (10 PV, 5 ET; Fig. 1). The most common reasons for discontinuations were AEs, study termination, investigator's decision, and withdrawal of consent (Fig. 1). In total, 28/39 (71.8%) patients received at least 12 weeks of treatment with momelotinib and 12/39 (30.8%) received 24 weeks of treatment.

The majority of enrolled patients were male (59.0%) and white (79.5%), with a median age (range) of 62.1 (34.4–81.0) years in the PV cohort and 51.1 (37.8–73.8) years in the ET cohort (Table 1). The median time from diagnosis was 5.2 years for PV patients and 6.6 years for ET patients. Prior PV- or ET-directed therapies (hydroxyurea, interferon, interferon-alpha 2A or 2B, pipobroman, or aspirin) were used by 12 (42.9%) PV patients and 5 (45.5%) ET patients, with a median of 1 prior therapy per cohort. In the PV cohort, 17 (60.7%) had a hematocrit  $\geq 45\%$ , 12 (42.9%) had platelet counts  $\geq 400 \times 10^9/L$ , 16 (57.1%) had WBC counts  $\geq 10 \times 10^9/L$ , and 7 (25.0%) had spleen size  $\geq 5$  cm below the costal margin. In the ET cohort, 11 (100%) had platelet counts  $\geq 400 \times 10^9/L$ , 1 (9.1%) had WBC counts  $\geq 10 \times 10^9/L$ , and none had spleen size  $\geq 5$  cm below the costal margin. The *JAK2*<sup>V617F</sup> mutation was evident in 45.5% of ET patients (n = 11) and 82.1% of PV patients (n = 28). The baseline mean  $\pm$  standard deviation *JAK2*<sup>V617F</sup> allele burden was  $18.9 \pm 22.3\%$  in PV patients and  $3.6 \pm 4.1\%$  in ET patients. Spleen size was more variable in PV patients (Table 1).

#### 3.2. Efficacy

Two PV patients treated with momelotinib (both taking the 200-mg daily dose) and none of the ET patients met the criteria for overall response. The total ORR for the study was 2/39 (5.1%) (Table 2). Among patients with abnormal values at baseline, there was 1 response each for hematocrit, WBC, and platelet count in PV patients and 1 WBC response in ET patients (Table 2). Two PV patients and none of the ET patients achieved spleen response (12 cm reduced to 0 cm and 5 cm reduced to 0 cm, respectively).

There was 1 confirmed overall response (2.6%) in the 200-mg PV cohort. Overall, 2/39 (5.1%) patients had a  $\geq 10$ -point decrease in the modified MPN-SAF TSS that lasted  $\geq 12$  weeks (Table 2). Momelotinib treatment did not significantly change *JAK2*<sup>V617F</sup> allele burden for patients that were *JAK2*<sup>V617F</sup>-positive at baseline (Table 2). At 4 weeks, plasma

C-reactive protein was 2-fold decreased in both cohorts (Supplemental Table 1). Changes for other inflammatory biomarkers at 4 weeks are included in Supplemental Table 1.

### 3.3. Pharmacokinetics

Steady state trough plasma concentrations of momelotinib were stable, with moderate variations, throughout the study. The 200-mg dose generally resulted in higher trough plasma concentrations than the 100-mg dose (Supplemental Table 2). Between weeks 2 and 24, the range of median plasma concentration was 12.1 to 26.8 ng/mL in the 100-mg PV and ET cohorts, and 22.3 to 51.3 ng/mL in the 200-mg PV and ET cohorts (Fig. 2). A similar trend was noted for momelotinib metabolites (not shown). The 2 patients who achieved overall response were not outliers in plasma momelotinib levels.

### 3.4. Safety

The median (min, max) duration of exposure to momelotinib was 143.5 (3.0, 175.0) days for PV patients and 167.0 (54.0, 169.0) days for ET patients. Of 39 patients enrolled in the study, 19 received momelotinib 100 mg/day (PV, n = 14; ET, n = 5) and 20 patients received momelotinib 200 mg/day (PV, n = 14; ET, n = 6). A total of 12/39 (30.8%) patients received momelotinib for 24 weeks. One PV patient treated with momelotinib 200 mg had a dose interruption due to AEs (asthma, hemoptysis, and noncardiac chest pain; none considered related to momelotinib). Six patients (PV, n = 4; ET, n = 2) had a dose reduction at the investigator's discretion (2 due to an AE [both in the PV 200 mg cohort] and 4 due to other reasons, including withdrawal necessitating dose taper). AEs leading to dose reduction were fatigue, nausea, impaired concentration, dizziness, dyspnea, and peripheral sensory neuropathy in 1 patient (considered related to momelotinib); and fatigue, pain, and dizziness in another patient (all related to momelotinib).

