

Pacritinib vs Best Available Therapy for the Treatment of Myelofibrosis Irrespective of Baseline Cytopenias: Results of the International, Randomized, Phase 3 PERSIST-1 Trial

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Abstract

Background: Available therapies for myelofibrosis may exacerbate cytopenias and are not indicated for patients with severe thrombocytopenia. The JAK2/FLT3 inhibitor pacritinib induced spleen responses with limited myelosuppression in phase 1/2 trials. We aimed to assess the efficacy and safety of pacritinib vs best available therapy in patients with myelofibrosis irrespective of baseline cytopenias.

Methods: In the international phase 3 PERSIST-1 trial, patients with higher-risk myelofibrosis (no exclusions for baseline anemia or thrombocytopenia) were randomized 2:1 to receive oral pacritinib 400 mg once-daily or best available therapy (BAT; excluding JAK2 inhibitors) until disease progression or unacceptable toxicity.

Randomization was stratified by risk category, platelet count, and region. The primary endpoint was spleen volume reduction (SVR) $\geq 35\%$ from baseline to week 24 in the intent-to-treat population as assessed by blinded, centrally reviewed magnetic resonance imaging or computed tomography. Herein, final data with a median follow-up 23.2 months are presented. This trial is registered with clinicaltrials.gov, NCT01773187.

Findings: Between 8Jan2013-1Aug2014, 327 patients were randomized 2:1 to pacritinib (n=220) or BAT (n=107). At week 24, the primary endpoint of SVR $\geq 35\%$ was achieved by 19.1% (n=42) vs 4.7% (n=5) of pacritinib- vs BAT-treated patients (P=0.0003). The most common grade 3/4 adverse events through week 24 were anemia (37 [16.8%]), thrombocytopenia (26 [11.8%]), and diarrhea (11 [5.0%]) with pacritinib, and anemia (16 [15.1%]), thrombocytopenia (12 [11.3%]), dyspnea (3 [2.8%]), and hypotension (3 [2.8%]) with BAT; the most common serious adverse events were anemia (10 [4.5%]), cardiac failure (5 [2.3%]), pyrexia (4 [1.8%]), and pneumonia (4 [1.8%]) with pacritinib, and anemia (5 [4.7%]), sepsis (2 [1.9%]), and dyspnea (2 [1.9%]) with BAT.

Interpretation: Pacritinib therapy was well-tolerated and induced significant and sustained SVR and symptom reduction, even in patients with severe baseline cytopenias. Pacritinib could be a treatment option for patients with myelofibrosis, including those with baseline cytopenias for whom current options are particularly limited.

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Research In Context

Evidence before this study

Myelofibrosis is a myeloproliferative neoplasm, the characteristics of which include marked splenomegaly, extramedullary hematopoiesis, bone marrow fibrosis that contributes to anemia and thrombocytopenia, and risk of transformation to acute leukemia. Currently, ruxolitinib, a Janus-associated kinase (JAK) 1/2 inhibitor, is the only approved therapy for patients with myelofibrosis. Although ruxolitinib reduces splenomegaly and constitutional symptoms, it is also associated with myelosuppression and is not indicated for patients with severe thrombocytopenia, a disease feature in approximately 1/4 of patients with myelofibrosis. Data from phase 2 studies of pacritinib in patients with myelofibrosis showed that pacritinib was effective at reducing splenomegaly and improving symptoms in patients with myelofibrosis, including those with anemia and severe thrombocytopenia.

Added value of this study

To our knowledge, PERSIST-1 is the first randomized study of pacritinib in patients with myelofibrosis that does not exclude patients with severe thrombocytopenia (baseline platelet count $<100,000/\mu\text{L}$).

Implications of all the available evidence

The results of this study indicate that pacritinib can induce significant reduction in splenomegaly and improvement in disease-related symptoms in patients with myelofibrosis, regardless of the presence of severe cytopenias, and is minimally myelosuppressive.

Introduction

Myelofibrosis may arise as primary myelofibrosis or evolve as secondary myelofibrosis from other myeloproliferative neoplasms, specifically essential thrombocythemia and polycythemia vera.¹⁻⁴ Characteristics of myelofibrosis may include debilitating constitutional symptoms, extramedullary hematopoiesis, cytopenias (anemia and thrombocytopenia), progressive bone marrow fibrosis, and risk of transformation to acute leukemia.^{2,4-6} In a retrospective analysis of 1000 patients, 38% presented with anemia and 18% with thrombocytopenia; prevalence increased to 58% and 28%, respectively, within 1 year.⁷ Severe anemia may have a substantial negative impact on patients' quality of life (QoL).^{5,8} Data from an international database of patients with myelofibrosis (n=418) showed that thrombocytopenia (platelets <100,000/ μ L) was associated with significantly increased rates of anemia, leukopenia, and red blood cell (RBC) transfusion dependence (RBC-TD), as well as more severe symptom burden as measured by a significantly higher total symptom score (TSS) per the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF).⁹ A retrospective analysis of patients from the MD Anderson Cancer Center (n=1100, from 1984-2013) also showed more severe symptom burden and significantly shorter overall survival for patients with platelets <50,000/ μ L.¹⁰

Currently, there are no effective, nonmyelosuppressive therapies approved for the reduction of splenomegaly and symptom burden in patients with myelofibrosis and cytopenias. The only US Food and Drug Administration (FDA)-approved agent for myelofibrosis, ruxolitinib, is not indicated for patients with platelets <50,000/ μ L and is associated with clinically significant and dose-limiting anemia and thrombocytopenia.^{11,12} Enrolment in both phase 3 studies of ruxolitinib (COMFORT-I and COMFORT-II) in higher-risk myelofibrosis required a platelet count \geq 100,000/ μ L.^{11,12} Furthermore, patients with baseline platelet counts between 100,000-200,000/ μ L received a lower starting dose of ruxolitinib (15mg vs 20 mg twice daily [BID]) in an attempt to minimize treatment-related cytopenias. It was reported that patients with platelet counts between 100,000-200,000/ μ L in COMFORT-I (ruxolitinib vs placebo in higher-risk myelofibrosis) had lower mean percentage changes in both spleen volume

and TSS when compared with those for patients with platelet counts $>200,000/\mu\text{L}$.¹³ Additionally, patients with baseline platelet counts between $100,000\text{--}200,000/\mu\text{L}$ frequently (33 of 43 [77%]) required further dose reductions (median final titrated dose of 10 mg BID) and median final titrated doses of <10 mg BID were associated with less reduction in spleen volume and myelofibrosis-related symptoms.¹⁴ In a separate phase 2 study of ruxolitinib in patients with platelet counts between $50,000\text{--}100,000/\mu\text{L}$, patients were initially treated with ruxolitinib 5 mg BID, with only ~50% (23 of 41) able to increase their dose to ≥ 10 mg BID.¹⁵ Results of a recent phase 3 trial of the immunomodulatory agent pomalidomide failed to show improvement in myelofibrosis-related anemia,¹⁶ and no established agents have been shown to induce RBC transfusion independence (RBC-TI). Pacritinib is a kinase inhibitor with specificity for JAK2, FLT3, IRAK1, and CSF1R and minimal activity against JAK1 at pharmacologically relevant levels.^{17,18} In a kinome analysis of pacritinib, IC_{50} (nM) for JAK2 (JAK2_{V617F}), FLT3, IRAK1, CSF1R, and JAK1 were 6.0 (9.4), 14.8, 13.6, 39.5, and inactive (82% control), respectively.¹⁸ Published results of kinase inhibition profiles of other JAK inhibitors in development (ruxolitinib, momelotinib, fedratinib) indicate that all demonstrate nM inhibition of both JAK1 and JAK2.¹⁹⁻²¹ The findings of previous, nonrandomized studies of pacritinib in myelofibrosis demonstrated significant reductions in splenomegaly, durable improvements in symptoms, and manageable toxicities, even in patients with baseline anemia and thrombocytopenia.²²

We describe here the results of PERSIST-1, a global, randomized, phase 3 study comparing pacritinib with best available therapy (BAT) in patients with primary myelofibrosis, post-essential thrombocythemia myelofibrosis, or post-polycythemia vera myelofibrosis with no exclusions for baseline platelet counts or hemoglobin levels. Based on data from January 17, 2015 (median follow-up 11.5 months), the FDA had placed pacritinib on a full clinical hold on February 8, 2016 due to concerns over interim survival results, bleeding, and cardiovascular events, and all therapy was discontinued. However, upon review of the final PERSIST-1 data, among supplementary information, the FDA removed that clinical hold on January 5, 2017. Herein, final data (end of treatment due to clinical hold) with a median follow-up 23.2 months are presented, including patients who crossed over from BAT to pacritinib.

Methods

Study design and participants

Eligible patients in the United States, Europe, Russia, Australia, and New Zealand were aged ≥ 18 years with primary myelofibrosis, post-essential thrombocythemia myelofibrosis, or post-polycythemia vera myelofibrosis (locally confirmed via bone marrow biopsy at screening), intermediate- or high-risk disease by the Dynamic International Prognostic Scoring System (DIPSS), and a palpable spleen ≥ 5 cm below the left costal margin. Patients must have had a TSS ≥ 13 as assessed by the MPN-SAF TSS 2.0, an Eastern Cooperative Oncology Group performance status 0-3, peripheral blast count $< 10\%$, absolute neutrophil count $> 500/\mu\text{L}$, adequate hepatic and renal function, and a life expectancy ≥ 6 months. No prior splenectomy or allogeneic stem cell transplant (alloSCT), or plans to undergo splenectomy or alloSCT were allowed. Patients must have also had ≥ 12 months from radioactive phosphorus, ≥ 6 months from splenic irradiation, ≥ 4 weeks from any experimental treatment for myelofibrosis, ≥ 4 weeks from erythropoietic agents, ≥ 2 weeks from thrombopoietic agents, ≥ 1 week from treatment with potent cytochrome P450 3A4 inhibitors, and ≥ 2 weeks from any other treatments for myelofibrosis. No treatment with prior JAK2 inhibitors was allowed. Patients were not excluded based on platelet or hemoglobin levels; patients with RBC-TD were eligible. Patients with inflammatory or chronic functional bowel disorders, or clinically symptomatic and uncontrolled cardiovascular disease were excluded. The study protocol was approved by the institutional review boards at each participating institution, and study procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki; all patients provided written informed consent before any study procedures were performed.

Randomization and masking

Patients were stratified at randomization by DIPSS risk category (intermediate-1 or -2 vs high-risk), platelet count ($< 50,000/\mu\text{L}$ vs $50,000$ - $< 100,000/\mu\text{L}$ vs $> 100,000/\mu\text{L}$), and region and randomized via a central interactive web or voice response system 2:1 to pacritinib or BAT. Treatment assignments were known to investigators, site

personnel, patients, clinical monitors, and pharmacovigilance personnel; the sponsor remained blinded until database lock for the primary analysis. Independent radiographic assessors remained blinded throughout the study.

Procedures

BAT consisted of any physician-selected treatment, excluding JAK2 inhibitors, and could also include no treatment (ie, watchful waiting) or symptom-directed treatment. Pacritinib was administered at a dose of 400 mg once daily; patients in both arms were treated until disease progression (increase in splenic volume $\geq 25\%$ from baseline as centrally assessed every 12 weeks by magnetic resonance imaging [MRI] or computed tomography, splenic irradiation, splenectomy, and/or leukemic transformation [peripheral blood blasts $\geq 20\%$ for ≥ 8 weeks or bone marrow blasts $\geq 20\%$, measured via week 24 bone marrow biopsy which may have been evaluated centrally in addition to locally]) or unacceptable toxicity. For management of grade 3/4 nonhematologic toxicities, or clinically significant worsening of myelosuppression for ≥ 7 days or associated with infection or bleeding, pacritinib dosing was interrupted. Pacritinib was resumed when the toxicity resolved to grade ≤ 1 or baseline grade. Up to 2 dose reductions were allowed, first to 300 mg once-daily, and then to 200 mg once-daily; no dose re-escalation was allowed. Patients randomized to BAT could crossover to pacritinib upon disease progression before 24 weeks or at 24 weeks and beyond without progression. After the first 24 weeks, patients were assessed every 12 weeks until study discontinuation. After discontinuing treatment, patients were followed for leukemia-free survival and overall survival. Adverse events were assessed, documented, and reported throughout the study in accordance with International Conference on Harmonization Good Clinical Practice guidelines and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Patients were called on day 4 of treatment to assess the need for modifying supportive treatments for gastrointestinal adverse events. Bleeding and cardiac events were further assessed by standardized MEDRA query (SMQ) analysis.

