

## CLINICAL TRIALS AND OBSERVATIONS

**Results of a phase 2 study of pacritinib (SB1518), a JAK2/JAK2(V617F) inhibitor, in patients with myelofibrosis**Rami S. Komrokji,<sup>1</sup> John F. Seymour,<sup>2,3</sup> Andrew W. Roberts,<sup>4,5</sup> Martha Wadleigh,<sup>6</sup> L. Bik To,<sup>7</sup> Robyn Scherber,<sup>8</sup> Elyce Turba,<sup>1</sup> Andrew Dorr,<sup>9</sup> Joy Zhu,<sup>10</sup> Lixia Wang,<sup>11</sup> Tanya Granston,<sup>11</sup> Mary S. Campbell,<sup>11</sup> and Ruben A. Mesa<sup>8</sup><sup>1</sup>Moffitt Cancer Center, Tampa, FL; <sup>2</sup>Peter MacCallum Cancer Center, Melbourne, Australia; <sup>3</sup>Sir Peter MacCallum Department of Oncology, <sup>4</sup>Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia; <sup>5</sup>Royal Melbourne Hospital, Melbourne, Australia; <sup>6</sup>Dana-Farber Cancer Institute, Boston, MA; <sup>7</sup>Royal Adelaide Hospital, Adelaide, Australia; <sup>8</sup>Mayo Clinic, Scottsdale, AZ; <sup>9</sup>Independent Consultant for S\*<sup>2</sup>BIO Pte Ltd., Singapore; <sup>10</sup>S\*<sup>2</sup>BIO Pte Ltd., Singapore; and <sup>11</sup>CTI BioPharma, Seattle, WA**Key Points**

- Pacritinib reduced myelofibrosis-related splenomegaly and patient symptoms without causing clinically significant myelosuppression.
- Pacritinib had activity and was well tolerated in patients with preexisting anemia and thrombocytopenia.

**Pacritinib (SB1518) is a Janus kinase 2 (JAK2), JAK2(V617F), and Fms-like tyrosine kinase 3 inhibitor that does not inhibit JAK1. It demonstrated a favorable safety profile with promising efficacy in phase 1 studies in patients with primary and secondary myelofibrosis (MF). This multicenter phase 2 study further characterized the safety and efficacy of pacritinib in the treatment of patients with MF. Eligible patients had clinical splenomegaly poorly controlled with standard therapies or were newly diagnosed with intermediate- or high-risk Lille score. Patients with any degree of cytopenia were eligible. Thirty-five patients were enrolled. At entry, 40% had hemoglobin <10 g/dL and 43% had platelets <100 000 × 10<sup>9</sup>/L. Up to week 24, 8 of 26 evaluable patients (31%) achieved a ≥35% decrease in spleen volume determined by magnetic resonance imaging and 14 of 33 (42%) attained a ≥50% reduction in spleen size by physical examination. Median MF symptom improvement was ≥50% for all symptoms except fatigue. Grade 1 or 2 diarrhea (69%) and nausea (49%) were the most common treatment-emergent adverse events. The study drug was discontinued in 9 patients (26%) due to adverse events (4 severe). Pacritinib is an**

**active agent in patients with MF, offering a potential treatment option for patients with preexisting anemia and thrombocytopenia. This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as #NCT00745550. (*Blood*. 2015;125(17):2649-2655)**

**Introduction**

The myeloproliferative neoplasms (MPNs) comprise a heterogeneous group of diseases arising from the clonal transformation of a pluripotent hematopoietic stem cell.<sup>1</sup> The dominant gain-of-function mutation in the Janus kinase 2 (JAK2) gene in patients with MPN involves the substitution of valine for phenylalanine at position 617 (V617F). This was the first acquired, somatic mutation in the hematopoietic stem cells described in these disorders.<sup>2-5</sup> Myelofibrosis (MF) is a subtype of MPN that may present as primary MF (PMF) or follow a prior diagnosis of essential thrombocythemia or polycythemia vera, termed PET-MF or PPV-MF. The hallmarks of MF include bone marrow fibrosis, splenomegaly, anemia and constitutional symptoms.<sup>1</sup> The outcome of MF varies based on the presence of certain risk factors, and survival ranges from <2 years to >10 years.<sup>6</sup> The frequency of the JAK2 (V617F) mutation in patients with PMF is 50% to 60% and >95% in patients with PPV-MF.<sup>7</sup> Recently, it was found that most patients with MF who do not have a JAK2 mutation or thrombopoietin receptor gene (MPL) mutation have a mutation in the calreticulin gene that

constitutively activates Janus kinase signal transducer and activator of transcription (JAK-STAT) signaling, functionally analogous to the JAK2(V617F) mutation.<sup>8</sup> Currently, ruxolitinib is the only targeted agent approved for the treatment of primary and secondary MF. Ruxolitinib is a pan-JAK inhibitor that strongly inhibits JAK1 as well as JAK2 phosphorylation.<sup>9</sup> Its approval was based on the results of 2 phase 3 studies, COMFORT-I and COMFORT-II, which demonstrated efficacy by reduction in splenomegaly and symptom improvement. Anemia, often requiring transfusions, and dose-related thrombocytopenia were the most clinically significant and dose-limiting toxicities.<sup>10,11</sup>

Pacritinib is a novel JAK2/ Fms-like tyrosine kinase 3 inhibitor that has demonstrated a favorable safety profile and a promising efficacy profile in phase 1 studies.<sup>12</sup> These studies established the recommended phase 2 dose of 400 mg once daily used in the current study. This article presents the final efficacy and safety results of a multicenter phase 2 study of pacritinib in patients with MF.

