

Pacritinib vs Best Available Therapy, Including Ruxolitinib, in Patients With Myelofibrosis

A Randomized Clinical Trial

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IMPORTANCE Myelofibrosis is a hematologic malignancy characterized by splenomegaly and debilitating symptoms. Thrombocytopenia is a poor prognostic feature and limits use of Janus kinase 1 (JAK1)/Janus kinase 2 (JAK2) inhibitor ruxolitinib.

OBJECTIVE To compare the efficacy and safety of JAK2 inhibitor pacritinib with that of best available therapy (BAT), including ruxolitinib, in patients with myelofibrosis and thrombocytopenia.

DESIGN, SETTING, AND PARTICIPANTS For this phase 3 randomized international multicenter study—the PERSIST-2 study—of pacritinib vs BAT, 311 patients with myelofibrosis and platelet count $100 \times 10^9/L$ or less were recruited for analysis. Crossover from BAT was allowed after week 24 or for progression of splenomegaly.

INTERVENTIONS Patients were randomized 1:1:1 to pacritinib 400 mg once daily, pacritinib 200 mg twice daily, or BAT.

MAIN OUTCOMES AND MEASURES Coprimary end points were rates of patients achieving 35% or more spleen volume reduction (SVR) and 50% or more reduction in total symptom score (TSS) at week 24. Efficacy analyses were performed on the intention-to-treat efficacy population, comprising all patients with a randomization date allowing for week 24 data.

RESULTS Overall, 311 patients (mean [SD] age, 63.70 [9.08] years; 171 men [55%] and 140 women [45%]) were included in the study; 149 patients (48%) had prior ruxolitinib. The most common BAT was ruxolitinib (44 patients [45%]); 19 patients (19%) received watchful-waiting only. The intention-to-treat efficacy population included 75 patients randomized to pacritinib once daily; 74, pacritinib twice daily, and 72, BAT. Pacritinib (arms combined) was more effective than BAT for 35% or more SVR (27 patients [18%] vs 2 patients [3%]; $P = .001$) and had a nonsignificantly greater rate of 50% or more reduction in TSS (37 patients [25%] vs 10 patients [14%]; $P = .08$). Pacritinib twice daily led to significant improvements in both end points over BAT ($\geq 35\%$ SVR: 16 patients [22%] vs 2 patients [3%]; $P = .001$; $\geq 50\%$ reduction in TSS: 24 patients [32%] vs 10 patients [14%]; $P = .01$). Clinical improvement in hemoglobin and reduction in transfusion burden were greatest with pacritinib twice daily. For pacritinib once daily, pacritinib twice daily, and BAT, the most common (>10%) grade 3 or 4 adverse events were thrombocytopenia (32 patients [31%], 34 patients [32%], 18 patients [18%]), and anemia (28 patients [27%], 23 patients [22%], 14 patients [14%]). In the pacritinib once daily, twice daily, and BAT arms, discontinuation owing to adverse events occurred in 15 patients (14%), 10 patients (9%), and 4 patients (4%).

CONCLUSIONS AND RELEVANCE In patients with myelofibrosis and thrombocytopenia, including those with prior anti-JAK therapy, pacritinib twice daily was more effective than BAT, including ruxolitinib, for reducing splenomegaly and symptoms.

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Myelofibrosis is a myeloproliferative neoplasm characterized by dysregulated Janus kinase/signal transducers and activators of transcription signaling and excessive production of inflammatory cytokines.¹ Advanced disease is characterized by progressive bone marrow fibrosis, cytopenias frequently requiring red blood cell (RBC) and/or platelet transfusions, splenomegaly, and debilitating systemic symptoms.²⁻⁴ Median survival is approximately 6 years.⁵ Thrombocytopenia is an adverse prognostic variable that increases in prevalence with disease progression and is associated with higher symptom burden and shorter survival.^{4,6-8} The Janus kinase 1 (JAK1)/Janus kinase 2 (JAK2) inhibitor ruxolitinib is approved by the US Food and Drug Administration (FDA) for patients with intermediate-risk or high-risk myelofibrosis and a baseline platelet count of $50 \times 10^9/L$ or more. Despite spleen volume reduction (SVR) and symptom improvement with ruxolitinib, an unmet clinical need exists for patients with baseline or treatment-emergent thrombocytopenia, and those relapsed after or refractory to ruxolitinib. Pacritinib, is a JAK2/tyrosine kinase 3 inhibitor with negligible activity against JAK1 that also suppresses the interleukin-1 directed inflammatory pathway via inhibition of interleukin 1 receptor associated kinase 1.^{9,10} Pacritinib was shown to be clinically active in patients with myelofibrosis with minimal myelosuppression.¹¹ In the phase 3 PERSIST-1 trial (NCT01773187) comparing pacritinib once daily with best available therapy (BAT) excluding ruxolitinib, pacritinib demonstrated significant and durable SVR and symptom control irrespective of baseline platelet count.¹² A full clinical hold was placed on pacritinib by the FDA on February 8, 2016, due to concerns over bleeding and cardiovascular events and deaths on PERSIST-1. The hold caused early termination of PERSIST-2 resulting in incomplete data. The FDA requested an additional study to determine if a lower dose of pacritinib would be safer with maintained efficacy. After review of mature PERSIST-1 data and complete PERSIST-2 data (NCT02055781), as well as submission of a study protocol comparing 3 doses of pacritinib (NCT03165734), the hold was removed on January 5, 2017. The final results (database lock August 19, 2016) of the PERSIST-2 trial comparing pacritinib with BAT (including ruxolitinib) in patients with intermediate/high-risk myelofibrosis and baseline platelet count less than or equal to $100 \times 10^9/L$ are reported herein. Population pharmacokinetic modeling predicted higher steady state exposure and lower maximum concentrations with twice daily vs once daily pacritinib (early-phase studies)¹³; thus PERSIST-2 evaluated both schedules.