Outcomes

The primary endpoint was spleen volume reduction (SVR) $\geq 35\%$ from baseline to week 24 as assessed by blinded, centrally reviewed MRI or computed tomography. The key secondary endpoint was the proportion of patients achieving $\geq 50\%$ reduction in TSS from baseline to week 24 on the MPN-SAF TSS 2.0, which was developed at the request of regulatory authorities to more accurately reflect the symptom burden of myelofibrosis. However, this trial was initiated using the original MPN-SAF TSS version; TSS 2.0 was introduced following a protocol amendment. Due to differences between questions and recall periods implemented in the two versions, patients administered MPN-SAF TSS questionnaires at study entry were analyzed separately and in combination with TSS 2.0 (6 common symptoms, appendix pg 3) as supportive analyses. Other secondary endpoints were the proportions of patients with baseline thrombocytopenia (platelets $< 100,000/\mu\text{L}$) or severe thrombocytopenia (platelets $< 50,000/\mu\text{L}$) who achieved SVR $\geq 35\%$ or $\geq 50\%$ reduction in TSS from baseline to week 24. Exploratory endpoints presented within included QoL, overall survival, achievement of RBC-TI by Gale criteria (no transfusions for 90 days),²³ and improvements in platelet and hemoglobin levels. Symptoms and QoL were assessed using the MPN-SAF TSS 2.0 and the Patient Global Impression of Change (PGIC) which consists of one domain with scores ranging from 1 (very much improved) to 7 (very much worse).

Statistical analysis

The primary hypothesis was that treatment with pacritinib would result in a greater proportion of patients achieving SVR $\geq 35\%$ at week 24 than treatment with BAT. A sample size of 270 patients (180 randomized to pacritinib, 90 randomized to BAT) is planned to provide 90% power to detect a treatment difference in the primary endpoint, at an α -level (2-sided) of 0.05. Efficacy analyses were performed using the intention-to-treat (ITT; all randomized patients) and evaluable populations. The evaluable population consisted of all randomized patients with baseline and follow-up assessments relevant for that endpoint. For the primary endpoint, this included patients with baseline and week 24 spleen assessments by MRI/CT. Treatment differences in proportions

of patients achieving SVR $\geq 35\%$ were tested using Fisher's exact test, with 95% CI based on the Agresti-Caffo method. Percentage reduction from baseline in TSS at week 24 was calculated by

$$\left(\frac{\text{Week 24 TSS} - \text{Baseline TSS}}{\text{Baseline TSS}} \right) \times 100$$
 where TSS at baseline was the mean of the daily TSS over the 7 consecutive days preceding randomization and TSS at week 24 was the mean of the daily TSS over the 28 days prior to the week 24 visit. A sensitivity analysis was conducted using the mean of the 7 daily TSS prior to the week 24 visit as the week 24 TSS; if fewer than 4 daily TSS were available, the TSS for week 24 was considered missing. The primary endpoint was tested at $\alpha=0.05$ (two-sided); secondary endpoints were tested in succession at $\alpha=0.05$ (two-sided) only if the primary endpoint was reached. Final end of treatment data (due to clinical hold) were used for these analyses. The safety population consisted of randomized patients who received ≥ 1 dose of pacritinib or BAT, and all those not receiving active drug (watchful waiting approach). SAS v9.4 was used for all statistical analyses. This study is registered with ClinicalTrials.gov, number NCT01773187.

Role of the funding source

The study was sponsored by CTI BioPharma Corp. CTI BioPharma was involved in the analysis and interpretation of the data. The first and senior authors prepared the first draft of the manuscript with assistance from a medical writer funded by CTI BioPharma. All authors had access to any data requested, reviewed and approved the manuscript, and vouch for the accuracy and completeness of the data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Baseline and Disposition

Three hundred twenty-seven patients were enrolled and randomized to pacritinib (n=220, 67.3%) or BAT (n=107, 32.7%). One patient randomized to BAT withdrew before receiving treatment and was the only patient not

included in the safety population. Median follow-up was 23·2 months (IQR 14·8, 28·7). Overall, 77·7% (171 of 220) and 76·6% (82 of 107) of patients in the pacritinib and BAT arms, respectively, completed 24 weeks of study treatment. The median duration of pacritinib treatment was 15·6 months (IQR 5·6, 23·7) and median duration of BAT treatment was 5·9 months (IQR 5·6, 6·5). Ninety patients randomized to BAT (84·1%) crossed over to receive pacritinib at a median of 6·3 months (IQR 5·8, 6·7). Median duration of pacritinib treatment post-crossover was 13·8 months (IQR 6·8, 17·8). Patient disposition throughout the study is shown in Figure 1.

Baseline demographic and disease characteristics were generally well balanced (Table 1); however, despite stratification, there were imbalances in some DIPSS risk factor components between pacritinib and BAT arms (appendix pg 3). The most frequently administered treatment in the BAT arm was hydroxyurea (n=60, 56·6%); 27 patients (25·5%) received only watchful waiting and the remainder received a variety of agents typically used to treat myelofibrosis but currently not approved for myelofibrosis (appendix pg 3). Overall, BAT-treated patients who had received hydroxyurea had better prognostic features than patients who received other agents or no therapy (appendix pg 4).

Spleen Volume Reduction

At week 24 in the ITT population, 19·1% (n=42) of pacritinib-treated patients achieved SVR \geq 35% vs 4·7% (n=5) of patients in the BAT arm (P=0·0003; Table 2). SVR at week 24 was not dependent on baseline spleen volume (Pearson Correlation Coefficient 0·0163, P=0·80). For patients with primary and secondary myelofibrosis, 19·4% (28 of 144) and 18·7% (14 of 75) of pacritinib-treated patients, respectively achieved SVR \geq 35% vs 3·4% (2 of 59) and 6·3% (3 of 48) of BAT-treated patients, respectively. For patients with platelets <50,000/ μ L and <100,000/ μ L, 22·9% (8 of 35) and 16·7% (12 of 72) of pacritinib-treated patients, respectively achieved SVR \geq 35% vs 0 BAT-treated patients in both platelet subgroups (P=0·045, P=0·0086; Table 2). The magnitude of this difference was increased in the evaluable population both overall and in the prespecified platelet subgroups (Table 2, Figure 2A). Median duration of SVR \geq 35% was 34·3 weeks (95% CI, 24·1-48·4) in the pacritinib arm and not applicable in the

BAT arm. For evaluable pacritinib-treated patients, the rate of SVR $\geq 35\%$ at week 24 (42 of 171 [24.6%]) remained similar through the last time point (week 108, 13 of 49 [26.5%]). The mean absolute reduction in spleen volume was $>20\%$ at all time points in the pacritinib arm (ITT population); in the BAT arm mean spleen volume was not different from baseline through week 24 (Figure 2B). Results were similar for patients with platelets $<50,000/\mu\text{L}$ and $<100,000/\mu\text{L}$ (appendix pg 17). For patients crossing over from BAT to pacritinib ($n=90$, ITT population), SVR $\geq 35\%$ was achieved in 11 patients (12.2%) at week 24 after crossover. For evaluable patients who crossed over, rate of SVR $\geq 35\%$ at week 24 (11 of 68 [16.2%]) remained similar through last time point measured post-crossover (week 84, 2 of 16 [12.5%]). The mean absolute reduction in spleen volume after crossover ranged from 12%–17% at all times points. Patients randomized to pacritinib also trended toward a greater median reduction in JAK2^{V617F} allele burden vs BAT at 24 weeks (-15.8% [IQR -41.0 , 1.4] vs -7.9% [IQR -21.3 , 2.4], respectively; $P=0.072$). For pacritinib-treated patients, the median greatest reduction in allele burden from baseline at any time point was -31.6% (IQR -57.5 , -7.5 ; appendix pg 4) and decrease in allele burden was strongly correlated with SVR ($P=0.0030$; appendix pg 4). Data for additional driver mutations of myelofibrosis was not collected.

Reduction in Symptoms

In the ITT population for TSS 2.0, 19 of 100 (19.0%) and 5 of 48 (10.4%) patients in the pacritinib- and BAT-treated arms, respectively, had a $\geq 50\%$ reduction in TSS 2.0 from baseline to week 24 ($P=0.24$; Table 3). Statistically significant differences in $\geq 50\%$ reduction of TSS 2.0 were observed in the evaluable population, with 19 of 53 (35.8%) and 5 of 36 (13.9%) patients in the pacritinib- and BAT-treated arms, respectively, achieving this endpoint ($P=0.029$). In the ITT population for TSS 2.0, 15 of 100 (15.0%) and 0 patients in the pacritinib- and BAT-treated arms, respectively, had a $\geq 50\%$ reduction in TSS 2.0 from baseline to week 48 ($P=0.0027$; Table 3). A greater proportion of pacritinib-treated patients with platelets $<50,000/\mu\text{L}$ and $<100,000/\mu\text{L}$ also achieved $\geq 50\%$ reduction in TSS 2.0 vs BAT-treated patients at weeks 24 and 48, but these results did not achieve statistical significance, likely due to limited numbers of patients in these groups (Table 3). Because of the consistent results found between the MPN-SAF TSS and MPN-SAF TSS 2.0 (appendix pg 4), the similar and consistent PGIC responses

based on the two versions (appendix pg 5), and to fully evaluate symptom reduction for all patients, a combined analysis was performed using the common six symptoms between both versions (fatigue/tiredness, early satiety, abdominal discomfort, night sweats, pruritus, and bone pain). At week 24, significantly more pacritinib-treated patients achieved $\geq 50\%$ reduction in TSS (6 common symptoms) vs BAT-treated patients (ITT: 24.5% [n=54] vs 6.5% [n=7], $P < 0.0001$; evaluable: 40.9% [54 of 132] vs 9.9% [7 of 71], $P < 0.0001$). Improvements with pacritinib were rapid and continued throughout the 48-week period (evaluable: 46.2% [42 of 91] vs 16.7% [1 of 6]; Figure 3A). Median improvements in each individual symptom score were also greater with pacritinib vs BAT at weeks 24 and 48 (appendix pg 5). Improvements in TSS correlated with improvements in PGIC (Figure 3B). Among evaluable patients who crossed over from BAT to pacritinib, rate of patients that achieved $\geq 50\%$ reduction in TSS (6 common symptoms) increased from 14.9% (7 of 47) at week 24 to 29.6% (8 of 27) at week 36 after crossover. At week 48 post-crossover, 3 of 18 (16.7%) patients had $\geq 50\%$ reduction in TSS.

Overall Survival

Prior to week 24, overall survival (ITT) was similar between the pacritinib and BAT arms (Figure 4). The probability of survival at 24 weeks was not significantly different: 95% (95% CI 91%-97%, n=199 at risk) vs 97% (95% CI 92%-99%, n=101 at risk) for pacritinib- vs BAT-treated patients, respectively. Achievement of SVR $\geq 35\%$, SVR 20% to $< 35\%$, and SVR 10% to $< 20\%$ at week 24 correlated with improved overall survival relative to achievement of SVR $< 10\%$ at week 24 in patients randomized to pacritinib (appendix pg 5). There was no correlation between SVR at week 24 and overall survival for BAT-treated patients. After week 24, there was a trend towards improved survival for the BAT arm, however 84.1% (n=90) of BAT-treated patients crossed over to receive pacritinib (primarily at week 24), which confounds the survival analysis. At time of analysis, 76 (34.5%) and 29 (27.1%) patients in pacritinib and BAT arms, respectively, had died (appendix pg 6).

To further examine the effect of baseline imbalances in prognostic variables for overall survival, post-hoc analyses were performed. A post-hoc, exploratory multivariate Cox analysis of randomization stratification variables, DIPSS

risk factors, and other baseline characteristics identified as potentially affecting overall survival showed that age, platelet count, white blood cell (WBC) count, and hemoglobin level were significantly associated with overall survival (appendix pg 6). After adjusting for these risk factors with Cox modeling, the hazard ratio for pacritinib vs BAT was 1.22 (95% CI, 0.79–1.88), vs 1.36 (95% CI, 0.89–2.09) in the primary ITT analysis. An analysis of various subgroups showed that baseline WBC >25,000/ μ L adversely affected overall survival (appendix pg 18), particularly for those randomized to pacritinib. Further examination of 6 key risk factors demonstrated that patients in the high WBC group randomized to pacritinib had notably higher rates and multiplicity of other adverse risk factors (appendix pg 3). Curves for overall survival by treatment arm, segmented by multiplicity of risk factors, are shown in the appendix, pg 18.