In total, 36/39 (92.3%) patients reported at least 1 AE (Supplemental Table 3). The most frequent AEs were headache (5/14, [35.7%]), somnolence (4/14, [28.6%]), and hypertension (3/14, [21.4%]) in the PV 100 mg cohort; and dizziness (6/14, [42.9%]), fatigue (4/14, [28.6%]), headache (4/14, [28.6%]), hypertension (4/14, [28.6%]), and nausea (4/14, [28.6%]) in the PV 200 mg cohort. In the ET 200 mg cohort, the most common AEs were dizziness (3/6, [50.0%]), headache (3/6, [50.0%]), and thrombocytosis (3/6, [50.0%]). Headache, diarrhea, thrombocytosis, and pain in extremity each occurred in 1/5 (20.0%) patients (all in the ET 100 mg cohort). Thrombocytosis was likely related to lack of treatment efficacy.

The most common AEs considered related to momelotinib treatment were headache, dizziness, somnolence, nausea, and fatigue (Table 3). Dizziness and somnolence were more common in PV patients (6 each) than in ET patients (1 with dizziness). Severe (grade 3) AEs included hypertension, dizziness, fatigue, and bone pain (Table 3). All AEs of interest were grade 1 and included peripheral neuropathy occurring in 7 (17.9%) patients (PV, n = 4; ET, n = 3) and 1 case of cataract (PV). In total, 9/39 (23.1%) patients discontinued the study due to at least 1 AE. In 7/39 (18.0%) patients, AEs leading to discontinuation were considered related to momelotinib (MF [likely progression of disease], palpitations, pain in extremity, fatigue, increased platelet count, thrombocytosis, and dyspnea). One patient died

due to cardiopulmonary arrest, which was considered unrelated to study treatment after review by the medical safety monitor.

The majority of recorded laboratory abnormalities were grade 1 or 2. Grade 3 events included 2 cases of hyperuricemia and 1 case each of elevated triacylglycerol lipase and hyperkalemia (both in PV patients). Decreased lymphocytes occurred in 1 ET patient. None of these events were considered clinically significant.

#### 4. Discussion

The results presented herein indicate that momelotinib treatment has very limited activity as therapy for PV or ET. Out of 39 patients enrolled in this study, 2 patients (5.1%) met the primary composite endpoint (ORR), with only 1 confirmed response. Both responders were PV patients receiving momelotinib 200 mg/day. Single component hematocrit, WBC, or platelet count responses were noted in 3 patients in the PV cohort and 1 patient in the ET cohort (WBC response). Two PV patients and none of the ET patients achieved a spleen response. In total, 1 PV patient and 1 ET patient had a 10-point decrease from baseline in modified MPN-SAF TSS that lasted 12 weeks.

This finding contrasts previously published nonclinical and clinical data. Momelotinib inhibited JAK1 and JAK2 at nanomolar concentrations in in vitro assays, and reduced ex vivo formation of erythroid colonies from *JAK2<sup>V617F</sup>*-positive PV patients [22]. In a mouse model of *JAK2<sup>V617F</sup>*-driven PV-like MPN, momelotinib reduced *JAK2<sup>V617F</sup>* allele burden and disease symptoms; and restored normal spleen size, hematocrit, white blood cell counts, and cytokine levels [24].

Two open-label phase 1/2 clinical trials support the efficacy of momelotinib in treatment of MF in patients with high- or intermediaterisk primary or post-PV/ET MF [25,26]. Spleen responses were achieved in 45.8% to 48% patients and anemia responses in 45% to 59% of patients [25,26]. Moreover, among patients with baseline transfusion-dependence, 51.7% achieved 8-week transfusion-independence [26] and 21.1% to 67% achieved 12-week transfusion-independence.

The explanation for this apparent discrepancy in the activity of momelotinib in different MPNs is unclear. The data reported for other JAK2 inhibitors vary. Lestaurtinib (CEP-701) achieved only a modest response rate (14%) in patients with PV and ET [19]. Trials evaluating TG101348 (SAR302503) in PV and ET patients ([ClinicalTrials.gov#NCT01420783](https://clinicaltrials.gov/ct2/show/study/NCT01420783)) [27] were halted due to toxicity [28]. Gandotinib (LY-2784544) was well tolerated and showed some clinical improvement in PV and ET patients in a phase 1 study [29]. Ruxolitinib has demonstrated efficacy in patients with PV in phase 2 and 3 studies [14,17,30] and is approved for PV patients who have resistance or intolerance to hydroxyurea treatment [31].