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## Methods

### Patients

Patients aged  $\geq 18$  years with MF (including primary MF, PPV-MF, and PET-MF) who required therapy and had splenomegaly clinically measured at  $\geq 5$  cm below the costal margin were eligible for enrollment if they met the following criteria: disease that had relapsed or was not well controlled with standard therapy, or newly diagnosed with intermediate- or high-risk disease according to the Lille score and not considered candidates for standard therapy (eg, were not candidates for stem cell transplantation, had contraindications to hydroxyurea or androgen therapy, or had excessive need for red blood cell [RBC] transfusions). Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status (ECOG) of 0 to 2; adequate renal and liver function defined by creatinine  $\leq 2.0$  mg/dL or calculated creatinine clearance  $\geq 60$  mL/min, liver transaminases  $\leq 2.5$  times the upper institutional normal limit, and total bilirubin  $\leq 2.0$  mg/dL; corrected QT interval (QTc)  $\leq 0.47$  s using the Bazett formula; and at least 2 weeks from any prior disease-directed therapy and at least 1 week from treatment with hydroxyurea and CYP3A4 inducers or inhibitors. Effective contraception was required for patients of reproductive age, and a negative pregnancy test result within 14 days prior to study-drug initiation was required for women of childbearing potential. Key exclusion criteria included concurrent malignancy; previous treatment with a JAK2 inhibitor; unwillingness or inability to undergo magnetic resonance imaging (MRI); known history of HIV or active hepatitis A, B, or C or latent hepatitis B; pregnancy or lactation; prior radiation therapy to  $>20\%$  of the hematopoietic bone marrow (prior spleen radiation allowed); and any other uncontrolled, intercurrent illness as judged by the treating physician. Patients with any baseline platelet count, neutrophil count, or hemoglobin value were eligible, as were patients who were RBC- or platelet-transfusion dependent.

### Study design

This was a multicenter, single-arm, open-label phase 2 study conducted in the United States and Australia. The study was approved by each institution's institutional review board (United States) or human research ethics committee (Australia). All patients signed informed consent. During screening, patients underwent physical examinations and medical histories. Complete blood counts, serum chemistry and liver function tests, JAK2(V617F) mutation status, a 12-lead electrocardiogram, bone marrow aspirate and biopsy, and abdominal MRI were performed. Complete blood counts and serum chemistry (including liver function tests) were repeated weekly during the first 28-day cycle; every other week during the second and third cycle; at the beginning of cycles 4, 5, and 6; and every 3 cycles thereafter. MRI for measurement of spleen volume was repeated on day 1 of cycle 4 and every third cycle through cycle 25. The Chronic Idiopathic Myelofibrosis Quality of Life and Symptom Assessment Form (MF-SAF)<sup>13</sup> was completed on day 1 of cycles 1, 2, and 4 and every third cycle through cycle 25. Bone marrow biopsies were required at baseline and to confirm partial responses and disease progression at cycles 6 and 12. Hematopoietic growth factors and CYP3A4 inducers/inhibitors were not allowed during the study, except for transient granulocyte colony-stimulating factor use for febrile neutropenia. Lille scores were used for risk assessment at study entry, and Dynamic International Prognostic Scoring System scores were calculated from baseline data in a post hoc analysis.

### Study treatment

Pacritinib was administered at the recommended dose of 400 mg once daily<sup>12</sup> in 28-day cycles.

### Safety assessment and dose adjustments

Toxicity was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. If patients experienced grade 3 or 4 toxicity, treatment interruptions of up to 2 weeks were allowed. After the adverse event (AE) resolved to grade  $\leq 1$  or to the baseline grade within 7 days, treatment could be resumed at the same dose

level or at a 25% dose reduction from the original dose. If the toxicity lasted for more than 7 days, a 25% dose reduction was required. Two dose reductions were allowed, and if the dose was reduced, it could not be re-escalated. Study drug interruption was required for subjects who had significant myelosuppression for  $>7$  days or myelosuppression associated with infection or bleeding. Patients were withdrawn from the study if treatment was interrupted for  $>4$  weeks. Safety analyses were based on patients with MF who received at least 1 dose of pacritinib.

### End-point assessment

The end point of the study was assessment of the spleen response rate, defined as the proportion of subjects achieving a  $\geq 35\%$  reduction in spleen volume from baseline up to week 24 as measured by MRI. Other end points included the proportion of patients with a  $\geq 50\%$  reduction in spleen size by physical examination and the proportion with a  $\geq 50\%$  reduction in symptom score as assessed by the MF-SAF<sup>13</sup> up to week 24 compared with baseline. Symptom score was computed as the sum of worst fatigue, early satiety, abdominal pain or discomfort, night sweats, itching (pruritus), and bone pain on the MF-SAF.<sup>13</sup> Spleen volume, spleen size, and symptom reductions were also assessed through end of treatment. Duration of spleen response and evaluation of the safety and tolerability of pacritinib were additional secondary end points. Actual dose intensity (ADI) and relative dose intensity (RDI) were calculated for each patient. ADI is a measure of the average dose of pacritinib received during the study and is defined for each patient as the total amount of pacritinib received in milligrams divided by treatment duration, ie,