Methods

Patients

Adult patients with primary or secondary myelofibrosis were eligible if they had intermediate-1, intermediate-2, or high-risk disease by the Dynamic International Prognostic Scoring System (DIPSS), platelet count less than or equal to $100 \times 10^9/L$, and palpable splenomegaly 5 cm or larger below the left costal margin. Additional eligibility criteria included: total symptom score (TSS) greater than or equal to 13 on the Myelo-

Key Points

Question Is pacritinib (400 mg once daily or 200 mg twice daily) superior to best available therapy for patients with myelofibrosis and thrombocytopenia?

Findings In this randomized clinical trial of 311 patients, pacritinib 200 mg twice daily was significantly more effective than best available therapy, including ruxolitinib, for reducing splenomegaly and symptoms in patients with myelofibrosis and thrombocytopenia, including those with prior ruxolitinib.

Meaning Pacritinib can provide a treatment option for patients with myelofibrosis and baseline thrombocytopenia, for whom current treatment options are limited.

proliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS 2.0); Eastern Cooperative Oncology Group performance status 0 to 3 (scale from 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing disability); peripheral blood blast count less than 10%; absolute neutrophil count greater than $0.5 \times 10^9/L$; adequate liver and renal function; and life expectancy 6 months or longer. Prior treatment with 1 or 2 other JAK inhibitors was allowed. Patients with active bleeding requiring hospitalization during screening or significant cardiac abnormalities (eg, recent history of myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, ongoing grade ≥ 3 dysrhythmias, prolonged QTc) were excluded (eMethods in Supplement 1). The study was approved by the institutional review boards at each participating institution and conducted in accordance with the principles outlined in the Declaration of Helsinki. All patients provided written informed consent, and the trial protocol is available in Supplement 2.

Randomization and Treatment

Patients were centrally randomized 1:1:1 via interactive web or voice response system to pacritinib 400 mg once daily, pacritinib 200 mg twice daily, or BAT; BAT included any physician-selected treatment for myelofibrosis, symptom-directed treatment, or watch-and-wait. Randomization was stratified by geographic region, risk category, and rebound platelet count. Note, "rebound" refers to recovery of platelet count between informed consent and randomization, indicating likelihood of drug-induced thrombocytopenia rather than thrombocytopenia associated with myelofibrosis (eMethods in Supplement 1). Permuted blocks within strata were used to restrict treatment allocation. A patient's treatment assignment was known to the investigator, site personnel, the patient, clinical monitors, and pharmacovigilance personnel. The sponsor remained blinded until database lock for the primary analysis and independent radiographic assessors remained blinded throughout the study. Patients in all arms were to be treated until progressive disease, unacceptable toxic effects, or the patient no longer derived benefit from treatment (eMethods in Supplement 1). Patients randomized to BAT could cross over to pacritinib for progression of splenomegaly or after 24 weeks of treatment with or without progression.

End Points

The primary objective was to compare the efficacy of the pooled pacritinib arms with BAT. The efficacy coprimary end points were the proportions of patients achieving 35% or more SVR (computed tomography/magnetic resonance imaging [CT/MRI]) and 50% or more reduction in TSS (MPN-SAF TSS 2.0) from baseline to week 24. A secondary objective was to separately compare efficacy of pacritinib once daily or twice daily vs BAT. Exploratory end points included overall survival, changes in hematologic parameters, and additional patient-reported outcomes. Safety and tolerability were assessed from time of informed consent through last day of study participation. Pharmacokinetics of pacritinib were characterized to assess exposure and exposure-response relationships (safety and efficacy).