There are notable differences in patients and study design between this study and the previous phase 2 and phase 3 ruxolitinib trials. First, the patients in ruxolitinib trials were resistant to or intolerant of hydroxyurea treatment [14,17,30], whereas this study did not require this for enrollment. Second, our primary endpoint had a different definition of

response for PV patients (hematocrit, WBC, platelet, and spleen responses) compared with the ruxolitinib trials (hematocrit response without phlebotomy or hematocrit response with reduction in spleen size).

The pharmacokinetic results of momelotinib 200 mg in PV and ET patients are generally consistent with findings in MF patients taking the equivalent 300-mg once-daily capsules, which showed efficacy in MF through JAK1/2 inhibition [25]. An additional dose (100 mg) of momelotinib was tested to identify the optimal dosage, which was discovered to be 200 mg. It is possible that treatment with a 200-mg momelotinib starting dose for longer than 24 weeks in patients with more advanced PV would have shown a greater overall response rate. In conclusion, momelotinib 100 mg or 200 mg was well tolerated in PV/ET patients for up to 24 weeks, but had limited efficacy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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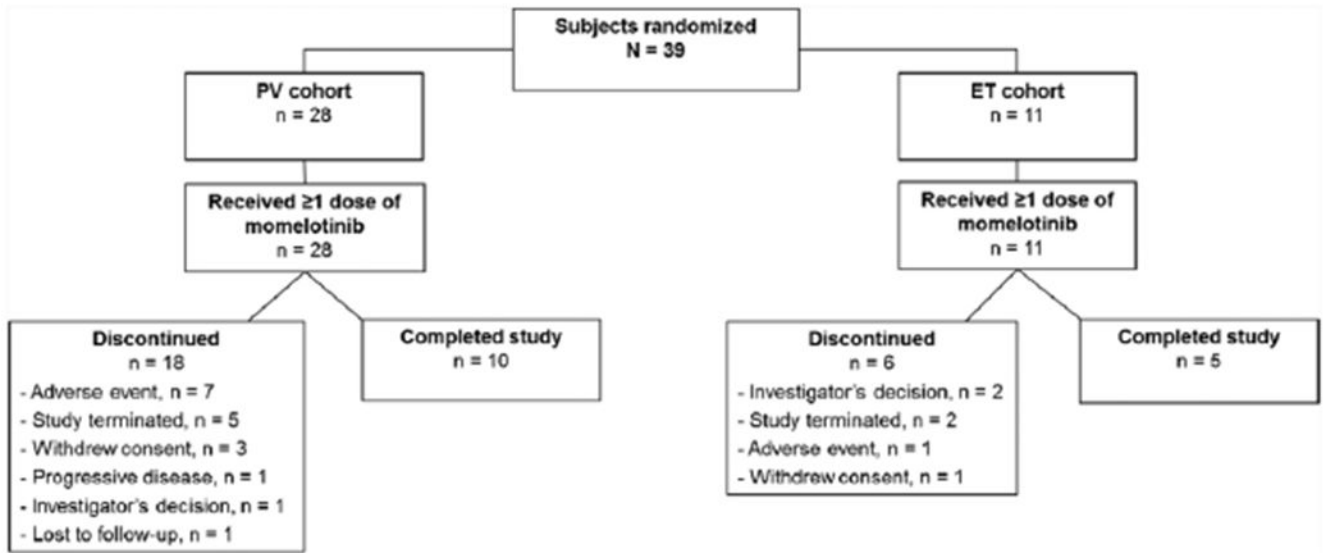
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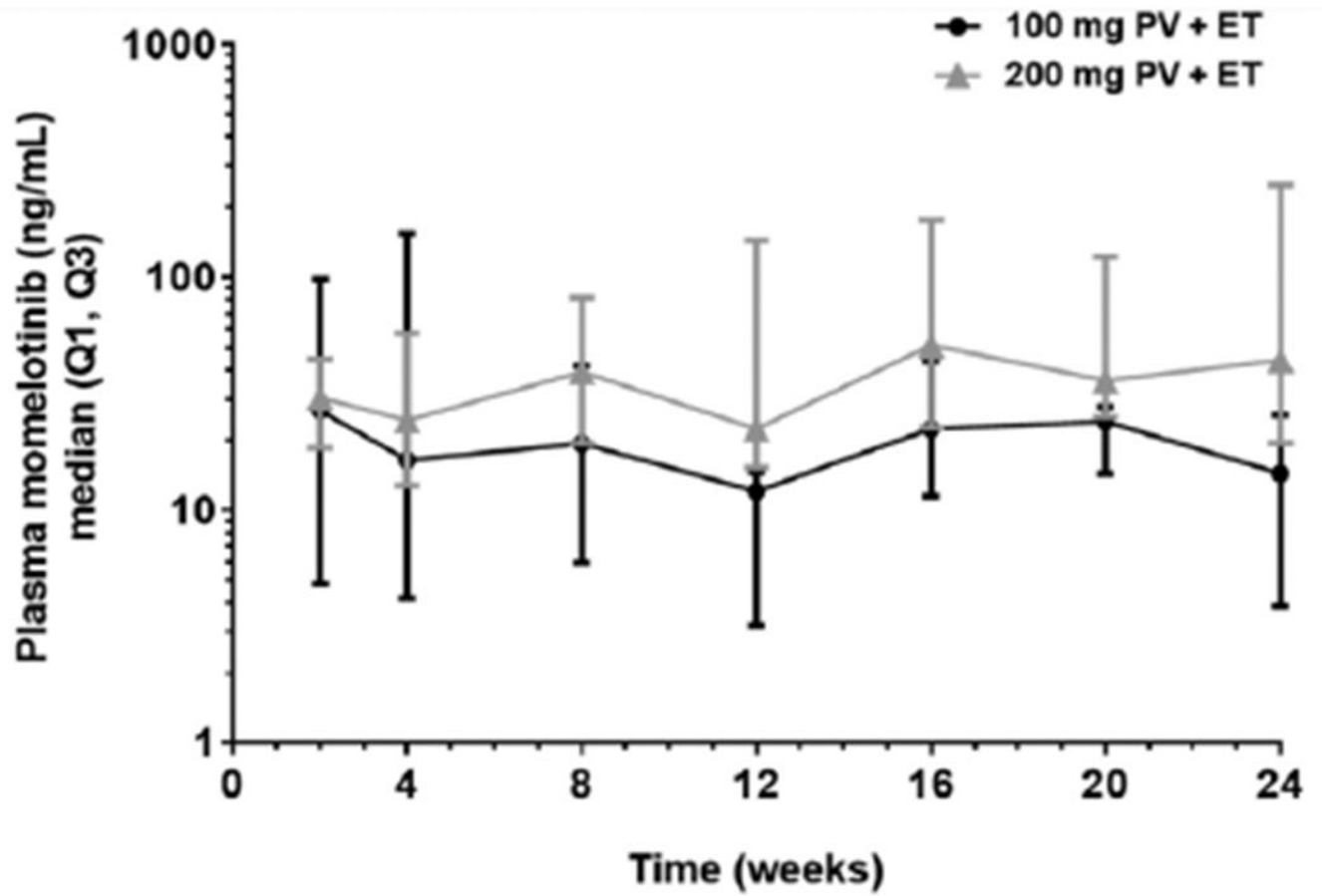