Changes in Hematologic Parameters

There was no significant difference in change in platelet levels from baseline between patients in the pacritinib and BAT arms through week 24 (appendix pg 19). In patients with baseline platelets <50,000/ μ L, treatment with pacritinib resulted in increases in platelets through week 24 ($P=0.055$, appendix pgs 19-20). Concerning anemia, differences in mean change in hemoglobin levels from baseline between the pacritinib and BAT arms for all patients and patients with baseline anemia (hemoglobin levels <10 g/dL) are presented in the appendix, pgs 20-21. For patients with baseline hemoglobin levels of <10 g/dL who did not receive transfusions, at week 24 the median hemoglobin on pacritinib increased from 9.1 to 10.4 g/dL ($P=0.017$) whereas patients in the BAT arm had a minimal change, from 9.2 to 9.5 g/dL ($P=0.18$). A significantly greater proportion of pacritinib-treated patients who were RBC-TD at baseline achieved RBC-TI during the study, compared with BAT (9 of 36 [25.0%] vs 0 of 16 [0%], respectively, $P=0.043$).

Safety

The total patient-years of exposure were 280.0 to pacritinib vs 60.0 to BAT. Diarrhea, nausea, and vomiting were the most frequently reported nonhematologic adverse events and were more frequent with pacritinib (Table 4,

appendix pg 7). More than half of these events with pacritinib were grade 1 in severity, both through week 24 and at any time on study. Grade 3 diarrhea, nausea, or vomiting occurred in 7·3%, 1·4%, and 2·7% of pacritinib-treated patients at any time on study (appendix pg 8), respectively; no grade 4 or 5 events were observed. The most common serious adverse events through week 24 were anemia (10 [4·5%]), cardiac failure (5 [2·3%]), pyrexia (4 [1·8%]), and pneumonia (4 [1·8%]) with pacritinib, and anemia (5 [4·7%]), sepsis (2 [1·9%]), and dyspnea (2 [1·9%]) with BAT (appendix pg 9).

Diarrhea was the most frequently observed gastrointestinal adverse event; median time to onset and resolution of first event among pacritinib-treated patients who had diarrhea was 3·1 (95% CI, 1·1-25·4) and 2·1 (95% CI, 1·1-4·0) weeks, respectively (appendix pg 9). Median time to resolution of first event of nausea and vomiting was 2·1 (95% CI, 1·4-4·3) and 0·3 (95% CI, 0·1-0·4) weeks, respectively. At any time on study, 9 (4·1%) patients discontinued pacritinib treatment due to gastrointestinal adverse events. Diarrhea led to discontinuation in 6 (2·7%) and dose reductions in 11 (5·0%) pacritinib-treated patients. Diarrhea, nausea, and vomiting were observed among 2 (0·6%), 2 (0·6%), and 3 (0·9%) patients, respectively, at baseline. Anemia and thrombocytopenia were the most frequently observed hematologic toxicities in both pacritinib- and BAT-treated patients. Worsening (grade) of preexisting thrombocytopenia and anemia was similar between arms (appendix pg 7). Overall, for patients with baseline assessments, 42·0% (129 of 307) had baseline grades 1-4 thrombocytopenia (16·3% [n=50] grade ≥3); 70·8% (231 of 326) had preexisting grades 1-3 anemia (8·9% [n=29] grade 3). Importantly, among the 90 patients in the BAT arm who crossed over to receive pacritinib, incidence of any-grade anemia and thrombocytopenia were similar after crossover (16 [17·8%] and 11 [12·2%] vs 19 [21·1%] and 15 [16·7%], before and after crossover, respectively), but incidence of diarrhea increased following crossover (10 [11·1%] vs 52 [57·8%]). In pacritinib-treated patients, adverse events and dose modifications due to adverse events were numerically higher in patients with baseline thrombocytopenia (appendix pg 10).

In patients randomized to pacritinib and BAT, bleeding events (SMQ) of any grade occurred in 43 (19·5%) vs 20 (18·9%) patients through week 24, respectively (appendix pg 11); severe bleeding events (SMQ) were infrequent

through week 24 (grade 3/4: 7 [3·2%] vs 2 [1·9%] for pacritinib vs BAT). For pacritinib-treated patients, 14 (6·4%) had grade 3/4 bleeding events at any time on study (median duration of treatment 15·6 months; appendix pgs 12 & 13); events reported in >1 pacritinib-treated patient were epistaxis (n=4), hematoma (n=2), and postprocedural hemorrhage (n=2). The majority of pacritinib-treated patients with severe bleeding events had resolution of first event (10 of 14 [71·4%]), at a median of 2·3 weeks (95% CI, 1·0-NA). Grade 3/4 bleeding events were reported at any time post-crossover to pacritinib in 7/90 patients (7·8%).

In patients randomized to pacritinib and BAT, cardiac events (SMQ) of any grade occurred through week 24 in 44 (20·0%) vs 22 (20·8%) patients, respectively (appendix pg 14). Severe cardiac events (SMQ) were infrequent through week 24 (grade 3/4: 8·2% [n=18] vs 5·7% [n=6] for pacritinib vs BAT). For pacritinib-treated patients, 27 (12·3%) had grade 3/4 cardiac events at any time on study (appendix pgs 14 & 15); events reported in >1 pacritinib-treated patient were cardiac failure (n=6), atrial fibrillation (n=4), congestive cardiac failure (n=4), electrocardiogram (ECG) QT prolonged (n=3), syncope (n=2), and pulmonary edema (n=2). The majority of pacritinib-treated patients with grade 3/4 cardiac events had resolution of first event (18 of 26 [69·2%]), at a median of 1·2 weeks (95% CI, 0·9-1·9). Grade 3/4 cardiac events were reported at any time post-crossover to pacritinib in 7/90 patients (7·8%). ECG QTc intervals >480 ms were reported in 8 (3·6%; 4 [1·8%] >500 ms) and 1 (0·9%) pacritinib- and BAT-treated patients, respectively. There were no meaningful differences in deaths due to cardiac or bleeding events between patients randomized to pacritinib vs BAT (appendix pg 6).

Median leukocyte and neutrophil counts decreased slightly from baseline to week 24 in both pacritinib- and BAT-treated patients (appendix pg 15). Peripheral neuropathy was observed in 2 (0·9%) pacritinib-treated patients and 4 (3·8%) BAT-treated patients. Incidence of serious opportunistic infections was low; herpes zoster infections were observed in 3 pacritinib-treated patients (1·4%) and no BAT-treated patients. Extrapulmonary tuberculosis was reported in 1 pacritinib-treated patient (0·5%) and progressive multifocal leukoencephalopathy was not reported in either arm. The mean relative dose intensity observed with pacritinib was 94·9%, and 104 (47·3%) pacritinib-treated patients required dose modifications due to adverse events. Through week 24, dose reductions

due to adverse events occurred in 22 (10·0%) vs 9 (8·5%) pacritinib- vs BAT-treated patients; 22 (10·0%) vs 3 (2·8%) pacritinib- vs BAT-treated patients, respectively, discontinued due to adverse events (appendix pg 10).

Deaths due to adverse events were observed in 27 (12·3%) patients randomized to pacritinib (8 [3·6%] during the first 24 weeks of treatment) and 14 (13·2%) patients randomized to BAT (11 [10·4%] after crossover to pacritinib, appendix pg 6). The most frequent adverse events leading to death in the pacritinib arm were disease progression (n=6) and pneumonia (n=3). Leukemic transformation was observed at any time in 11 (5·0%) pacritinib- vs 2 (1·9%) BAT-treated patients (P=0·23).

Discussion

In this phase 3 study of pacritinib vs BAT in patients with myelofibrosis, pacritinib therapy was well-tolerated and induced significant and sustained SVR and symptom reduction, even in patients with severe baseline cytopenias. Treatment options for patients with myelofibrosis and severe anemia and/or thrombocytopenia are limited. Approximately 58% and 28% of patients will become anemic or thrombocytopenic, respectively, within a year from diagnosis; this trend continues to increase with time and is associated with shorter survival.^{6,7} These patients constitute a significantly underserved population. Currently, the only disease-specific approved therapy for patients with myelofibrosis, ruxolitinib, is not indicated for initiation in patients with platelets <50,000/ μ L, and its efficacy (particularly in terms of SVR) has been shown to be reduced in patients with platelets <100,000/ μ L due to the need for dose reduction.¹⁵ Other JAK2 inhibitors and novel agents in development have also been associated with a relatively high incidence of grade 3/4 thrombocytopenia.^{24,25} In this randomized, phase 3 study, treatment with pacritinib resulted in a significantly greater proportion of patients achieving SVR \geq 35% at week 24 vs BAT, regardless of the inclusion of patients with low baseline platelet counts and specifically in the subsets of patients with platelets <100,000/ μ L or <50,000/ μ L. Due to missed assessments at baseline or week 24, there was a discrepancy in patient numbers between ITT and evaluable populations; however, the difference in SVR \geq 35%

between pacritinib- and BAT-treated patients reached statistical significance in both populations. Responses to pacritinib were durable, with rates of SVR $\geq 35\%$ maintained through week 108.

In addition, among evaluable patients, pacritinib was associated with significant and durable improvements in TSS; the proportion of pacritinib-treated patients with $\geq 50\%$ reduction in TSS increased over time through week 48 (last symptom assessment). In patients with baseline cytopenias (platelets $< 50,000/\mu\text{L}$ or hemoglobin $< 10 \text{ g/dL}$) treated with pacritinib, meaningful improvements were observed in platelet and hemoglobin levels. Among patients who were RBC-TD at baseline, only pacritinib-treated patients achieved RBC-TI.

The most frequently occurring adverse events with pacritinib were manageable gastrointestinal symptoms, particularly diarrhea and nausea. While gastrointestinal adverse events have been reported with JAK inhibitors, the mechanisms for this have not been elucidated. In this study, gastrointestinal adverse events were primarily grade 1/2 and generally resolved with standard measures without precluding continued pacritinib therapy.

Although there were greater incidences of cardiac and bleeding events in patients randomized to pacritinib, the longer exposure to pacritinib vs BAT and the disproportionate number of patients with adverse risk factors in the pacritinib arm may have been partially contributory. While pacritinib is a potent inhibitor of JAK2, the lack of activity against JAK1 may contribute to the relative absence of dose-related thrombocytopenia and anemia.¹⁸ Additionally, though inhibition of JAK1 has known anti-inflammatory effects,²⁶ observed anti-inflammatory activity with pacritinib may instead be due to inhibition of IRAK1 and CSF1R.^{27,28}

Final data presented herein demonstrated similar incidence of cardiac and bleeding adverse events (SMQ) with pacritinib or BAT through week 24, and infrequent reports of severe cardiac or bleeding adverse events with pacritinib at any time on study. For patients randomized to pacritinib vs BAT, overall survival was not significantly different. There were imbalances in baseline covariates with known prognostic effects on overall survival and crossover of 90 patients (84.1%) from the BAT arm. Crossover from BAT and the resulting differences in time on treatment and patient-years of exposure also impact safety analyses; most deaths occurred after week 24.

Despite confounding factors, results of the current study demonstrate that treatment with pacritinib induces significant reduction in splenomegaly and improvement in symptoms in patients with myelofibrosis, regardless of the presence of severe cytopenias, and is minimally myelosuppressive. The separate phase 3 PERSIST-2 study of pacritinib (400 mg once-daily or 200 mg twice-daily) vs BAT, including ruxolitinib, in patients with myelofibrosis and baseline thrombocytopenia (platelets $\leq 100,00/\mu\text{L}$) has also demonstrated that pacritinib was significantly more effective than BAT for SVR with an improved benefit/risk profile.²⁹ Additional studies of pacritinib in patients with myelofibrosis are planned, including a dose-exploration trial in patients with primary myelofibrosis who have failed prior ruxolitinib therapy.

Author contributions

RAM, AMV, AM, ME, AS, AS, JJ, AP, RP, JM, JD, PG, PatB, JY, J-JK, and CNH were study investigators and as such collected data and contributed to the analysis and interpretation of data; RAM and CNH were also study co-chairs. JPD contributed to study design, data analysis, and interpretation of data. JWS contributed to study design and interpretation of data. HZ contributed data analysis and interpretation of data. All authors participated in drafting and revising the manuscript and approved the final version before submission.