Assessments

Spleen volume by CT/MRI was reviewed centrally by a blinded, independent radiology facility at baseline and every 12 weeks through 48 weeks until progressive disease or withdrawal from study treatment. Patient-reported symptoms were recorded daily (MPN-SAF TSS 2.0) through 48 weeks or until end of study treatment, whichever occurred first. Scores for Patient Global Impression Assessment were assessed every 8 weeks through week 24, then every 12 weeks until discontinuation. Adverse events were classified and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

Statistical Analysis

A sample size of 300 patients was planned to provide greater than 99% power in detecting treatment differences (pacritinib vs BAT) in SVR and TSS reduction at a level (2-sided) of .05. This sample size also provided 96% and greater than 99% power to detect treatment differences (pacritinib once daily or pacritinib twice daily vs BAT) in SVR and TSS reduction, respectively, at a level (2-sided) of .025. A 20% and 45% difference in the proportion of pacritinib vs BAT patients with 35% or more SVR and 50% or more reduction in TSS at week 24, respectively, was assumed for power calculation. Efficacy analyses were performed on the intention-to-treat efficacy population, comprising all patients with a randomization date allowing for week 24 data (≥ 22 weeks prior to clinical hold). Treatment differences in proportion of patients achieving SVR or TSS reduction were tested using the Fisher exact test, and confidence intervals were based on the Agresti-Caffo method. Time-to-event analyses were censored on the date of clinical hold. The safety population included all patients who received 1 or more dose of study treatment. Final end-of-treatment data were used.

Results

Patients and Study Treatment

From July 2014 to February 2016, 311 patients were randomized to pacritinib once daily ($n = 104$), pacritinib twice daily ($n = 107$), or BAT ($n = 100$; **Figure 1**). The most commonly used active single agents in the BAT arm were ruxolitinib ($n = 44$

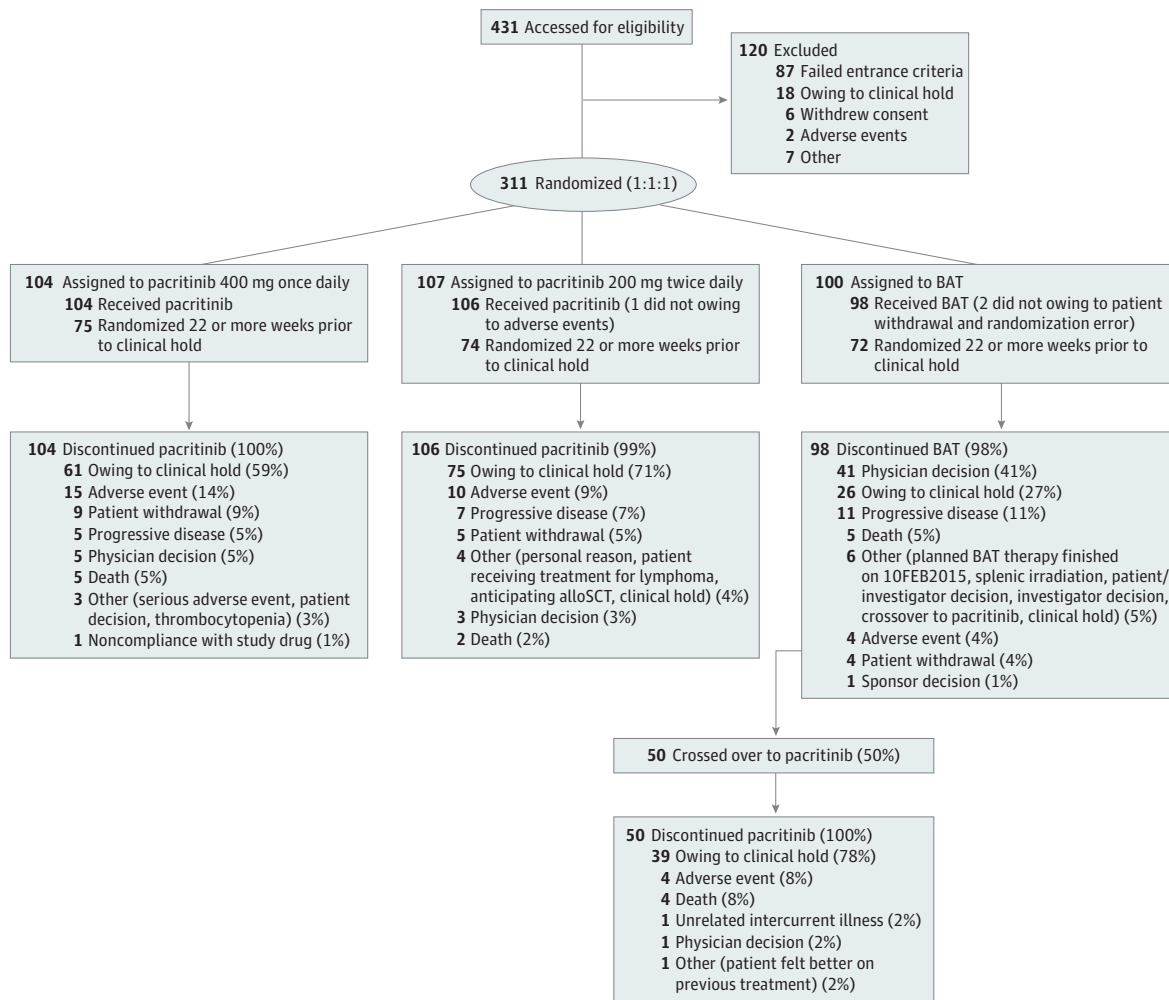
[45%]), hydroxyurea ($n = 19$ [19%]), and prednisone and/or prednisolone ($n = 13$ [13%]); 19 patients (19%) received watchful-waiting only (eTable 1 in **Supplement 1**). One patient randomized to pacritinib twice daily and 2 patients randomized to BAT withdrew before receiving treatment and were excluded from the safety population. The intention-to-treat efficacy population included 75, 74, and 72 patients randomized to pacritinib once daily, twice daily, and BAT, respectively. Baseline demographics and disease characteristics were balanced across arms (eTable 2 in **Supplement 1**). One-hundred fifteen patients (52%) had an intermediate-2 DIPSS score, and 66 (30%) had high-risk DIPSS scores. In the pacritinib once daily, twice daily, and BAT arms, 38 patients (51%), 31 patients (42%), and 32 patients (44%) had baseline platelet count less than $50 \times 10^9/L$, respectively.