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**Fig. 1.**  
Patient disposition.  
ET, essential thrombocythemia; PV, polycythemia vera.



**Fig. 2.**  
Momelotinib plasma concentration over time by dose.  
ET, essential thrombocythemia; PV, polycythemia vera; Q1, first quartile; Q3, third quartile.

Table 1

Demographic and baseline clinical characteristics.

	PV Cohort		ET Cohort		Total (N = 11)
	100 mg (N = 14)	200 mg (N = 14)	100 mg (N = 5)	200 mg (N = 6)	
Age [years]					
Median (Range)	61.1 (34.4–81.0)	62.1 (51.7–75.2)	62.1 (34.4–81.0)	47.8 (39.6–70.7)	51.1 (37.8–73.8)
Hematocrit [%]					
Median (Range)	44.0 (36.0–54.0)	47.5 (39.0–55.0)	45.5 (36.0–55.0)	42.5 (38.0–45.0)	42.0 (30.0–45.0)
Platelets [x 10 <sup>9</sup> /L]					
Median (Range)	446.5 (107.0–955.0)	282.5 (116.0–877.0)	357.5 (107.0–955.0)	747.0 (516.0–765.0)	739.0 (516.0–1055.0)
WBC count [x 10 <sup>9</sup> /L]					
Median (Range)	12.0 (5.2–71.7)	9.4 (3.6–31.9)	10.1 (3.6–71.7)	7.4 (5.6–8.9)	7.1 (3.0–10.9)
Spleen Size [LCM], n (%)					
0 cm	8 (57.1)	11 (78.6)	19 (67.9)	6 (100.0)	10 (90.9)
> 0–< 5 cm	1 (7.1)	0	1 (3.6)	0	1 (9.1)
5 – < 10 cm	3 (21.4)	2 (14.3)	5 (17.9)	0	0
10 cm	1 (7.1)	1 (7.1)	2 (7.1)	0	0
Not Done	1 (7.1)	0	1 (3.6)	0	0
<i>JAK2</i> <sup>V617F</sup> Mutation Status, n (%)					
Positive	9 (64.3)	14 (100.0)	23 (82.1)	3 (50.0)	5 (45.5)
Negative	2 (14.3)	0	2 (7.1)	3 (50.0)	6 (54.5)
Unknown	2 (14.3)	0	2 (7.1)	0	0
Missing	1 (7.1)	0	1 (3.6)	0	0

ET, essential thrombocythemia; LCM, left costal margin; PV, polycythemia vera; WBC, white blood cell.

**Table 2**

Efficacy findings.

	PV Cohort		ET Cohort			
	100 mg (N = 14)	200 mg (N = 14)	Total (N = 28)	100 mg (N = 5)	200 mg (N = 6)	Total (N = 11)
Overall response						
n	14	14	28	5	6	11
Yes, n (%)	0	2 (14.3)	2 (7.1)	0	0	0
90% CI	0–19.3	2.6–38.5	1.3–20.8	0–45.1	0–39.3	0–23.8
Hematocrit response, 45% at baseline						
n	7	10	17	N/A	N/A	N/A
Yes, n (%)	0	1 (10.0)	1 (5.9)	N/A	N/A	N/A
90% CI	0–34.8	0.5–39.4	0.3–25.0	N/A	N/A	N/A
Platelet response, 400 x 10 <sup>9</sup> /L at baseline						
n	7	5	12	5	6	11
Yes, n (%)	0	1 (20.0)	1 (8.3)	0	0	0
90% CI	0–34.8	1–65.7	0.4–33.9	0–45.1	0–39.3	0–23.8
WBC count response, 10 x 10 <sup>9</sup> /L at baseline						
n	10	6	16	1	0	1
Yes, n (%)	0	1 (16.7)	1 (6.3)	1 (100.0)	0	1 (100.0)
90% CI	0–25.9	0.9–58.2	0.3–26.4	5–100	N/A	5–100
Spleen response <sup>d</sup>						
n	4	3	7	0	0	0
Yes, n (%)	1 (25.0)	1 (33.3)	2 (28.6)	0	0	0
90% CI	1.3–75.1	1.7–86.5	5.3–65.9	N/A	N/A	N/A
Response in modified MPN-SAF TSS, n (%)						
Yes	0	1 (7.1)	1 (3.6)	0	1 (16.7)	1 (9.1)
No	14 (100.0)	13 (92.9)	27 (96.4)	5 (100.0)	5 (83.3)	10 (90.9)
<i>JAK2</i> <sup>V617F</sup> allele burden response in patients with <i>JAK2</i> V617F mutation at baseline						
Median baseline allele burden						
n	22			5		
% (range)	21.8 (1.4, 73.2)			5.3 (0.3, 10.3)		

	PV Cohort		ET Cohort	
	100 mg (N = 14)	200 mg (N = 14)	100 mg (N = 28)	200 mg (N = 6)
Median change in allele burden at week 24 <sup>a</sup> ,				
n	13		3	
% (range)	99 (49, 172) <sup>b</sup>		155 (62, 179) <sup>b</sup>	

CI, confidence interval; ET, essential thrombocythemia; JAK, Janus kinase; MPN-SAF TSS, Modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; N/A, not available; PV, polycythemia vera; WBC, white blood cell.

Overall Response: Patient must meet hematocrit, WBC, platelet, and spleen response criteria in PV cohort; must meet WBC, platelet, and spleen response in ET cohort at some point during the treatment period. These criteria do not have to be met for the same 4 weeks.