Declaration of Interests

RAM: Research support from Incyte, Gilead, CTI BioPharma, Promedior, Genentech, Lilly, and NS Pharma; consultancy for Novartis, Galena, and Ariad; **AMV:** grants and personal fees from Novartis; **AP,** speaker funding from Novartis; **JM:** grants, personal fees, and non-financial support from Cell Therapeutics, Inc.; grants from Novartis; **JWS, HZ, JPD:** Employment and stock in CTI BioPharma; **PatB:** personal fees from Novartis, CTI BioPharma, Alexion, BMS, and Gilead; **JJK:** grants and personal fees from Novartis; **CNH:** personal fees from CTI BioPharma; research funding from Novartis; speaker funding from CTI BioPharma, Novartis, Sanofi, and Baxter;

advisor fees from CTI BioPharma, Novartis, Gilead, and Baxter. **AM, ME, AS, AS, JJ, RP, JD, PG, JN:** Nothing to disclose.

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Tables

Table 1. Baseline Characteristics.

Characteristic	Pacritinib (n=220)	BAT (n=107)
Median age, years (IQR)	67 (60-73)	65 (59-72)
≥65 years, n (%)	135 (61.4)	55 (51.4)
Sex, n (%)		
Male	125 (56.8)	60 (56.1)
Female	95 (43.2)	47 (43.9)
ECOG PS, n (%)		
0-1	192 (87.3)	96 (89.7)
2-3	28 (12.7)	11 (10.3)
Myelofibrosis diagnosis, n (%)		
Primary myelofibrosis	144 (65.5)	59 (55.1)
Post-polycythemia vera myelofibrosis	48 (21.8)	33 (30.8)
Post-essential thrombocythemia myelofibrosis	27 (12.3)	15 (14.0)
Missing	1 (0.5)	0
DIPSS score, n (%)		
Intermediate-1	124 (56.4)	49 (45.8)
Intermediate-2	63 (28.6)	43 (40.2)
High	32 (14.5)	15 (14.0)
Missing	1 (0.5)	0
Median spleen length by physical exam*, cm (IQR)	12 (8-16)	12 (8-17)
Median spleen volume by MRI/CT†, cm ³ (IQR)	2005.6 (1396.6-2889.0)	2152.7 (1545.2-3136.0)
JAK2 ^{V617F} -positive, n (%)‡	154 (70.0)	92 (86.0)
Bone marrow biopsy completed, n (%)	219 (99.5)	107 (100.0)
Reticulin and collagen fibrosis staging‡		
MF 0-1	32 (14.6)	18 (16.8)
MF 2-3	180 (82.2)	83 (77.6)

Missing	7 (3·2)	6 (5·6)
Peripheral blasts, n (%)		
<1%	78 (35·5)	44 (41·1)
≥1%	94 (42·7)	38 (35·5)
<5%	159 (72·3)	74 (69·2)
≥5%	13 (5·9)	8 (7·5)
Missing	48 (21·8)	25 (23·4)
White blood cell count		
Median × 10 ⁹ /L (IQR)	9·9 (6·1-21·1)	11·7 (6·3-24·5)
≤25 ×10 ⁹ /L, n (%)	177 (80·5)	80 (74·8)
>25 ×10 ⁹ /L, n (%)	43 (19·5)	26 (24·3)
Hemoglobin, n (%)		
<10 g/dL	84 (38·2)	47 (43·9)
≥10 g/dL	136 (61·8)	59 (55·1)
RBC transfusion dependence [§] , n (%)		
Dependent	35 (15·9)	15 (14·0)
Independent	156 (70·9)	75 (70·1)
Indeterminate	29 (13·2)	14 (13·1)
Missing	0	3 (2·8)
Platelet count, n (%)		
<50,000/μL	35 (15·9)	16 (15·0)
≥50,000 to <100,000/μL	37 (16·8)	18 (16·8)
≥100,000/μL	148 (67·3)	73 (68·2)

*n=219 for pacritinib, n=106 for BAT; † n=218 for pacritinib, n=107 for BAT; ‡P<0·05 for patients randomized to pacritinib vs

BAT; §≥6 units per 90 days as defined as per Gale criteria²³

BAT, best available therapy; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; JAK, Janus-associated kinase; MRI/CT, magnetic resonance imaging/computed tomography; RBC, red blood cell.

Table 2. Patients in the intention-to-treat and evaluable populations overall and by prespecified baseline platelet subgroups who achieved $\geq 35\%$ reduction in spleen volume at week 24.

n/N (%)	Intention-to-treat			Evaluable		
	Pacritinib, %	BAT, %	P value	Pacritinib, %	BAT, %	P value
Overall	42/220 (19.1)	5/107 (4.7)	0.0003	42/168 (25.0)	5/85 (5.9)	0.0001
Platelets <100,000/ μL	12/72 (16.7)	0/34 (0)	0.0086	12/51 (23.5)	0/24 (0)	0.0072
Platelets <50,000/ μL	8/35 (22.9)	0/16 (0)	0.045	8/24 (33.3)	0/11 (0)	0.037

Table 3. Patients in the intention-to-treat population, overall and prespecified platelet subgroups achieving $\geq 50\%$ reduction in Total Symptom Score 2.0 at weeks 24 and 48.

n/N (%)	Week 24			Week 48		
	Pacritinib, %	BAT, %	P value	Pacritinib, %	BAT, %	P value
Overall	19/100 (19.0)	5/48 (10.4)	0.24	15/100 (15.0)	0/48 (0)	0.0027
Platelets <100,000/ μL	7/28 (25.0)	1/13 (7.7)	0.40	3/28 (10.7)	0/13 (0)	0.54
Platelets <50,000/ μL	3/11 (27.3)	0/5 (0)	0.51	2/11 (18.2)	0/5 (0)	1.0

Table 4. Most Common Adverse Events Through Week 24 or Initial Treatment Discontinuation.

All grade in >5% or grade 3 in >1% of Pacritinib-Treated Patients, n (%)	Pacritinib (n=220)					BAT (n=106)				
	Grade 1/2	Grade 3	Grade 4	Grade 5	All	Grade 1/2	Grade 3	Grade 4	Grade 5	All
Diarrhea	109 (49.5)	11 (5.0)	0	0	120 (54.5)	11 (10.4)	0	0	0	11 (10.4)
Nausea	58 (26.4)	2 (0.9)	0	0	60 (27.3)	7 (6.6)	0	0	0	7 (6.6)
Anemia	15 (6.8)	32 (14.5)	5 (2.3)	0	52 (23.6)	5 (4.7)	13 (12.3)	3 (2.8)	0	21 (19.8)
Thrombocytopenia	11 (5.0)	12 (5.5)	14 (6.4)	0	37 (16.8)	3 (2.8)	9 (8.5)	3 (2.8)	0	15 (14.2)
Vomiting	34 (15.5)	2 (0.9)	0	0	36 (16.4)	6 (5.7)	0	0	0	6 (5.7)
Fatigue	17 (7.7)	5 (2.3)	0	0	22 (10.0)	9 (8.5)	1 (0.9)	0	0	10 (9.4)
Abdominal pain	18 (8.2)	3 (1.4)	0	0	21 (9.5)	10 (9.4)	0	0	0	10 (9.4)
Peripheral edema	16 (7.3)	1 (0.5)	0	0	17 (7.7)	12 (11.3)	1 (0.9)	0	0	13 (12.3)
Decreased appetite	11 (5.0)	1 (0.5)	0	0	12 (5.5)	3 (2.8)	0	0	0	3 (2.8)
ECG QT prolonged	9 (4.1)	3 (1.4)	0	0	12 (5.5)	1 (0.9)	0	0	0	1 (0.9)
Pyrexia	7 (3.2)	4 (1.8)	0	0	11 (5.0)	10 (9.4)	1 (0.9)	0	0	11 (10.4)
Pneumonia	3 (1.4)	4 (1.8)	0	1 (0.5)	8 (3.6)	0	0	0	0	0
Leukopenia	3 (1.4)	3 (1.4)	1 (0.5)	0	7 (3.2)	0	2 (1.9)	0	0	2 (1.9)
Hypertension	2 (0.9)	5 (2.3)	0	0	7 (3.2)	1 (0.9)	0	0	0	1 (0.9)
Cardiac failure	1 (0.5)	5 (2.3)	0	0	6 (2.7)	0	1 (0.9)	0	1 (0.9)	2 (1.9)
Atrial fibrillation	1 (0.5)	3 (1.4)	0	0	4 (1.8)	1 (0.9)	0	0	0	1 (0.9)

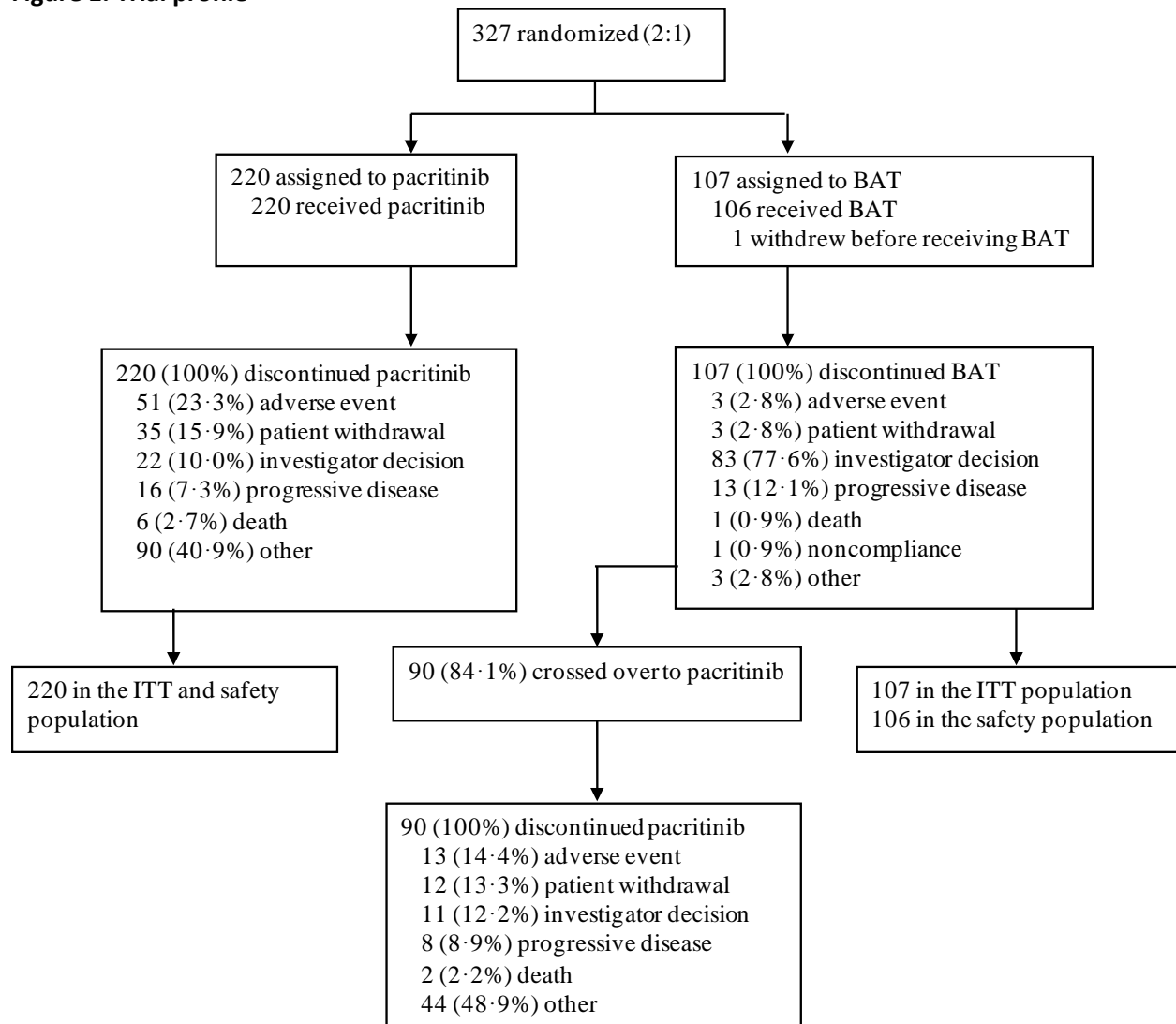
BAT, best available therapy.