$$ADI = \frac{\sum_{\text{all doses}} (\text{dose received} * \text{number of days at dose})}{\text{treatment duration}}$$

where treatment duration (the number of days on pacritinib treatment) = the last date on pacritinib treatment – first date on pacritinib treatment + 1. RDI, expressed as a percentage, is a measure of the proportion of the average dose of pacritinib received over the entire study relative to the ideal dose. It is defined as:

$$RDI = \frac{ADI}{400 \text{ mg}} * 100.$$

Disease progression was also assessed using the MF International Working Group consensus criteria.<sup>14</sup> The efficacy evaluable patient population included all enrolled patients with both baseline and postbaseline assessments for a given end point.

The planned sample size of 29 patients provided 80% power to detect a spleen response rate of at least 30% ( $\geq 30\%$  of patients with a  $\geq 35\%$  reduction in spleen volume at week 24 compared with baseline, assessed by MRI) vs the null hypothesis of a response rate of  $\leq 10\%$ , with  $\alpha = .05$  (2 sided).

## Results

### Patient characteristics

The study enrolled 35 patients at 6 centers between January 28 and June 8, 2010 (Table 1). Twenty-two patients (63%) had PMF and 6 (17%) each had PPV-MF and PET-MF, with a median time since diagnosis of 31.8 months (range, 2-588). One patient without MF, but with polycythemia vera, was enrolled due to a diagnostic error. The patient population had a median age of 69 years (range, 44-84). Eighty-nine percent had an ECOG performance status of 0 to 1 and were predominantly white and male. In a post hoc analysis of the Dynamic International Prognostic Scoring System, 12 patients (34%) were intermediate-1 risk, 13 (37%) were intermediate-2 risk, and 7 (20%) were high risk (3 patients were not evaluable). At baseline, 54%, 43%, and 20% of the patients had platelet counts  $<150\,000/\mu\text{L}$ ,  $<100\,000/\mu\text{L}$ , and  $<50\,000/\mu\text{L}$ , respectively. Forty percent of patients had hemoglobin  $<10$  g/dL, and 23% had leukocytes  $>25 \times 10^9/\mu\text{L}$  at baseline. Ten patients (28.6%) were RBC-transfusion dependent at baseline, and

**Table 1. Baseline patient characteristics**

	All patients (N = 35)
Median age (range), y	69 (44-84)
Male:female	26 (74%):9 (26%)
Median time from initial diagnosis (mo)	31.8
Prior therapy for MF	30 (86%)
Medical therapy	30 (86%)
Radiotherapy	3 (9%)
Median number of prior therapies (range)	1 (0-6)
<b>ECOG performance status</b>	
0	10 (29%)
1	21 (60%)
2	2 (6%)
Missing	2 (6%)
<b>MF diagnosis</b>	
Primary MF	22 (63%)
PPV-MF	6 (17%)
PET-MF	6 (17%)
Other (ineligible, not MF)*	1 (3%)
<b>Baseline DIPSS risk category</b>	
High	7 (20%)
Intermediate-1	12 (34%)
Intermediate-2	13 (37%)
Indeterminate†	3 (9%)
<b>Baseline Lille score</b>	
High risk	10 (29%)
Intermediate risk	12 (34%)
Low risk	13 (37%)
JAK2 mutation positive	28 (80%)
<b>Hematologic parameters</b>	
<b>Hemoglobin (g/L)</b>	
Median (range)	102 (55-181)
Mean (SD)	104 (23)
Grade 0-2	31 (89%)
Grade 3-4	4 (11%)
RBC-transfusion dependent	10 (28.6%)
<b>Platelets (<math>\times 10^3/\mu\text{L}</math>)</b>	
Median (range)	121 (15-859)
Mean (SD)	186 (184)
Grade 0-2	28 (80%)
Grade 3-4	7 (20%)
<b>Patients with baseline platelets</b>	
<150 000/ $\mu\text{L}$	19 (54%)
<100 000/ $\mu\text{L}$	15 (43%)
< 50 000/ $\mu\text{L}$	7 (20%)
<b>Leukocytes (<math>\times 10^3/\mu\text{L}</math>)</b>	
Median (range)	11.7 (1.1-89.6)
Mean (SD)	17.9 (19.0)
<b>Leukopenia</b>	
Grade 0	32 (91%)
Grade 3	3 (9%)
Median spleen volume by MRI (range), mL	2300 (404-7818)
Median spleen size by physical examination below left costal margin (range), cm	13 (5-30)
Median symptom score (range)	18 (0-44)
<b>Median score for individual symptoms (range)</b>	
Abdominal pain	2 (0-10)
Bone pain	0 (0-8)
Early satiety	5 (0-10)
Fatigue (worst)	5 (0-10)
Inactivity	3 (0-10)
Night sweats	1 (0-10)
Pruritus	1 (0-9)

Data are expressed as n (%), unless otherwise indicated. Source: supplemental Tables 2, 3, 5.2, 5.5, 14, and 18.

DIPSS, Dynamic International Prognostic Scoring System.