Hematocrit response: Hematocrit < 45% in the absence of phlebotomy that lasts 4 weeks (applicable to PV cohort only).

Platelet response: Platelet count  $400 \times 10^9/L$  that lasts 4 weeks.

WBC response: WBC <  $10 \times 10^9/L$  that lasts 4 weeks.

Spleen response: Resolution or 50% reduction of palpable splenomegaly postbaseline.

MPN-SAF TSS response: Proportion of patients with 10-point decrease from baseline in modified MPN-SAF TSS that lasted 12 weeks.

<sup>a</sup>Patients with baseline spleen size 5 cm are evaluated for spleen response and serve as denominator for spleen response rate calculation.

<sup>b</sup>Not significant by Wilcoxon test.

**Table 3**

Frequency of severe TEAEs of grade 3 and momelotinib-related AEs in 2 patients.

	PV Cohort			ET Cohort		
	100 mg (N = 14)	200 mg (N = 14)	Total (N = 28)	100 mg (N = 5)	200 mg (N = 6)	Total (N = 11)
No. (%) of patients with any grade 3 TEAE	4 (28.6)	6 (42.9)	10 (35.7)	0	1 (16.7)	1 (9.1)
Hypertension	2 (14.3)	2 (14.3)	4 (14.3)	0	0	0
Dizziness	0	1 (7.1)	1 (3.6)	0	1 (16.7)	1 (9.1)
Fatigue	0	1 (7.1)	1 (3.6)	0	1 (16.7)	1 (9.1)
Bone pain	1 (7.1)	0	1 (3.6)	0	0	0
Cardiorespiratory arrest	1 (7.1)	0	1 (3.6)	0	0	0
Dyspnea	0	0	0	0	1 (16.7)	1 (9.1)
Night sweats	1 (7.1)	0	1 (3.6)	0	0	0
Pain in extremity	1 (7.1)	0	1 (3.6)	0	0	0
Platelet count increased	0	1 (7.1)	1 (3.6)	0	0	0
Thrombocytosis	0	1 (7.1)	1 (3.6)	0	0	0
Urinary bladder polyp	0	1 (7.1)	1 (3.6)	0	0	0
No. (%) of patients with any TEAE related to MMB	9 (64.3)	13 (92.9)	22 (78.6)	4 (80.0)	5 (83.3)	9 (81.8)
Headache	3 (21.4)	4 (28.6)	7 (25.0)	1 (20.0)	1 (16.7)	2 (18.2)
Dizziness	0	6 (42.9)	6 (21.4)	0	1 (16.7)	1 (9.1)
Somnolence	4 (28.6)	2 (14.3)	6 (21.4)	0	0	0
Nausea	1 (7.1)	3 (21.4)	4 (14.3)	0	2 (33.3)	2 (18.2)
Fatigue	0	4 (28.6)	4 (14.3)	0	2 (33.3)	2 (18.2)
Diarrhea	1 (7.1)	1 (7.1)	2 (7.1)	1 (20.0)	2 (33.3)	3 (27.3)
Vomiting	1 (7.1)	2 (14.3)	3 (10.7)	0	2 (33.3)	2 (18.2)
Pruritus	2 (14.3)	2 (14.3)	4 (14.3)	0	0	0
Dyspnea	2 (14.3)	1 (7.1)	3 (10.7)	0	1 (16.7)	1 (9.1)
Abdominal pain	0	1 (7.1)	1 (3.6)	0	2 (33.3)	2 (18.2)
Peripheral sensory neuropathy	1 (7.1)	1 (7.1)	2 (7.1)	1 (20.0)	0	1 (9.1)
Pain in extremity	1 (7.1)	1 (7.1)	2 (7.1)	1 (20.0)	0	1 (9.1)
Cough	2 (14.3)	0	2 (7.1)	0	1 (16.7)	1 (9.1)
Asthenia	0	2 (14.3)	2 (7.1)	0	0	0



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	PV Cohort			ET Cohort		
	100 mg (N = 14)	200 mg (N = 14)	Total (N = 28)	100 mg (N = 5)	200 mg (N = 6)	Total (N = 11)
Rhinorhea	2 (14.3)	0	2 (7.1)	0	0	0
No. of patients with any grade 3 TEAE related to MMB	1 (7.1)	3 (21.4)	4 (14.3)	0	1 (16.7)	1 (9.1)

AE, adverse event; ET, essential thrombocythemia; MMB, momelotinib; PV, polycythemia vera; TEAE, treatment-emergent adverse event.