Additional grade 4 or 5 adverse events with pacritinib: neutropenia (4 gr 4), platelet count decreased (3 gr 4), hyperuricemia (2 gr 4), hyperkalemia (1 gr 4), cardiac failure congestive (1 gr 4), thrombocytosis (1 gr 4), sepsis (1 gr 4), disease progression (1 gr 5), cardio-respiratory arrest (1 gr 5), multi-organ failure (1 gr 5), delayed hemolytic transfusion reaction (1 gr 4), neutrophil count decreased (1 gr 4), cerebral hemorrhage (1 gr 4), acute respiratory distress syndrome (1 gr 4).

Additional grade 4 or 5 adverse events with BAT: neutropenia (1 gr 4), colon neoplasm (1 gr 4), hypoglycemia (1 gr 4), sepsis (1 gr 4, 1 gr 5), disease progression (1 gr 5), hyponatremia (1 gr 4), septic shock (1 gr 4), acute respiratory distress syndrome (1 gr 4).

Figures

Figure 1. Trial profile



Note: the majority of patients who discontinued pacritinib due to “other” did so due to the clinical hold placed by the FDA in February 2016 (hold removed in January 2017) and the majority of patients who discontinued BAT due to “investigator decision” did so in order to cross over to pacritinib treatment.

Figure 2. Spleen Volume Reduction According to Treatment Group. (A) Best percentage change from baseline in spleen volume in the first 24 weeks of treatment for evaluable patients. (B) Mean percentage change in spleen volume over time for evaluable patients. BAT, best available therapy.

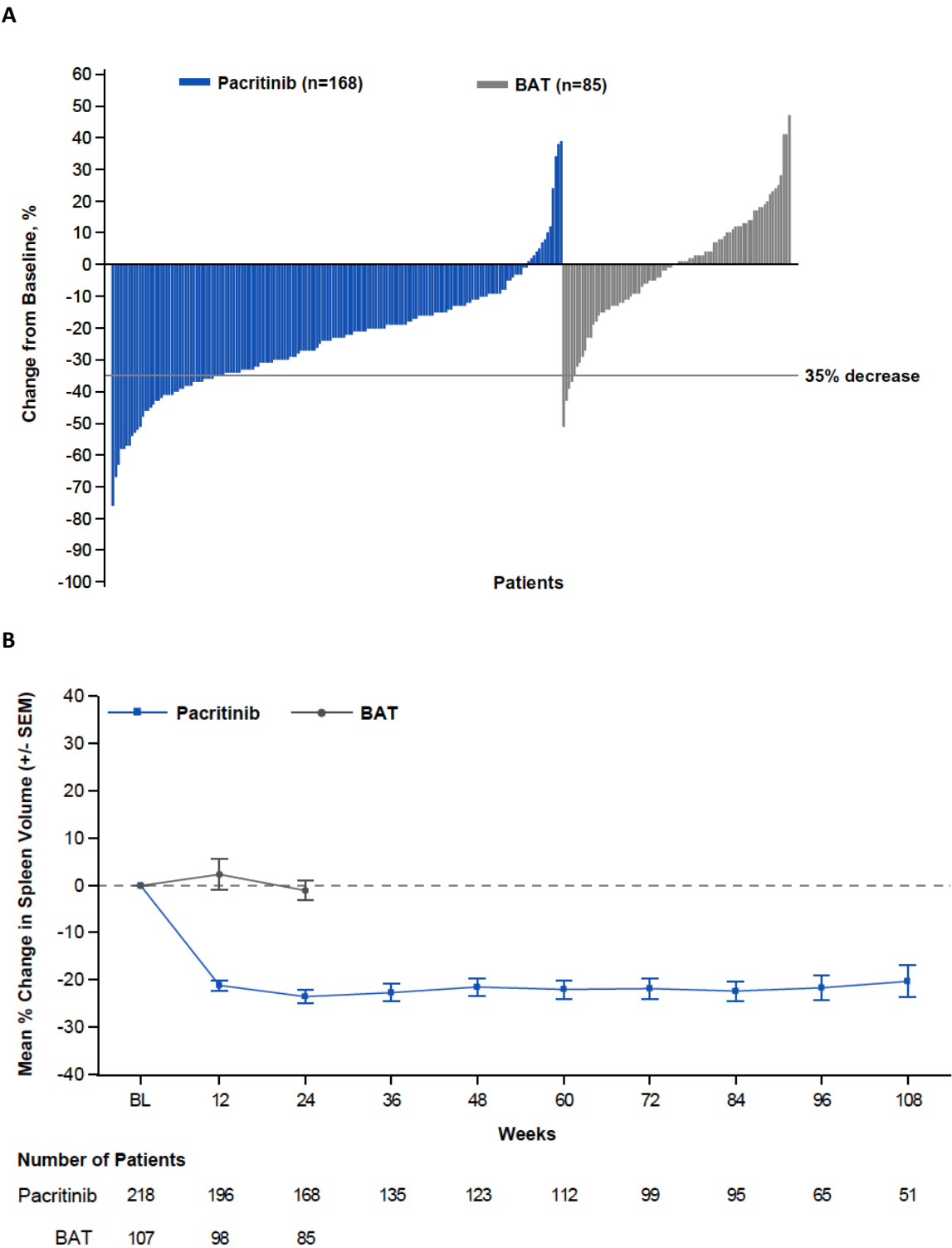
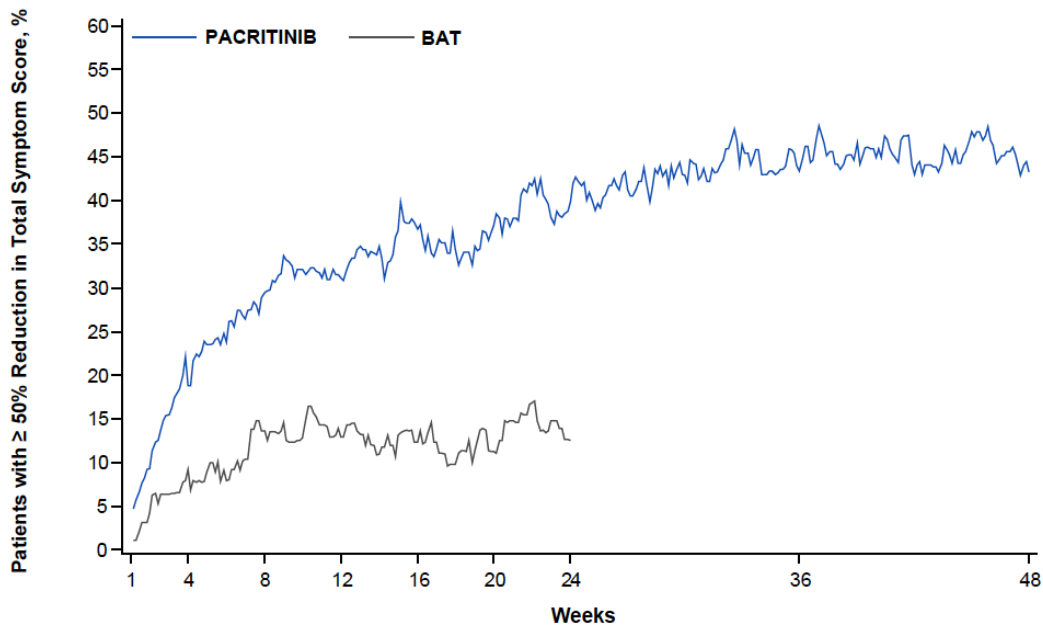


Figure 3. Change in Total Symptom Score. (A) Percentage of evaluable patients achieving $\geq 50\%$ reduction over time for the 6 common symptoms between the MPN-SAF TSS original version and TSS 2.0. Most responses with pacritinib occurred rapidly and continued to improve throughout treatment. (B) Patient Global Impression of Change responses for evaluable patients at week 24.

A



B

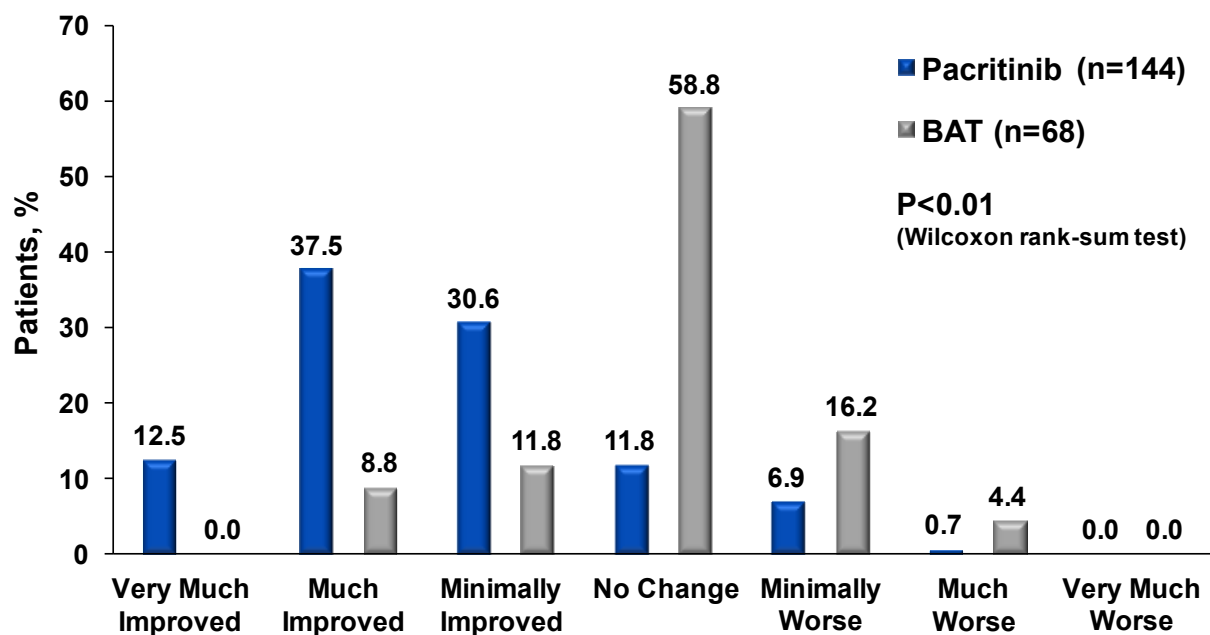
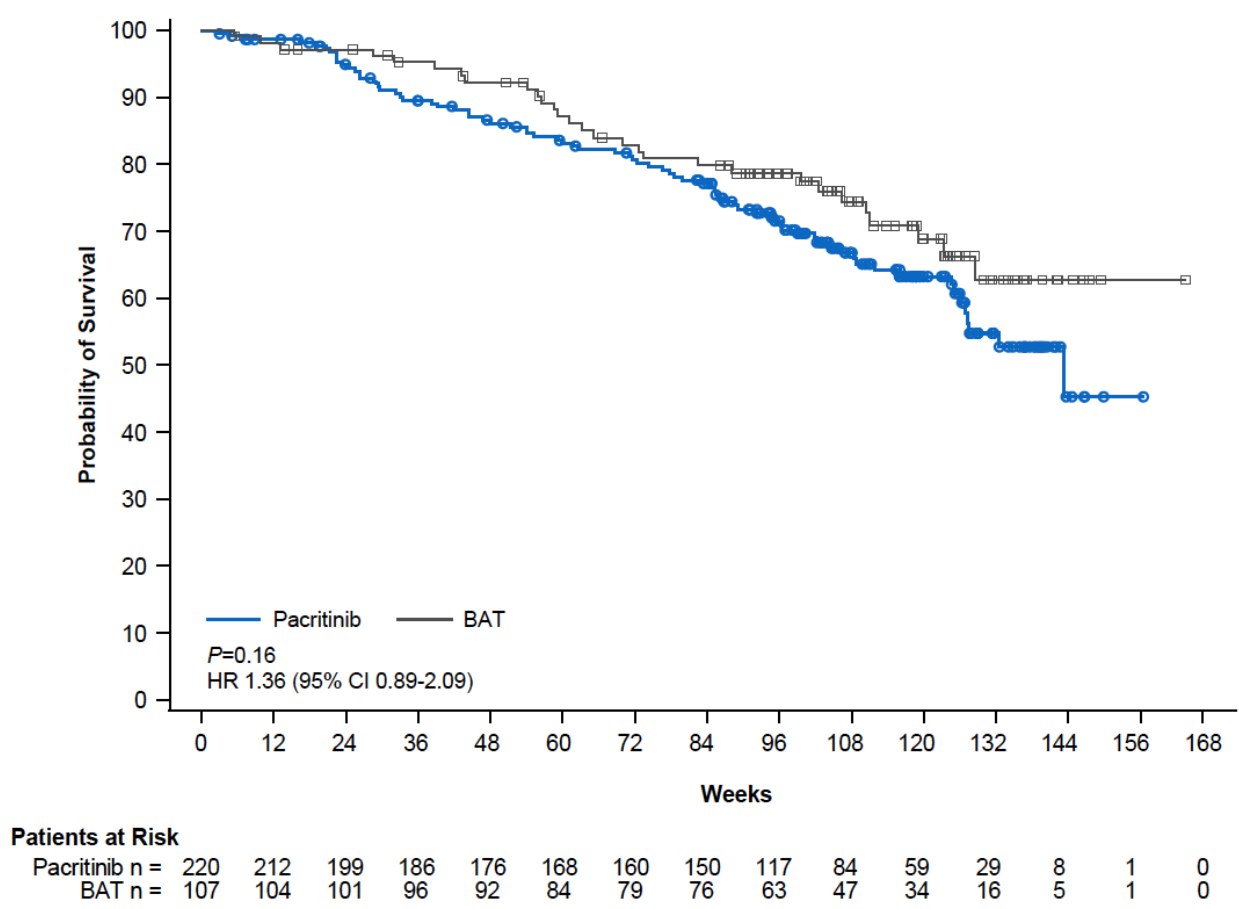


Figure 4. Overall Survival (Intention-to-Treat Population). Patients randomized to pacritinib or BAT treatment.