\*Patient was enrolled due to a diagnostic error (not MF).

†DIPSS could not be calculated for 3 patients due to lack of baseline data.

2 patients (6.1%) had received platelet transfusions within 180 days prior to study enrollment. Twenty-eight patients (80%) were JAK2 (V617F) positive, and 86% of patients had received prior therapies, with hydroxyurea being the most common (supplemental Table 1 available at the *Blood* Web site).

### Patient study-drug exposure and disposition

Patients received study treatment of a median of 272 days (range, 2-589 days) (Table 2) and received a median pacritinib dose of 394 mg/day (range, 87.5-400 mg) for a median relative dose intensity of 98.5% (range, 22% to 100%).

Nine patients (26%) had permanent dose reductions during the study, with reduction to 200 mg in 1 and 300 mg in the remaining 8. Adverse events accounting for these dose reductions included abnormal serum chemistry results (increased lipase, increased aspartate aminotransferase, and hyponatremia), gastrointestinal (GI) AEs (nausea, vomiting, and diarrhea), pruritus, septic shock, and anemia. An additional 4 patients had single transient dose reductions for AEs of febrile neutropenia, diarrhea, and anemia.

The most common reason for study drug discontinuation was AE/serious AE (SAE) in 9 patients (26%). Of the 9 discontinuations for AE/SAE, 6 were considered related to pacritinib (hypersensitivity [SAE], pruritus, thrombocytopenia, hyperbilirubinemia [SAE], subdural hematoma [SAE], and nausea) and 3 were considered unrelated to pacritinib (GI bleed [SAE], thrombocytopenia, and sepsis [SAE]). The second most common reason for study-drug discontinuation (23% of patients) was study termination by the sponsor (S\*Bio Pte Ltd, Singapore) for commercial reasons in October 2011, when all patients were required to discontinue therapy even if they had an ongoing response. At the time the sponsor terminated the study, 8 patients (23%) were still receiving pacritinib therapy, with treatment duration ranging from 424 to 589 days. Other reasons for study drug discontinuation included disease progression (20%), lack of response (17%), withdrawn consent (11%), and protocol deviation (3%).

### Efficacy

Assessed by MRI, 8 of 26 patients (31%) had a  $\geq 35\%$  reduction in spleen volume from baseline up to week 24 (Figure 1A). Fourteen of 33 patients (42%) had a maximum reduction in spleen length below the costal margin of  $\geq 50\%$  by physical examination from baseline up to week 24 (Figure 1B). When evaluated through the last visit on study treatment of all evaluable patients, 42% and 46% met the above MRI-based and physical-examination criteria for spleen response, respectively (Table 3). Reductions in spleen volume and length through 60 weeks of treatment were observed (supplemental Figures 1 and 2).

A durable improvement in MF-related symptom score was observed with duration of  $>9$  months, including the symptoms of abdominal pain, bone pain, early satiety, fatigue, inactivity, night sweats, and pruritus (Figure 2). Up to week 24, a  $\geq 50\%$  reduction in total symptom score from baseline was observed in 15 of 31 patients (48.4%). Of those who responded on or before week 24, 6 also had responses after week 24. Eighteen of 31 patients (58.1%) had a  $\geq 50\%$  reduction in total symptom score up to the last visit on treatment (Table 3). These 3 additional responses occurred at week 36; 1 patient did not have symptom data collected at week 24, and the other 2 had responses beginning at 36 weeks through the end of study treatment.

### Safety

The most common treatment-emergent AEs ( $\geq 10\%$ ) are listed by grade in Table 4. Grade 1 or 2 GI toxicities, predominantly diarrhea, nausea, vomiting, and abdominal pain, were the most common side effects of

**Table 2. Study-drug exposure and disposition**

All Patients (N = 35)	
<b>Drug exposure</b>	
Median treatment duration, days (range)	272 (2-589)
Actual dose intensity (mg/day)	394 (87.5-400)
Relative dose intensity (%)	98.5 (22-100)
<b>Reason for study-drug discontinuation</b>	
AE/SAE	9 (26%)
Sponsor's decision to terminate the study*	8 (23%)
Disease progression	7 (20%)
Lack of response	6 (17%)
Subject withdrew consent	4 (11%)
Protocol deviation	1 (3%)†

Source: supplemental Table 1.