After 23, 25, and 21 median weeks on pacritinib once daily, twice daily, and BAT, respectively, all 308 treated patients had discontinued therapy (eTable 3 in **Supplement 1**); of the patients that had discontinued therapy 62 of 104 patients treated with pacritinib once daily, 75 of 106 patients treated with pacritinib twice daily, and 27 of 98 patients treated with BAT were discontinued due to institution of the clinical hold. The majority of BAT discontinuations were owing to crossover to pacritinib; 50 of 98 patients (51%) treated with BAT crossed over primarily ($n = 43$ [86%]) at or after week 24. Of these patients, 39 (78%) continued on pacritinib until the clinical hold. Prior to the hold, discontinuations owing to adverse events trended higher with pacritinib once daily (15 patients [14%]) vs other arms (10 patients [9%] with pacritinib twice daily, 4 patients [4%] with BAT), and discontinuation due to progressive disease trended higher with BAT (10 patients [10%]) vs pacritinib (once daily, 5 patients [5%]; twice daily, 7 patients [7%]). At the time of the clinical hold, 76 patients (71%) randomized to pacritinib twice daily vs 61 patients (59%) randomized to pacritinib once daily were on study treatment. Dose interruptions due to adverse events were higher with pacritinib (once daily, 39 patients [38%]; twice daily, 29 patients [27%]) vs BAT (10 patients [10%]) and dose reductions due to adverse events were higher with pacritinib once daily (21 patients [20%]) vs other arms (13 patients [12%] with pacritinib twice daily; 7 patients [7%] with BAT) (eTable 3 in **Supplement 1**).

Spleen Volume Reduction

At week 24, 27 patients (18%) on pacritinib arms (11 [15%], pacritinib once daily; 16 [22%], pacritinib twice daily) achieved SVR 35% or more compared with 2 patients (3%) on BAT ($P = .001$, $P = .02$, $P = .001$, respectively) (**Table**) (**Figure 2**). Only 1 of 32 patients (3%) on the BAT arm who received ruxolitinib achieved SVR 35% or more. Of note, the majority of ruxolitinib-treated patients began with 5 mg twice daily dosing (at discretion of treating physician). With pacritinib once daily and twice daily, SVR 35% or more was achieved in 2 patients (6%) and 4 patients (13%) with prior ruxolitinib (**Table**). Additional subgroup analyses demonstrated pacritinib patients achieved SVR 35% or more regardless of subgroup, including as defined by sex, age, *JAK2* V617F mutation status, prior treatment with *JAK2* inhibitors, and baseline cytopenias (eFigure 1 in **Supplement 1**).

Figure 1. CONSORT Diagram



Outcomes for all randomized patients are shown. BAT indicates best available therapy; alloSCT, allogeneic stem cell transplant.

Symptom Reduction

At week 24, 37 patients (25%) on pacritinib arms (13 [17%], once daily; 24 [32%], twice daily) achieved reduction in TSS 50% or more, compared with 10 patients (14%) on BAT ($P = .08$, $P = .65$, and $P = .01$, respectively) (Table) (Figure 2). Six of 32 patients (19%) on BAT who received ruxolitinib achieved reduction in TSS 50% or more. With pacritinib once daily and twice daily, TSS reduction greater than or equal to 50% was achieved in 3 patients (10%) and 10 patients (32%) with prior ruxolitinib (Table). Median percent change in TSS at week 24 was -27% , -41% , and -15% with pacritinib once daily, twice daily, and BAT, respectively. Median percent change in individual MPN-SAF TSS 2.0 symptom scores also showed greater improvements with pacritinib once daily and twice daily in 7 of 8 and 8 of 8 symptoms, respectively, vs BAT (eFigure 2 in Supplement 1). Additionally, the number of patients with much-improved or very much-improved Patient Global Impression Assessment scores were 16 of 45 (36%) and 26 of 46 (57%) with pacritinib once daily and twice daily vs 11 of 40 (28%) with BAT (eFigure 3 in Supplement 1).