Supplementary Appendix

Investigator List

Study Site	Principal Investigator	Patients Randomized, n
First Republican Clinical Hospital of Ministry of Health of the Udmurt Republic	Alexander Suvorov	14
Kaposi Mor Okato Korhaz	Miklos Egyed	14
SZTE II. Sz Belgyogyoszlai Klinika es Kardiologiai Kozpont	Zita Borbenyi	14
Bekes Megyei Pandy Kalman Korhaz	Janos Jakucs	13
Haematology and Oncology Clinics of Australia	Andrew Perkins	12
Royal Hobart Hospital	Ritam Prasad	10
Semmelweis Egyetem AOK	Judit Demeter	10
Faculty Hospital Brno-Bohunice	Jiri Mayer	10
Andrew Love Cancer Centre	Philip Campbell	9
Canterbury District Health Board	Peter Ganly	8
CHU Caremeau Nimes	Eric Jourdan	7
CHU Purpan	Chrisitan Recher	7
Debreceni Egyetem Orvos-es Egesz Segtudomanyi Centrum Belgyogyaszati Intezet	Arpad Illes	7
Van Megyei Markusovszky Korhoz Nonprofit Zrt	Janos Laszlo Ivanyi	7
North Shore Hospital	Anna Elinder-Camburn	7
Republican Hospital n.a. V.A. Baranov	Aleksandr Myasnikov	7
University Hospital Maastricht	Harry Schouten	6
Erasmus MC	Peter te Boekhorst	6
University Medical Center Utrecht	Reinier Raymakers	6
Haematology Research Center	Elena Lukina	6
CHU Amiens Picardie	Jean Pierre Marolleau	6
Russian Research Institute of Haematology & Transfusiology	Kudrat Mugutdinovich Abdulkadyrov	6
Gosford Hospital	Campbell Tiley	6
Box Hill Hospital	Paul Coughlin	5
Hospital St. Louis	Jean-Jacques Kiladjian	5
Military Medical Academy n.a. S Kirov	Vadim Vitalievich Tyrenko	5
Volgograd Regional Clinical Oncology Dispensary #1	Kamil Kaplanov	5
Ospedale "Infermi", Rimini	Patrizia Tosi	5
The Christie NHS Foundation Trust	Tim Somerville	5
Cardiff University/Hospital of Wales	Steven Knapper	5
Guys and St Thomas – NHS Foundation Trust	Claire Harrison	5
Faculty Hospital Olomouc	Karel Indrak	5
Dunedin Hospital	Shingirai Chiruka	4
Saint-Petersburg State Medical University n.a. academician I.P. Pavlov	Boris Afanasyev	4
Samara Regional Clinical Hospital n.a. M.I.Kalinin	Victor Rossiev	4
Hammersmith Hosp – ICH NHS Trust	Dragana Milojkovic	4
Coffs Harbour Health Campus	Martin Browne	4
Dipartimento di Oncoematologia	Fabio Ciceri	4
University Hospital Pilsen	Pavel Jindra	3
Istituto di Ematologia L. & A. Seragnoli	Giovanni Martinelli	3
San Gerardo Hospital	Carlo-Gambacorti-Passerini	3
VU University Medical Center	Sonja Zweegman	3
Hematology-Oncology Associates of Northern Jersey	Charles Farber	3
ZNA – Stuivenberg	Pierre G G B J Zachee	3
Hospital Claude Huriez	Nathalie Cambier	3
Hopital Haut-Leveque	Axelle Lascaux	3
Jasz-Nagykun-Szolnok	Gyorgy Ujj	3
Oxford University Hospitals NHS Trust	Adam Mead	3
University of Florence, Hospital Careggi	Alessandro Vannucchi	3
CHU de Strasbourg	Shanti Natarajan-Ame	2
ZNA – Middelheim	Dr. De Bock	2
Centre Hospitalier de Jolimont-Lobbés	Nicole Straetmans	2
Upstate Oncology Associates	Fahd Quddus	2
Bács-Kiskun Megyei Kórház Szegedi Tudományegyetem	Mihaly Gurzo	2
Azienda Ospedaliera di Padova	Maria Randi	2
Addenbrookes Hospital	Anthony Green	2
Klinik I für Innere Medizin, Universität Köln	Christof Scheid	2
Municipal Health Care Institution Sochi Oncology Dispensary No2	Dmitriy Petrovich Udovitsa	2

AZ Sint Jan Brugge-Oostende AV	Jan van Droogenbroeck	1
Cliniques Universitaires Saint-Luc	Laurent Knoops	1
CHU de Caen	Khaled Benabed	1
Centre Hospitalier Lyon Sud	Fiorenza Barraco	1
S.C. Ematologia, A.O. Arcispedale Santa Maria Nuova-IRCCS	Alessia Tieghi	1
Birmingham Heartlands Hospital	Jo Ewing	1
Gemeinschaftspraxis Hämatologie/Onkologie	Thomas Illmer	1
University Hospital Leipzig	Dietget Niederwieser	1
Waikato Hospital	Shadul Islam	1
Mayo Clinic Arizona	Ruben A Mesa	0
Central Clinical Hospital #2 n.a. Semashko	Andrey Gubkin	0
University of Munster	Tim Sauer	0
Universitätsklinikum Essen	Juergen Novotny	0
University of Nebraska	Krishna Gundabolu	0
Städtisches Klinikum München GmbH	Meinolf Karthaus	0
Universitätsklinikum Mainz	Thomas Kindler	0
Campus Virchow, Charite, Humboldt University, Berlin	Phillipp Le Coutre	0
The Royal Bournemouth Hospital	Joseph Chacko	0
Uniklinik Freiburg	Nikolas von Bubnoff	0
Institute of Haematology and Blood Transfusion	Jiri Schwarz	0
Centre Hospitalo Universitaire de Grenoble	Jean-Yves Cahn	0
Centre Hospitalier de Lens	Brigitte Dupriez	0
Hopital St Antoine	Nicole Casadevall	0

Supplementary Table 1. Six Common Symptoms Across MPN-SAF TSS Versions.

TSS (Original Version)	TSS 2·0
Fatigue (weariness, tiredness)	Tiredness
Filling up quickly when you eat (early satiety)	Filling up quickly when you eat (early satiety)
Abdominal discomfort	Abdominal discomfort
Inactivity*	Inactivity*
Problems with concentration – compared to prior to my MPD	NA
Night sweats	Night sweats
Itching (pruritus)	Itching (pruritus)
Bone pain (diffuse not joint pain or arthritis)	Bone pain (diffuse not joint pain or arthritis)
Fever (>100° F)	NA
Unintentional weight loss last 6 months	NA
NA	Pain under ribs on the left side

*Inactivity is not counted in TSS.

MPD, myeloproliferative disorder; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; NA, not applicable; TSS, total symptom score.

Supplementary Table 2. Distribution of Risk Factors at Baseline by Randomized Treatment and Baseline White Blood Cell (WBC) Risk Group.

Other Risk Factors at Baseline, n (%)	WBC>25,000/μL		WBC≤25,000/μL	
	Pacritinib (n=43)	BAT (n=26)	Pacritinib (n=177)	BAT (n=80)
Peripheral blood blasts ≥1%	29 (67·4)	11 (42·3)	83 (46·9)	36 (45·0)
Platelet count <100,000/μL	18 (41·9)	6 (23·1)	54 (30·5)	27 (33·8)
Hemoglobin <10 g/dL	19 (44·2)	7 (26·9)	65 (36·7)	40 (50·0)
MF Fibrosis Grade >1	40 (93·0)	19 (73·1)	140 (79·1)	64 (80·0)
Age >65 years	30 (69·8)	12 (46·2)	96 (54·2)	37 (46·3)
Number of risk factors, n (%)				
6	8 (18·6)	0	0	0
5	8 (18·6)	5 (19·2)	9 (5·1)	3 (3·8)
4	14 (32·6)	5 (19·2)	32 (18·1)	18 (22·5)
3	9 (20·9)	5 (19·2)	38 (21·5)	15 (18·8)
2	4 (9·3)	7 (26·9)	49 (27·7)	25 (31·3)
1	0	1 (3·8)	24 (13·6)	11 (13·8)
0	0	0	9 (5·1)	4 (5·0)
Missing	0	3 (12)	16 (9·0)	4 (5·0)

BAT, best available therapy.

Supplementary Table 3. Most Common Treatments in the BAT Arm.

WHO Drug Term, n (%)	BAT (n=106)	BAT (n=106)	
Watchful waiting (no active treatment)	27 (25·5)		
Hydroxyurea	60 (56·6)	Anagrelide	1 (0·9)
Prednisone	7 (6·6)	Azacitidine	1 (0·9)
Interferon alfa	7 (6·6)	Epoetin alfa	1 (0·9)
Thalidomide	6 (5·7)	Epoetin theta	1 (0·9)
Danazol	4 (3·8)	Everolimus	1 (0·9)
Prednisolone	4 (3·8)	Lenalidomide	1 (0·9)
Busulfan	2 (1·9)	Mercaptopurine	1 (0·9)
Cytarabine	2 (1·9)	Methotrexate	1 (0·9)
Peginterferon alfa-2a	2 (1·9)	Vincristine	1 (0·9)

BAT, best available therapy.

Supplementary Table 4. Demographic and Disease Characteristics With Apparent Imbalances Across BAT Therapies

Characteristic, n (%)	Watch and Wait Only (n=27)	Hydroxyurea Only (n=40)	Other (n=40)
Age ≥65 years	11 (40.7)	17 (42.5)	27 (67.5)
Male sex	15 (55.6)	20 (50.0)	25 (62.5)
ECOG PS 2-3	4 (14.8)	1 (2.5)	6 (15.0)
Hypocellular (<20%) bone marrow	5 (18.5)	5 (12.5)	7 (17.5)
<i>JAK2</i> ^{V617F} -positive	23 (85.2)	38 (95.0)	31 (77.5)
Platelet count			
<50,000/μL	6 (22.2)	4 (10.0)	6 (15.0)
≥50,000 to <100,000/μL	8 (29.6)	2 (5.0)	8 (20.0)
Primary myelofibrosis	19 (70.4)	16 (40.0)	24 (60.0)
Anemia	21 (77.8)	19 (47.5)	30 (75.0)
Current DIPSS intermediate-2 or high	16 (59.3)	17 (42.5)	25 (62.5)
RBC-TD (Gale criteria)	6 (22.2)	3 (7.5)	6 (15.0)

BAT, best available therapy; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; RBC-TD, red blood cell transfusion-dependent.

Supplementary Table 5. Spleen Volume Reduction (SVR) at Week 24 by Treatment and Baseline *JAK2* Status

Treatment	Baseline <i>JAK2</i> Status	Percent SVR at Week 24				
		n	Mean (SD)	Median (IQR)	Min	Max
Pacritinib	<i>JAK2</i> ^{WT}	58	-24.3 (19.80)	-24.5 (-34.0, -13.0)	-76.0	38.0
	<i>JAK2</i> ^{V617F}	109	-23.4 (16.92)	-23.0 (-35.0, -14.0)	-67.0	39.0
BAT	<i>JAK2</i> ^{WT}	42	-5.9 (18.73)	-5.0 (-15.0, 7.0)	-51.0	47.0
	<i>JAK2</i> ^{V617F}	42	5.4 (15.13)	3.0 (-5.0, 17.0)	-27.0	41.0

BAT, best available therapy; WT, wild type.