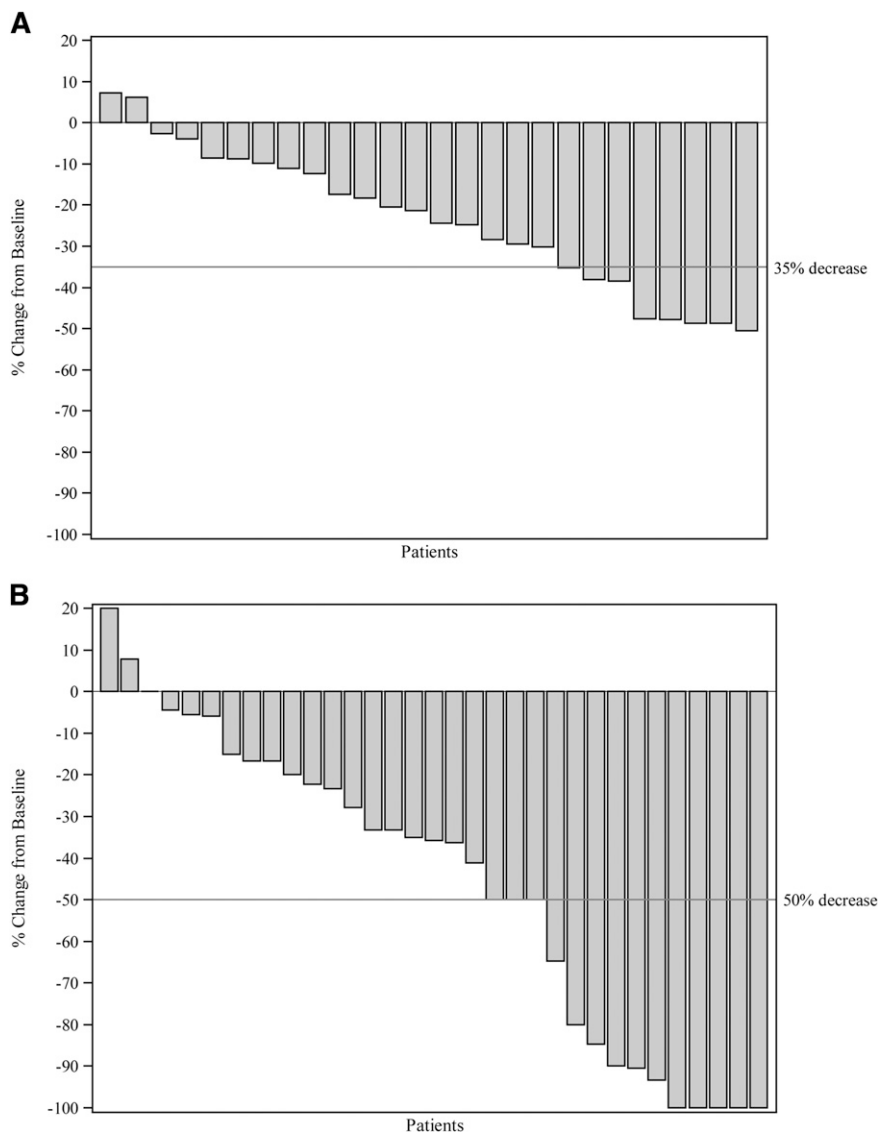
\*The sponsor terminated the study in October 2011 for commercial reasons.

†The study drug was discontinued after a protocol deviation was recognized, consisting of a patient enrolled due to a diagnostic error (not MF).

pacritinib (Table 4). Of the 27 patients with diarrhea, 22 (81%) received antidiarrheal medications, but of the 20 patients with nausea and/or vomiting, only half received antiemetics. Only 6 patients with GI

toxicity required dose interruptions and/or dose reductions due to diarrhea, nausea, or vomiting, and only 1 patient discontinued treatment due to a GI AE (grade 1 nausea) (supplemental Table 2). As expected in patients with MF, anemia and thrombocytopenia AEs were also common and are discussed below.

SAEs considered related to the study drug included febrile neutropenia, thrombocytopenia, myocardial infarction, hyperbilirubinemia, hypersensitivity, septic shock, subdural hematoma, supra-therapeutic international normalized ratio in a patient anticoagulated with warfarin, dehydration, hyperuricemia, and hyponatremia, all occurring in 1 patient each. There were 5 deaths, 3 due to SAEs and 2 due to disease progression. Of the 3 deaths due to AEs, 1 death, due to a subdural hematoma occurring in an 85-year-old woman with a history of coronary artery disease on aspirin and clopidogrel whose baseline platelet count was 227 000/ $\mu$ L, was considered possibly related to the study drug. The patient presented with the subdural hematoma 8 days after initiation of pacritinib with a platelet count of 135 000/ $\mu$ L. The other 2 AEs were considered unrelated to the study drug (*Staphylococcus aureus* sepsis in a nonneutropenic patient and septic shock in a patient with progressive MF and pancytopenia).



**Figure 1. Best spleen response.** (A) Best percentage change in spleen volume from baseline up to week 24 by MRI. Depicts the maximum percentage of the change in spleen volume from baseline through week 24 for each patient. Each patient has a baseline measurement and at least 1 postbaseline measurement. Patients at or below the 35% threshold horizontal line are spleen-volume responders. (B) Best percentage change in spleen length from baseline up to week 24 by physical examination. Depicts the maximum percentage of the change in spleen length from baseline through week 24 for each patient. Each patient has a baseline measurement and at least 1 postbaseline measurement. Patients at or below the 50% threshold horizontal line are spleen-length responders.



**Table 3. Summary of overall efficacy**

End point	Time period	Evaluable patients	Response, n (%)
≥50% spleen-length reduction by physical examination	Up to week 24	33	14 (42.4%)
≥50% spleen-length reduction by physical examination	Up to treatment termination	33	15 (45.5%)
≥35% reduction by MRI	Up to week 24	26	8 (30.8%)
≥35% reduction by MRI	Up to treatment termination	26	11 (42.3%)
≥50% reduction in total symptom score from baseline	Up to week 24	31	15 (48.4%)
≥50% reduction in total symptom score from baseline	Up to treatment termination	31	18 (58.1%)

Patients included in the analysis are those patients who had a nonmissing baseline measurement and postbaseline measurement at or through the time point specified. Source: supplemental Tables 5.1 and 5.6.