Overall Survival

Overall survival curves from randomization dates to clinical hold are shown in eFigure 4 in Supplement 1. Differences between the 3 arms did not reach significance (hazard ratios vs BAT for pacritinib once daily and twice daily: 1.18; 95% CI, 0.57-2.44 and 0.68; 95% CI, 0.30-1.53). For patients on the BAT arm, the overall death rate was lower for those who crossed over to pacritinib (4 patients [8%]) vs those who did not (10 patients [20%]). Subgroup analyses for survival by risk factors showed that hazard ratios for pacritinib twice daily were less than 1 with the exception of patients who were more than 1.5 years from diagnosis or secondary myelofibrosis (eFigure 5A in Supplement 1). Similar analyses of pacritinib once daily vs BAT are shown in eFigure 5B in Supplement 1, where hazard ratios were more disparate across arms.

Changes in Hematologic Parameters

For patients who received 1 or more RBC unit on study, transfusion requirements at weeks 12 and 24 were lower in each pacritinib arm vs BAT (eFigure 6 in Supplement 1). For patients not

Table. Efficacy Summary of the Intention-to-Treat Efficacy Population

Reductions From Baseline to Week 24	Pacritinib 400 mg Once Daily	Pacritinib 200 mg Twice Daily	BAT
Overall			
Patients with $\geq 35\%$ SVR			
Overall population, No.	75	74	72
Achieved end point, No. (%)	11 (15)	16 (22)	2 (3)
95% CI for the % ^a	7.6-24.7	12.9-32.7	0.3-9.7
P value vs BAT	.02	.001	NA
Patients with $\geq 50\%$ reduction in TSS			
Overall population, No.	75	74	72
Achieved end point, No. (%)	13 (17)	24 (32)	10 (14)
95% CI for the % ^a	9.6-27.8	22.0-44.3	6.9-24.1
P value vs BAT	.65	.01	NA
Patients With Prior Ruxolitinib			
Patients with $\geq 35\%$ SVR			
Overall population, No.	31	31	33
Achieved end point, No. (%)	2 (6)	4 (13)	1 (3)
95% CI for the % ^a	0.8-21.4	3.6-29.8	0.1-15.8
Patients with $\geq 50\%$ reduction in TSS			
Overall population, No.	31	31	33
Achieved end point, No. (%)	3 (10)	10 (32)	5 (15)
95% CI for the % ^a	2.0-25.8	16.7-51.4	5.1-31.9
Patients With Baseline Platelets $< 50 \times 10^9/L$			
Patients with $\geq 35\%$ SVR from baseline to week 24			
Overall population, No.	38	31	32
Achieved end point, No. (%)	7 (18)	9 (29)	1 (3)
95% CI for the % ^a	7.7-34.3	14.2-48.0	0.1-16.2
Patients with $\geq 50\%$ reduction in TSS			
Overall population, No.	38	31	32
Achieved end point, No. (%)	6 (16)	7 (23)	4 (13)
95% CI for the % ^a	6.0-31.3	9.6-41.1	3.5-29.0

Abbreviations: BAT, best available therapy; NA, not applicable; SVR, spleen volume reduction; TSS, total symptom score.

^a Clopper-Pearson method.

RBC transfusion-independent at baseline (Gale criteria¹⁴), the proportion of patients with reduced RBC transfusion burden at week 24 was higher with pacritinib once daily (7 of 37 patients [19%]) and pacritinib twice daily (8 of 36 patients [22%]) vs BAT (3 of 35 patients [9%]). Transfusion independence (Gale criteria¹⁴) was achieved in 2 patients, 1 each with pacritinib once daily and twice daily. For patients with hemoglobin less than 10 g/dL at baseline, the proportion of patients with clinical improvement in hemoglobin at week 24 (International Working Group response criteria, increase of ≥ 2.0 g/dL or RBC transfusion independence for ≥ 8 weeks prior) was greatest with pacritinib twice daily (11 of 44 patients [25%]) vs pacritinib once daily (6 of 45 patients [13%]) or BAT (5 of 41 patients [12%]). For patients with baseline platelet count less than $50 \times 10^9/L$, median percent changes in platelets through week 24 are shown in eFigure 7 in Supplement 1. No evidence for increasing thrombocytopenia or neutropenia with pacritinib or BAT was noted.