Supplementary Table 6. Reductions in Allele Burden

Treatment	n	Mean	Std Dev	Median	Q1	Q3	Min	Max
Pacritinib	154	-34.4	39.87	-31.6	-57.5	-7.5	-100.0	101.3
BAT	89	-11.1	42.12	-10.4	-28.0	0.4	-100.0	200.0

BAT, best available therapy; Std Dev; standard deviation; Q, quartile.

Supplementary Table 7. Proportion of Patients Achieving ≥50% Reduction in TSS at Week 24 by TSS Version.

Patients Achieving ≥50% TSS Reduction, n/N (%) [95% CI]	TSS (Original Version)			TSS 2.0		
	Pacritinib	BAT	P value	Pacritinib	BAT	P value
All Patients	36/120 (30.0) [22.0-39.0]	3 (5.1) [1.1-14.1]	<0.0001	19/100 (19.0) [11.8-28.1]	5/48 (10.4) [3.5-22.7]	0.24
Platelets <100,000/μL	11/44 (25.0) [13.2-40.3]	2/21 (9.5) [1.2-30.4]	0.19	6/28 (21.4) [8.3-41.0]	1/13 (7.7) [0.2-36.0]	0.40
Platelets <50,000/μL	4/24 (16.7) [4.7-37.4]	1/11 (9.1) [0.2-41.3]	1.0	2/11 (18.2) [2.3-51.8]	0/5 (0.0) [0.0-52.2]	1.0
Platelets ≥100,000/μL	25/76 (32.9) [22.5-44.6]	1/38 (2.6) [0.1-13.8]	0.0001	13/72 (18.1) [1.00-28.9]	4/35 (11.4) [3.2-26.7]	0.57

BAT, best available therapy; TSS, total symptom score.

Supplementary Table 8. Summary of Patient Global Impression of Change by TSS Version in Evaluable Patients at Week 24.

Patient Global Impression of Change, n/N (%)	TSS (Original Version)		TSS 2·0	
	Pacritinib (n=76)	BAT (n=33)	Pacritinib (n=68)	BAT (n=35)
Very much improved	9 (11·8)	0	9 (13·2)	0
Much improved	32 (42·1)	4 (12·1)	22 (32·4)	2 (5·7)
Minimally improved	19 (25·0)	5 (15·2)	25 (36·8)	3 (8·6)
No change	10 (13·2)	16 (48·5)	7 (10·3)	24 (68·6)
Minimally worse	5 (6·6)	5 (15·2)	5 (7·4)	6 (17·1)
Much worse	1 (1·3)	3 (9·1)	0	0
Very much worse	0	0	0	0

BAT, best available therapy; TSS, total symptom score.

Supplementary Table 9. Mean Change From Baseline in Individual Symptom Scores.

Percentage change, mean* (IQR) [range]	Week 24			Week 48		
	Pacritinib (n=146)	BAT (n=73)	BAT Crossover [†] (n=56)	PAC (n=99)	BAT (n=6)	BAT Crossover [†] (n=22)
Worst fatigue/tiredness	-21 (-50, -3) [-100, 279]	+48 (-26, 32) [-100, 2850]	+5 (-17, 8) [-66, 233]	-25 (-61, -2) [-100, 144]	+5 (-33, 53) [-100, 112]	-15 (-29, 4) [-94, 31]
Early satiety	-35 (-73, -3) [-100, 148]	+4 (-27, 22) [-100, 313]	-16 (-46, 7) [-100, 76]	-42 (-99, -11) [-100, 200]	+86 (-21, 192) [-42, 312]	-35 (-74, -6) [-100, 55]
Abdominal discomfort	-26 (-83, -4) [-100, 600]	+82 (-32, 27) [-100, 3436]	+10 (-45, 6) [-98, 736]	-30 (-84, -26) [-100, 600]	+48 (-88, 62) [-98, 338]	-8 (-41, 2) [-97, 136]
Night sweats	-53 (-100, -35) [-100, 600]	+101 (-34, 47) [-100, 2025]	-25 (-82, 0) [-100, 185]	-55 (-100, -36) [-100, 133]	+96 (-71, 102) [-100, 536]	-27 (-66, 20) [-100, 100]
Pruritus	-33 (-89, 7) [-100, 470]	+39 (-49, 28) [-100, 1250]	+16 (-80, 12) [-100, 1369]	-52 (-100, -39) [-100, 250]	+198 (56, 315) [56, 315]	-18 (-84, 0) [-100, 104]
Bone pain	-24 (-97, 4) [-100, 509]	+4 (-36, 39) [-100, 242]	-14 (-28, 2) [-100, 70]	-14 (-100, -1) [-100, 653]	-65 (-97, -35) [-100, -4]	0 (-23, 46) [-100, 68]

*Green indicates improvement from baseline; red indicates worsening from baseline.

[†]From time of crossover.

BAT, best available therapy.

Supplementary Table 10. Correlation of Overall Survival with Spleen Volume Reduction at Week 24

	Pacritinib (n=220)		BAT (n=107)	
	n	HR (95% CI)	n	HR (95% CI)
SVR, %				
≥35	42	0·234 (0·113-0·485)	5	0·000 (0·000-NR)
20 to <35	60	0·246 (0·133-0·454)	6	1·851 (0·551-6·216)
≥10 to <20%	38	0·387 (0·207-0·726)	15	0·922 (0·317-2·676)
<10%	80	Reference	81	Reference

BAT, best available therapy; SVR, spleen volume reduction.

Supplementary Table 11. Deaths on Study.

Cause of Death	Events, n
Pacritinib arm	76
≤24 weeks	11
>24 weeks	65
Disease progression	28
Adverse event	28
Disease progression	6
Pneumonia	3
Cardiac failure acute	2
Acute myeloid leukemia	2
Pneumonia aspiration	1
Renal failure, acute	1
Multiorgan failure	1
Hemorrhage	1
Traumatic intracranial hemorrhage	1
Shock	1
Hypoxia	1
Cardiopulmonary arrest	1
Cardiac arrest	1
Sudden death	1
Head injury	1
Sepsis	1
Myocardial infarction	1
Hepatic failure	1
Cardiac failure congestive	1
Other	20
BAT arm	29
≤24 weeks	7
>24 weeks	22
Disease progression	8
Adverse event (during initial study phase)	3
Disease progression	1
Cardiac failure	1
Sepsis	1
Adverse event (after crossover)	11
Sudden death	2
Pneumonia	2
Status epilepticus	1
Disseminated intravascular coagulation	1
Splenic rupture	1
Disease progression	1
Hemorrhage intracranial	1
Acute leukemia	1
Metastatic squamous cell carcinoma	1
Other	7

Supplementary Table 12. Multivariate Cox Model of OS

Covariates in the final model	HR (95% CI)
Baseline platelet count (per 100 unit of 10 ⁹ /L)	0.785 (0.685-0.899)
Baseline hemoglobin (per 10 unit g/L)	0.827 (0.752-0.910)
Baseline WBC (per 10 unit of 10 ⁹ /L)	1.229 (1.132 -1.334)
Age (per 10 years)	1.463 (1.161-1.843)

All variables assessed: DIPSS risk, platelet count, hemoglobin, white blood cells (WBCs), RBC-transfusion dependency, primary vs secondary myelofibrosis, JAK2 mutation status, time from diagnosis, myelofibrosis fibrosis grade, ECOG PS, age.

Supplementary Table 13. Hematologic Toxicities at Baseline and Worst Grade, Through Week 24 or Initial Treatment Discontinuation

	Pacritinib (n=220)					BAT (n=106)				
	Baseline grade					Baseline grade				
	0	1	2	3	4	0	1	2	3	4
Hemoglobin, n (%)*	n=62	n=74	n=71	n=13	n=0	n=33	n=26	n=30	n=16	n=0
Grade 0	36 (58.1)	6 (8.1)	1 (1.4)	1 (7.7)	0	19 (57.6)	2 (7.7)	1 (3.3)	1 (6.3)	0
Grade 1	13 (21.0)	27 (36.5)	13 (18.3)	2 (15.4)	0	4 (12.1)	11 (42.3)	4 (13.3)	1 (6.3)	0
Grade 2	0	22 (29.7)	27 (38.0)	1 (7.7)	0	1 (3.0)	1 (3.8)	7 (23.3)	2 (12.5)	0
Grade 3	0	1 (1.4)	9 (12.7)	2 (15.4)	0	0	1 (3.8)	2 (6.7)	6 (37.5)	0
Grade 4	0	0	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0	0	0
Platelet count, n (%)*	n=119	n=39	n=16	n=21	n=13	n=59	n=19	n=5	n=6	n=10
Grade 0	69 (58.0)	7 (17.9)	1 (6.3)	0	0	27 (45.8)	2 (10.5)	0	0	0
Grade 1	15 (12.6)	10 (25.6)	1 (6.3)	2 (9.5)	0	2 (3.4)	6 (31.6)	0	0	0
Grade 2	2 (1.7)	6 (15.4)	0	2 (9.5)	0	1 (1.7)	2 (10.5)	0	0	1 (10.0)
Grade 3	1 (0.8)	3 (7.7)	4 (25.0)	7 (33.3)	2 (15.4)	0	2 (10.5)	3 (60.0)	1 (16.7)	1 (10.0)
Grade 4	1 (0.8)	0	0	2 (9.5)	4 (30.8)	0	0	0	0	5 (50.0)
Grade 5	0	0	0	0	0	0	0	0	0	0

*Green indicates ≥ 1 grade improvement from baseline; red indicates a ≥ 1 grade worsening from baseline.

BAT, best available therapy.

Supplementary Table 14. Most Common Adverse Events and Hematologic Toxicities With Pacritinib at Any Time on Study

All grade in >10% or grade 3 in >2% of Patients, n (%)	Pacritinib (n=220)				
	Grade 1/2	Grade 3	Grade 4	Grade 5	All
Diarrhea	127 (57.7)	16 (7.3)	0	0	143 (65.0)
Nausea	67 (30.5)	3 (1.4)	0	0	70 (31.8)
Anemia	10 (4.5)	48 (21.8)	9 (4.1)	0	67 (30.5)
Thrombocytopenia	14 (6.4)	16 (7.3)	21 (9.5)	0	51 (23.2)
Vomiting	41 (18.6)	6 (2.7)	0	0	47 (21.4)
Fatigue	28 (12.7)	5 (2.3)	0	0	33 (15.0)
Abdominal pain	24 (10.5)	6 (2.7)	0	0	30 (13.6)
Peripheral edema	24 (10.9)	1 (0.5)	0	0	25 (11.4)
Pneumonia	8 (3.6)	12 (5.5)	2 (0.9)	3 (1.4)	25 (11.4)
Pyrexia	14 (6.4)	5 (2.3)	0	0	19 (8.6)
Hypertension	5 (2.3)	6 (2.7)	0	0	11 (5.0)
Leukopenia	2 (0.9)	5 (2.3)	2 (0.9)	0	9 (4.1)
Cardiac failure	3 (1.4)	6 (2.7)	0	0	9 (4.1)
Febrile neutropenia	0	5 (2.3)	0	0	5 (2.3)
Hematologic Toxicity Worst					
Baseline grade					
Grade, n (%)*	0	1	2	3	4
Hemoglobin	n=62	n=74	n=71	n=13	n=0
Grade 0	33 (53.2)	1 (1.4)	0	0	0
Grade 1	21 (33.9)	22 (29.7)	3 (4.2)	0	0
Grade 2	8 (12.9)	36 (48.6)	26 (36.6)	1 (7.7)	0
Grade 3	0	15 (20.3)	40 (56.3)	12 (92.3)	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Platelet count	n=119	n=39	n=16	n=21	n=13
Grade 0	69 (58.0)	4 (10.3)	0	0	0
Grade 1	34 (28.6)	10 (25.6)	0	0	0
Grade 2	9 (7.6)	14 (35.9)	6 (37.5)	1 (4.8)	0
Grade 3	3 (2.5)	10 (25.6)	7 (43.8)	8 (38.1)	0
Grade 4	2 (1.7)	1 (2.6)	3 (18.8)	12 (57.1)	12 (92.3)
Grade 5	0	0	0	0	0

*Green indicates ≥ 1 grade improvement from baseline; red indicates a ≥ 1 grade worsening from baseline.