Grade 3 QTc prolongation (487 ms) was reported in one patient with preexisting first-degree atrioventricular block and baseline prolonged QTc interval of 455 ms and was considered possibly related to the study drug. The QT prolongation event occurred during hospitalization for grade 3 atrial fibrillation (considered an SAE unrelated to the study drug) and while the patient was receiving concomitant treatment with ondansetron.

**Hematologic toxicity**

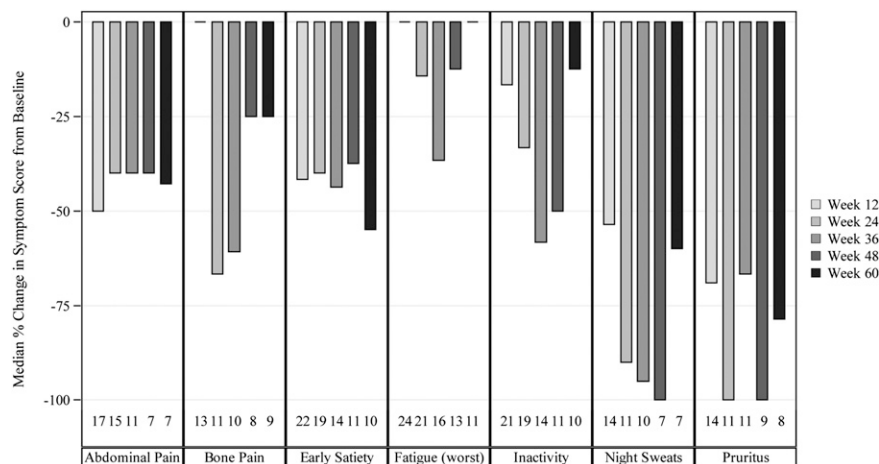
Anemia and thrombocytopenia AEs were reported in 12 (34.3%) and 8 (22.9%) of patients, respectively (Table 4). However, treatment with pacritinib did not appear to substantially alter median hemoglobin levels. The percentage change in hemoglobin measurements at each study visit relative to the baseline visit stayed within a median of 6% (range, -38% to +105%) and a mean of 8% (maximum standard deviation [SD] 22.87%) (supplemental Table 3). Single episodes of dose reduction and dose interruption were attributed to anemia (supplemental Table 2). No patients discontinued treatment due to anemia.

At baseline, 10 patients were considered RBC-transfusion dependent and 16 patients had received RBC transfusions within 180 days prior to study entry. During the study, 22 patients received RBC transfusions. Of those, 9 had not received RBC transfusions prior to the study, 3 of whom had received prior erythropoiesis-stimulating agents prior to the study and were required to discontinue them for inclusion in the current study. The study was not designed to assess changes

in transfusion requirements, so data collection was insufficient to analyze trends in red-cell requirements in patients who were transfusion dependent at entry.

Platelet counts decreased modestly on treatment (week 12: median -12% [range, -27% to +18%]/mean -0.3% [SD 43%]; week 24: median -17.6% [range, -80% to +157%]/mean 5% [SD 54%]), but platelet levels remained stable at these levels through week 60 (supplemental Table 3). Platelet count decreases of ≥2 grades per CTCAE occurred in 3 patients. One patient had a platelet count of 214 000/μL at baseline, was on treatment for 449 days, and then went on to receive an allogeneic stem cell transplant. The patient’s pretransplant platelet count was grade 1 (113 000/μL). Grade 4 thrombocytopenia (platelet count of 10 000/μL) occurred in the posttransplant period and >1 month after the patient had discontinued pacritinib. Two patients with grade 1 thrombocytopenia at baseline were noted to have single measurements of grade 3 thrombocytopenia. One patient had a platelet count of 86 000/μL at baseline and had an isolated grade 3 platelet count of 47 000/μL on day 29 relative to the start of study treatment. The platelet count spontaneously improved to the 53 000 to 87 000/μL range for the remainder of the study. Another patient had a baseline platelet count of 119 000/μL and with a single platelet count of 45 000/μL on day 421 relative to the start of study treatment while being treated for an upper respiratory tract infection. Subsequently, the platelet count spontaneously improved to 65 000/μL on day 503. Finally, another patient with grade 2 platelet levels at baseline (67 000/μL) developed a single episode of grade 4 thrombocytopenia (platelet count of 23 000/μL) on day 142 relative to the start of study treatment that spontaneously rose into the grade 3 range of 28 000 to 43 000/μL for the remainder of the study.

Thrombocytopenia led to drug interruptions and/or discontinuations in a total of 3 patients (supplemental Table 2). The drug was interrupted and discontinued due to thrombocytopenia in 1 patient who had baseline, nadir, and end-of-study platelet counts of 33 000/μL, 19 000/μL, and 35 000/μL, respectively. Another patient with a baseline platelet count of 34 000/μL developed intermittent epistaxis and had a 15-day treatment interruption for thrombocytopenia, during which the platelet count ranged from 25 000 to 32 000/μL and the patient received 1 platelet transfusion. After the treatment interruption, the patient resumed the study drug at 400 mg and remained on treatment at that dose for a total of 506 days, during which the 2 additional platelet transfusions were given and the platelet count ranged from 14 000 to 44 000/μL. Pacritinib was discontinued on day 44 in a third patient who had a decline in platelet count from 205 000/μL at baseline to 73 000/μL. The thrombocytopenia developed during hospitalization



**Figure 2. Median percentage change in symptom score over time.** Each panel depicts median percentage change in a symptom score from baseline at each 12-week interval on treatment. The number of patients contributing to the median percentage change is below each bar.