Pharmacokinetics

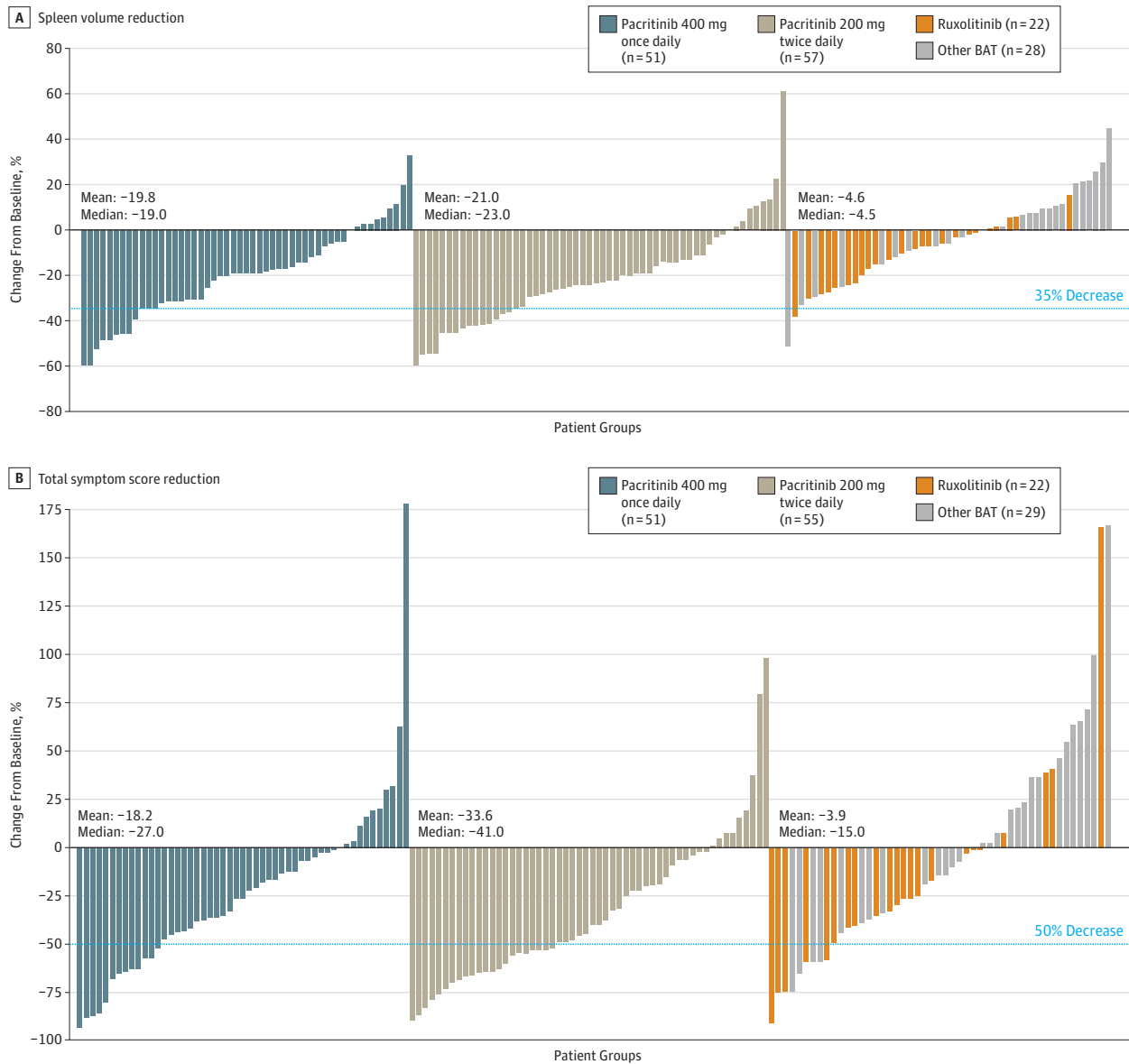
As predicted by pharmacokinetic modeling and simulation data, in 144 pacritinib-treated patients with up to 24-week post-dose samples, pacritinib twice daily was associated with higher

systemic exposure (ie, steady state minimum serum concentration [C_{min}]) relative to pacritinib once daily (eTable 4 in Supplement 1). In an exposure-response analysis, no trends were detected for a relationship between observed steady state C_{min} and death, cardiovascular death, hemorrhagic death, cardiac events (grade ≥ 2 or ≥ 3), hemorrhagic events, thrombocytopenia (grade ≥ 2 or ≥ 3), anemia (grade ≥ 2 or ≥ 3), gastrointestinal events (any grade, grade ≥ 2 , or ≥ 3), or maximum QTcF greater than 450 ms. Treatment with pacritinib twice daily but not once daily was associated with a trend for increased SVR and TSS reduction with increased C_{min}.