**Table 4. Treatment-emergent AEs by grade occurring in at least 10% of patients**

Preferred term	All patients (N = 35)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Diarrhea	15 (42.9%)	9 (25.7%)	3 (8.6%)	0	27 (77.1%)
Nausea	15 (42.9%)	1 (2.9%)	0	0	16 (45.7%)
Fatigue	4 (11.4%)	5 (14.3%)	3 (8.6%)	1 (2.9%)	13 (37.1%)
Anemia	0	3 (8.6%)	6 (17.1%)	3 (8.6%)	12 (34.3%)
Vomiting	8 (22.9%)	3 (8.6%)	0	0	11 (31.4%)
Abdominal pain	5 (14.3%)	2 (5.7%)	2 (5.7%)	0	9 (25.7%)
Pruritus	6 (17.1%)	1 (2.9%)	1 (2.9%)	0	8 (22.9%)
Thrombocytopenia	1 (2.9%)	0	5 (14.3%)	2 (5.7%)	8 (22.9%)
Decreased appetite	4 (11.4%)	3 (8.6%)	0	0	7 (20.0%)
Dehydration	1 (2.9%)	3 (8.6%)	2 (5.7%)	0	6 (17.1%)
Dizziness	5 (14.3%)	1 (2.9%)	0	0	6 (17.1%)
Flatulence	6 (17.1%)	0	0	0	6 (17.1%)
Aspartate aminotransferase increased	3 (8.6%)	0	2 (5.7%)	0	5 (14.3%)
Bone pain	4 (11.4%)	1 (2.9%)	0	0	5 (14.3%)
Dyspnea	1 (2.9%)	4 (11.4%)	0	0	5 (14.3%)
Hyperuricemia	3 (8.6%)	0	1 (2.9%)	1 (2.9%)	5 (14.3%)
Insomnia	5 (14.3%)	0	0	0	5 (14.3%)
Alopecia	4 (11.4%)	0	0	0	4 (11.4%)
Asthenia	2 (5.7%)	1 (2.9%)	1 (2.9%)	0	4 (11.4%)
Constipation	3 (8.6%)	1 (2.9%)	0	0	4 (11.4%)
Headache	3 (8.6%)	0	1 (2.9%)	0	4 (11.4%)
Musculoskeletal pain	2 (5.7%)	2 (5.7%)	0	0	4 (11.4%)
Pyrexia	3 (8.6%)	1 (2.9%)	0	0	4 (11.4%)

Data are expressed as n (%). No grade 5 events occurred at  $\geq 10\%$  frequency. Source: supplemental Table 7.2.1.

for SAEs of pneumonia and congestive heart failure, was attributed to MF, and was assessed as unrelated to the study drug. After discontinuation of the study drug, the patient had 3 additional hospital admissions for persistent pneumonia and recurrent congestive heart failure, during which platelet counts were 8,000/ $\mu\text{L}$  and 20 000/ $\mu\text{L}$ . The patient died of septic shock 2 months after discontinuation of pacritinib

Two bleeding events led to treatment discontinuation. One patient with baseline grade 3 thrombocytopenia had an SAE of grade 3 GI hemorrhage, which was considered unrelated to pacritinib but still led to study-drug discontinuation. Another patient with normal baseline platelet counts, on aspirin and clopidogrel due to a history of coronary artery disease with prior coronary stenting, developed a subdural hematoma on day 8 and the study drug was discontinued.

Four patients received platelet transfusions during the study. Of the patients who received platelet transfusions, baseline platelet counts were 34 000/ $\mu\text{L}$ , 23 000/ $\mu\text{L}$ , 15 000/ $\mu\text{L}$ , and 205 000/ $\mu\text{L}$  and 2 had received platelet transfusions within the 180 days prior to study. One patient was platelet-transfusion dependent at baseline and continued to receive frequent platelet transfusions during the study. The remaining 3 received platelet transfusions for AEs, 2 of whom had thrombocytopenia and 1 of whom had a GI bleed in the setting of stable grade 4 thrombocytopenia.

Leukocyte AEs were not commonly reported, with leukopenia, lymphopenia, and febrile neutropenia occurring in 1 patient each (2.9%) and neutropenia in 2 patients (5.7%). The study drug was interrupted twice and reduced once due to leukocyte AEs, but no study-drug discontinuations occurred. The median neutrophil count was 7,000/ $\mu\text{L}$  at baseline and ranged from 4,200 to 9,300 during the study (supplemental Table 3). Neutrophil count decreases of  $\geq 2$  grades occurred in 5 patients, all of whom had normal baseline neutrophil counts. The

neutropenia was considered clinically significant in only 1 case, in which study drug dosing was interrupted. In another case, the grade 3 neutropenia occurred 1 month after study-drug discontinuation and was attributable to the pre-engraftment period following an allogeneic stem cell transplant. Median peripheral blast percentages in the study population remained stable in the 0% to 1% range throughout the study (supplemental Table 3).

## Discussion

In this phase 2 multicenter study, pacritinib was effective in reducing splenomegaly and produced durable improvement in disease-related symptoms. Once daily dosing was well tolerated with manageable and predominantly grade 1 or 2 diarrhea, nausea, and vomiting as the most common side effects. On-target Fms-like tyrosine kinase 3 inhibition may contribute to these toxicities. Hematologic toxicities were modest and did not substantially impact treatment duration or dose intensity.

The study population was notable for inclusion of patients without restriction of baseline platelet count or hemoglobin level, resulting in enrollment of a patient population with substantially impaired hematoipoiesis. One limitation of this study was its termination by the sponsor while some patients were still deriving benefit. This was the second-leading cause of treatment discontinuation (8 patients, 23%) and limited the study's capacity to report long-term follow-up data. Despite this, treatment duration exceeded 1 year for patients with these baseline characteristics, ranging from 424 to 589 days. Although the rate of treatment discontinuation due to treatment-emergent AEs was 26% (n = 9), dose intensity of 98.5% and dose duration of 272 days suggest that pacritinib was tolerated well in this population, and 3 of these 9 AEs (33%) (GI bleed, thrombocytopenia, and sepsis) were deemed unrelated to the study drug. All 8 patients who were on the study drug when the sponsor terminated the study had been on treatment of more than 1 year and 5 had ongoing MRI spleen volume reduction of  $\geq 35\%$  at the time of study termination.

Patients treated with pacritinib had meaningful responses in spleen size, with 31% achieving a  $\geq 35\%$  reduction in spleen volume by MRI and 42% achieving a  $\geq 50\%$  reduction in spleen size by physical examination up to week 24. Higher proportions (42% and 46%, respectively) achieved these responses up to the last visit on study treatment. Patients also experienced substantial and prolonged symptomatic responses as assessed by the MF-SAF, with 48% and 58% of patients, respectively, having a  $>50\%$  reduction in symptom scores up to week 24 and up to the last visit on study treatment. The responses to pacritinib observed in this phase 2 study are consistent with its mechanism of action as an inhibitor of JAK2 and provide further evidence for the importance of JAK-STAT dysregulation in the pathophysiology of MPNs.

The minimal hematologic suppression with pacritinib treatment may arise from its selectivity within the JAK-STAT pathway, particularly its lack of inhibition of JAK1. As a consequence of the minimal anemia and thrombocytopenia observed during pacritinib treatment in phase 1 studies,<sup>12,15,16</sup> the current study allowed patients to enroll irrespective of their baseline hemoglobin or platelet counts. Although the rate of investigator-reported treatment-emergent grade 3 or 4 anemia was 25.7%, median hemoglobin levels remained relatively stable during pacritinib treatment, with fluctuations falling within a median of 6% compared with the baseline value (range -38% to +105%).

Thrombocytopenia has been identified as an adverse prognostic feature in MF.<sup>17-21</sup> Patients in the current study had a median baseline

platelet count of 120 000/ $\mu$ L, with 43% having baseline platelet counts <100 000/ $\mu$ L at study entry. Fifty-three percent of patients in the current study had thrombocytopenia at baseline of CTCAE grade 1 or higher, and 20.6% were grade 3 or 4. Despite the high prevalence of thrombocytopenia at baseline, only 2 patients discontinued treatment with pacritinib due to treatment-emergent thrombocytopenia. The minimal impact of pacritinib on existing anemia and thrombocytopenia in patients with MF and the minimal treatment-emergent effects of pacritinib on hematologic parameters long-term suggest that non-dose-adjusted therapy may provide an important therapeutic alternative for patients with significant cytopenias or who are unable to tolerate currently available therapies due to treatment-emergent toxicities.

In summary, pacritinib is an active and well-tolerated agent for the treatment of MF with manageable GI toxicity and minimal myelosuppression compared with ruxolitinib. Pacritinib may provide a therapeutic option for MF patients with baseline cytopenias and is currently being evaluated in 2 phase 3 trials. PERSIST-1 and PERSIST-2 will assess pacritinib's efficacy in MF patients who have not received prior anti-JAK therapy (PERSIST-1) and in patients who have baseline platelets <100 000/ $\mu$ L with or without prior anti-JAK therapy (PERSIST-2).

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## Authorship

Contribution: R.S.K., A.W.R., J.F.S., M.W., L.B.T. performed research, analyzed and interpreted data, and wrote the manuscript; R.S. performed research and wrote the manuscript; E.T. performed research; R.A.M. designed and performed research, analyzed and interpreted data, and wrote the manuscript; L.W. and T.G. performed statistical analysis and wrote the manuscript; M.S.C. analyzed data and wrote the manuscript; and J.Z. and A.D. designed research.

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Correspondence: Rami Komrokji, Moffitt Cancer Center and Research Institute, 12902 Magnolia Dr, Tampa, FL 33612; e-mail: rami.komrokji@moffitt.org.



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Rami S. Komrokji, John F. Seymour, Andrew W. Roberts, Martha Wadleigh, L. Bik To, Robyn Scherber, Elyce Turba, Andrew Dorr, Joy Zhu, Lixia Wang, Tanya Granston, Mary S. Campbell and Ruben A. Mesa

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