Safety

The most commonly reported ($\geq 15\%$) nonhematologic adverse events with pacritinib were gastrointestinal adverse events, fatigue, peripheral edema, and dizziness; with BAT (including 19 patients with watchful-waiting only) were abdominal pain, fatigue, diarrhea, and peripheral edema (eTable 3 in Supplement 1); the majority of common nonhematologic adverse events were grade 1 or 2 in severity. Diarrhea was the most frequently observed adverse event with pacritinib (112 instances [53%], grade 1/2; 9 instances [4%], grade 3), most often occurring during weeks 1 to 8. Incidence of diarrhea was

Figure 2. Spleen Volume Reduction and Reduction in Total Symptom Score in Evaluable Patients



Waterfall plots for spleen volume reduction (A) and total symptom score reduction (B) from baseline for evaluable patients are shown. Mean and median percent decreases from baseline were greater with pacritinib vs BAT. Of note, SVR \geq 10% was achieved in 72.5%, 78.9%, and 36.0% of evaluable patients

with pacritinib once daily, pacritinib twice daily, and best available therapy, respectively. BAT indicates best available therapy. Each bar represents a single patient.

lower with pacritinib twice daily vs once daily (51 instances [48%] vs 70 instances [67%]) (eTable 5 in Supplement 1). Diarrhea was manageable with standard antidiarrheal agents (eg, loperamide) and generally resolved within 1 to 2 weeks (eTable 5 in Supplement 1). The most common adverse event leading to discontinuation was thrombocytopenia with pacritinib once daily (4 instances [4%]) and BAT (2 instances [2%]) and anemia with pacritinib twice daily (3 instances [3%]) (eTable 6 in Supplement 1). Rate of on-study death was lowest with pacritinib twice daily (6 instances [6%]) vs BAT (9 instances [9%]) or pacritinib once daily (14 instances [14%]) (eTable 7 in Supplement 1).

The incidence of all hematologic adverse events was similar for patients with baseline platelet count less than $50 \times 10^9/L$ vs $50 \times 10^9/L$ or more with pacritinib once daily (27 patients [54%] vs 27 patients [52%]) and pacritinib twice daily (28 patients [60%] vs 33 patients [57%]), but was higher for patients with a baseline platelet count less than $50 \times 10^9/L$ vs $50 \times 10^9/L$ or more with BAT (22 patients [52%] vs 21 patients [38%]). Cardiac events (per standardized MedDRA query, see eMethods in Supplement 1) were reported at similar rates in all arms (67 patients [32%], pacritinib once daily or twice daily; 27 patients [28%], BAT) and were most commonly peripheral edema in all arms (13%-20%). Grade 3 or 4 cardiac events were

reported in 13 patients (13%) treated with pacritinib once daily, 7 patients (7%) treated with pacritinib twice daily, and 9 patients (9%) treated with BAT (eTable 8 in Supplement 1). No cardiac event led to discontinuation of therapy in 2 or more patients (eTable 6 in Supplement 1). Bleeding events (per standardized MedDRA query, see eMethods in Supplement 1) were reported at similar rates in all arms (37 patients [36%], 45 patients [42%], and 40 patients [41%] treated with pacritinib once daily, twice daily, and BAT, respectively) and were most commonly epistaxis in all arms (11%-13%). Grade 3 or 4 bleeding events were reported in 7 patients (7%), 15 patients (14%), and 7 patients (7%) treated with pacritinib once daily, twice daily, and BAT, respectively (eTable 8 in Supplement 1). Epistaxis was the only bleeding event that led to discontinuation in 2 or more patients (1 pacritinib twice daily, 1 BAT) (eTable 6 in Supplement 1). Rates of grade 3 or 4 bleeding events were similar for patients with baseline platelet count less than $50 \times 10^9/L$ vs $50 \times 10^9/L$ or more with pacritinib twice daily (7 patients [15%] vs 8 patients [14%]) and higher for those with less than $50 \times 10^9/L$ with pacritinib once daily (6 patients [12%] vs 1 patient [2%]) and BAT (5 patients [12%] vs 2 patients [4%]).

When the clinical hold was put in place and patients abruptly discontinued pacritinib, spleen size increased, and symptoms recurred rapidly and were difficult to control. While withdrawal syndrome is a potential safety concern, the longer elimination half-life of pacritinib (approximately 40 hours) may reduce exposure more gradually.

Discussion

Myelofibrosis is a chronic progressive myeloproliferative neoplasm with no proven therapeutic options for patients with thrombocytopenia,² which increases in prevalence and severity with disease progression.⁶ Patients ineligible for, or who fail therapy with JAK1/JAK2 inhibitor ruxolitinib, lack therapeutic options and have extremely poor prognosis.¹⁵ In the primary analysis of the PERSIST-2 study at week 24, the combined pacritinib arms were significantly more effective than BAT for SVR and trended toward improved TSS reduction in patients with my-

elofibrosis and thrombocytopenia. The benefit of pacritinib in terms of SVR and TSS reduction was observed in patients with baseline platelet count less than $50 \times 10^9/L$ and those with prior ruxolitinib treatment (comprising >40% of patients). The pacritinib twice daily arm met both coprimary SVR and TSS reduction end points. The pharmacokinetic profile of pacritinib twice daily also supports the use of this dose schedule.

Pacritinib was well tolerated and gastrointestinal toxic effects were generally low grade, less frequent with twice daily dosing, and rarely led to treatment discontinuation. Clinical improvement in hemoglobin and reduction in transfusion requirements were also more frequent in patients who received pacritinib, particularly with twice-daily dosing. A potential increased risk of grade 3 or 4 bleeding was noted with pacritinib twice daily but appeared to be independent of platelet count. Rate of grade 3 or 4 cardiac events was lowest with pacritinib twice daily vs other arms and no cardiac failure or deaths due to cardiac events occurred with pacritinib twice daily.

Limitations

Study truncation due to the clinical hold compromised the ability to evaluate the effect of treatment on week 24 end points (including coprimary end points) by reducing the effective sample size, and also compromised time-to-event end points (including overall survival) by reducing follow-up time for assessment that would enable analyses that follow the intention-to-treat principle.¹⁶ Time-to-event analyses were also confounded by patient crossover. Truncation of the study also limited the follow-up of patients for additional safety data. Despite these limitations, pacritinib 200 mg twice daily was more effective than BAT with a benefit-risk profile that compared favorably with pacritinib once daily and BAT.

Conclusions

The results of PERSIST-2 demonstrate the clinical benefit of pacritinib in patients with myelofibrosis and thrombocytopenia (platelet count $\leq 100 \times 10^9/L$), including those with prior JAK2 inhibitor therapy.

ARTICLE INFORMATION

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advisory role for CTI BioPharma Corp and Novartis and is on the speaker's bureau for Novartis and Celgene. Drs Granston, Daly, and Al-Fayoumi, and Ms Callahan are employed by CTI BioPharma Corp. Dr Singer is employed by and has equity ownership in CTI BioPharma Corp. Dr Gotlib has received research funding from CTI BioPharma Corp. Dr Jamieson has received research funding from Johnson & Johnson, GlaxoSmithKlein, CTI BioPharma Corp and is employed by Impact Biomedicines. Dr Harrison has received research funding from Novartis, is on the speaker's bureau for CTI BioPharma Corp, Novartis, Sanofi, and Baxter, and has a consultancy and/or advisory role for CTI BioPharma Corp, Novartis, Gilead, Baxter. Dr Mesa has received research funding from Incyte, Gilead, CTI BioPharma Corp, Promedior, and Celgene, and has a consultancy and/or advisory role for Novartis, Ariad, Galena. Dr Verstovsek has received research funding from Incyte, Roche, AstraZeneca, Lilly Oncology, Geron, NS Pharma, Bristol-Myers Squibb, and Celgene. No other conflicts are reported.

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Invited Commentary

Improved JAK Inhibition in Myelofibrosis—The Long Road Ahead

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Whoever strives with all his might, that man we can redeem.
J. W. von Goethe, Faust¹

Myelofibrosis (MF) is characterized by bone marrow fibrosis, extramedullary hematopoiesis and abnormal cytokine expression, which often manifest with severe splenomegaly, crippling constitutional symptoms and cytopenias.² The identification of the Janus kinase 2 (JAK2) V617F mutation and the subsequent approval of ruxolitinib for the treatment of intermediate-risk and high-risk MF by the US Food and Drug Administration (FDA) in 2011 changed the therapeutic landscape in MF.² Ruxolitinib effectively reduced splenomegaly and improved constitutional symptoms and quality of life in patients with intermediate-2 or high International Prognostic Scoring System risk compared with placebo or best available

therapy (BAT) in the randomized phase 3 COMFORT I and COMFORT II trials, respectively.²

Use of ruxolitinib is, however, not without significant limitations.² Ruxolitinib is not a curative therapy and has a limited disease-modifying effect at best. In the COMFORT trials, the JAK2 V617F allele frequency was reduced only by 7% to 21% and improvement in marrow fibrosis was minimal.² This is not surprising as the underlying pathophysiology is complex. The JAK2 V617F mutation occurs in only 55% to 60% of patients and multiple other mutations have been identified.² Ruxolitinib frequently induces or worsens anemia and thrombocytopenia, which complicates its use especially in patients with significant baseline cytopenia(s). Indeed, ruxolitinib is contraindicated if the platelet count is less than 50 000/μL.² Lastly, while survival prolongation has been observed with longer follow-up of patients in the landmark ruxolitinib trials, the advantage magnitude, again, is minor.³ Over half of the patients discontinue treatment within three years because of either side effects or loss of response.²



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