AE, adverse event; BAT, best available therapy.

Additional grade 4 or 5 adverse events with pacritinib: neutropenia (6 gr 4), bone marrow failure (1 gr 4), thrombocytosis (1 gr 4), cardiac failure congestive (1 gr 4, 1 gr 5), pericardial effusion (1 gr 4), gastric varices hemorrhage (1 gr 4), gastrointestinal hemorrhage (1 gr 4), esophageal hemorrhage (1 gr 4), disease progression (2 gr 4, 5 gr 5), portal hypertension (1 gr 4), anaphylactoid reaction (1 gr 4), lobar pneumonia (1 gr 4), sepsis (2 gr 4, 1 gr 5), septic shock (1 gr 4), delayed hemolytic transfusion reaction (1 gr 4), subdural hematoma (1 gr 4), platelet count decreased (4 gr 4), neutrophil count decreased (1 gr 4), blood glucose decreased (1 gr 4), hyperuricemia (3 gr 4), hypercalcemia (1 gr 4), hyperkalemia (1 gr 4), hypomagnesemia (1 gr 4), syncope (1 gr 4), cerebral hemorrhage (1 gr 4), coma (1 gr 4), diabetic neuropathy (1 gr 4), renal failure acute (1 gr 4, 1 gr 5), acute respiratory distress syndrome (1 gr 4), pharyngeal hemorrhage (1 gr 4), hypertensive crisis (2 gr 4), shock hemorrhagic (1 gr 4).

Supplementary Table 15. Most Common Serious Adverse Events, Through Week 24 or Initial Treatment Discontinuation

Serious adverse events in >1 patient in either arm, n (%)	Pacritinib (n=220)	BAT (n=106)
Anemia	10 (4.5)	5 (4.7)
Cardiac failure	5 (2.3)	1 (0.9)
Pyrexia	4 (1.8)	1 (0.9)
Pneumonia	4 (1.8)	1 (0.5)
Atrial fibrillation	3 (1.4)	0
Cardiac failure congestive	3 (1.4)	0
Diarrhea	3 (1.4)	0
Lobar pneumonia	2 (0.9)	0
Basal cell carcinoma	2 (0.9)	0
Squamous cell carcinoma of skin	2 (0.9)	0
Renal failure acute	2 (0.9)	0
Pleural effusion	2 (0.9)	1 (0.9)
Epistaxis	2 (0.9)	0
Sepsis	1 (0.5)	2 (1.9)
Dyspnea	1 (0.5)	2 (1.9)

BAT, best available therapy.

Supplementary Table 16. Incidence of Diarrhea Over Time (All Grades)

Time Interval	Pacritinib (n=220), n/n at risk (%)	BAT Initial Treatment (n=106), n/n at risk (%)	BAT Crossover (n=90), n/n at risk (%) ^a
Week 1 – Week 8	113/220 (51.4)	6/106 (5.7)	42/90 (46.7)
Week 8 – Week 16	26/210 (12.4)	4/103 (3.9)	13/83 (15.7)
Week 16 – Week 24	17/195 (8.7)	5/100 (5.0)	7/75 (9.3)
Week 24 – Week 32	11/177 (6.2)	1/89 (1.1)	1/72 (1.4)
Week 32 – Week 40	12/157 (7.6)	1/33 (3.0)	3/65 (4.6)
Week 40 – Week 48	4/140 (2.9)	1/13 (7.7)	2/61 (3.3)
Week 48 – Week 56	5/131 (3.8)	1/7 (14.3)	1/55 (1.8)
Week 56 – Week 64	4/121 (3.3)	1/6 (16.7)	3/48 (6.3)
Week 64 – Week 72	8/114 (7.0)	1/6 (16.7)	0/38
Week 72 – Week 80	7/109 (6.4)	0/5	1/32 (3.1)
Week 80 – Week 88	4/103 (3.9)	0/5	0/19
Week 88 – Week 96	2/93 (2.2)	0/5	0/13
Week 96 – Week 104	3/73 (4.1)	1/4 (25.0)	0/7
Week 104 – Week 112	1/60 (1.7)	0/3	1/5 (20.0)
Week 112 – Week 120	1/49 (2.0)	1/3 (33.3)	0/2
Week 120 – Week 128	1/41 (2.4)	0/3	0/1
Week 128 – Week 136	1/24 (4.2)	0/1	0
Week 136 – Week 144	0/13	0/1	0
Week 144 – Week 152	0/6	0	0
Week 152 – Week 160	0/1	0	0
Week 160 – Week 168	0	0	0

^a From the time of crossover.
BAT, best available therapy.

Supplementary Table 17. Adverse Events Through Week 24 or Initial Treatment Discontinuation in Patients With Baseline Platelet Count <50,000/ μ L vs Overall

Pacritinib-treated patients, n (%)	<50,000/ μ L (n=35)	Overall (n=220)
All grade AEs	33 (94.3)	192 (87.3)
Grade 3/4 AEs	24 (68.6)	107 (48.6)
Serious AEs	14 (40.0)	65 (29.5)
AEs leading to drug interruption	13 (37.1)	48 (21.8)
AEs leading to dose reduction	4 (11.4)	22 (10.0)
AEs leading to discontinuation	5 (14.3)	22 (10.0)
AEs leading to death	3 (8.6)	8 (3.6)
BAT-treated patients, n (%)	<50,000/ μ L (n=15)	Overall (n=106)
All grade AEs	11 (73.3)	79 (74.5)
Grade 3/4 AEs	6 (40.0)	42 (39.6)
Serious AEs	3 (20.0)	23 (21.7)
AEs leading to drug interruption	0	5 (4.7)
AEs leading to dose reduction	0	9 (8.5)
AEs leading to discontinuation	0	3 (2.8)
AEs leading to death	1 (6.7)	3 (2.8)

Note: additional data for additional platelet subgroups (as shown below in Supplementary Table 18) are not available here as week 24 was not the primary analysis point for safety. AE, adverse event.

Supplementary Table 18. Adverse Events at Any Time on Study in Pacritinib-Treated Patients by Baseline Platelet Count Subgroups and Overall

Pacritinib-treated patients, n (%)	Platelets <50,000/ μ L (n=35)	Platelets <100,000/ μ L (n=72)	Platelets \geq 100,000/ μ L (n=148)	Overall (n=220)
All grade AEs	34 (97.1)	69 (95.8)	138 (93.8)	207 (94.1)
Grade 3/4 AEs	29 (82.9)	61 (84.7)	96 (64.9)	157 (71.4)
Serious AEs	20 (57.1)	43 (59.7)	77 (52.0)	120 (54.5)
AEs leading to drug interruption	17 (48.6)	31 (43.1)	47 (31.8)	78 (35.5)
AEs leading to dose reduction	6 (17.1)	12 (16.7)	21 (14.2)	33 (15.0)
AEs leading to discontinuation	14 (40.0)	25 (34.7)	25 (16.9)	50 (22.7)
AEs leading to death	9 (25.7)	14 (19.4)	13 (8.8)	27 (12.3)

AE, adverse events.

Supplementary Table 19. Bleeding Events By SMQ Through Week 24

Bleeding events, n (%)	Pacritinib (n=220)		BAT (n=106)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Epistaxis	10 (4.5)	2 (0.9)	9 (8.5)	1 (0.9)
Contusion	7 (3.2)	0	5 (4.7)	0
Hematoma	7 (3.2)	1 (0.5)	4 (3.8)	0
Hematuria	3 (1.4)	1 (0.5)	0	0
Purpura	3 (1.4)	0	0	0
Gingival bleeding	3 (1.4)	0	2 (1.9)	0
Conjunctival hemorrhage	2 (0.9)	0	0	0
Post procedural hemorrhage	2 (0.9)	1 (0.5)	0	0
Spontaneous hematoma	1 (0.5)	1 (0.5)	0	0
Hemoglobin decreased	1 (0.5)	1 (0.5)	0	0
Cerebral hemorrhage	1 (0.5)	1 (0.5)	0	0
Vitreous hemorrhage	1 (0.5)	0	1 (0.9)	0
Eye hemorrhage	1 (0.5)	0	1 (0.9)	0
Hemorrhoidal hemorrhage	1 (0.5)	0	0	0
Vessel puncture site bruise	1 (0.5)	0	0	0
Ear hemorrhage	1 (0.5)	0	0	0
Traumatic hematoma	1 (0.5)	0	1 (0.9)	0
Subdural hematoma	1 (0.5)	0	0	0
Traumatic intracranial hemorrhage	1 (0.5)	0	0	0
International normalized ratio increased	1 (0.5)	0	0	0
Petechia	1 (0.5)	0	1 (0.9)	0
Skin hemorrhage	1 (0.5)	0	0	0
Bleeding varicose vein	1 (0.5)	0	0	0
Melena	0	0	1 (0.9)	0
Rectal hemorrhage	0	0	1 (0.9)	0
Anal hemorrhage	0	0	1 (0.9)	1 (0.9)
Periorbital hematoma	0	0	1 (0.9)	0
Subarachnoid hemorrhage	0	0	1 (0.9)	0
Hemarthrosis	0	0	1 (0.9)	0
Hemothorax	0	0	1 (0.9)	1 (0.9)
Hemorrhage subcutaneous	0	0	1 (0.9)	0

BAT, best available therapy.

Supplementary Table 20. Incidence of Bleeding Events By SMQ Over Time (Grade 3/4)

Time Interval	Pacritinib (n=220), n/n at risk (%)	BAT Initial Treatment (n=106), n/n at risk (%)	BAT Crossover (n=90), n/n at risk (%) ^a
Week 1 – Week 8	2/220 (0.9)	1/106 (0.9)	3/90 (3.3)
Week 8 – Week 16	3/210 (1.4)	1/103 (1.0)	2/83 (2.4)
Week 16 – Week 24	3/195 (1.5)	0/100	0/75
Week 24 – Week 32	2/177 (1.1)	0/89	0/72
Week 32 – Week 40	2/157 (1.3)	1/33 (3.0)	2/65 (3.1)
Week 40 – Week 48	1/140 (0.7)	0/13	1/61 (1.6)
Week 48 – Week 56	2/131 (1.5)	0/7	0/55
Week 56 – Week 64	0/121	0/6	0/48
Week 64 – Week 72	1/114 (0.9)	0/6	0/38
Week 72 – Week 80	1/109 (0.9)	0/5	1/32 (3.1)
Week 80 – Week 88	0/103	0/5	0/19
Week 88 – Week 96	1/93 (1.1)	0/5	0/13
Week 96 – Week 104	0/73	0/4	0/7
Week 104 – Week 112	0/60	0/3	0/5
Week 112 – Week 120	0/49	0/3	0/2
Week 120 – Week 128	0/41	0/3	0/1
Week 128 – Week 136	0/24	0/1	0
Week 136 – Week 144	0/13	0/1	0
Week 144 – Week 152	0/6	0	0
Week 152 – Week 160	0/1	0	0
Week 160 – Week 168	0	0	0

^a From the time of crossover.
BAT, best available therapy.

Supplementary Table 21. Bleeding Events By SMQ With Pacritinib at Any Time on Study

Bleeding events, n (%)	Pacritinib (n=220)	
	All Grade	Grade 3/4
Epistaxis	19 (8.6)	4 (1.8)
Contusion	11 (5.0)	0
Hematoma	9 (4.1)	2 (0.9)
Hematuria	6 (2.7)	1 (0.5)
Gingival bleeding	5 (2.3)	0
Post procedural hemorrhage	4 (1.8)	2 (0.9)
Petechia	3 (1.4)	0
Purpura	3 (1.4)	0
Gastrointestinal hemorrhage	2 (0.9)	1 (0.5)
Subdural hematoma	2 (0.9)	1 (0.5)
Hemarthrosis	2 (0.5)	1 (0.5)
Hemoglobin decreased	2 (0.9)	1 (0.5)
Conjunctival hemorrhage	2 (0.9)	0
International normalized ratio increased	2 (0.9)	0
Spontaneous hematoma	1 (0.5)	1 (0.5)
Melena	1 (0.5)	1 (0.5)
Abdominal wall hematoma	1 (0.5)	1 (0.5)
Esophageal hemorrhage	1 (0.5)	1 (0.5)
Cerebral hemorrhage	1 (0.5)	1 (0.5)
Pharyngeal hemorrhage	1 (0.5)	1 (0.5)
Shock hemorrhagic	1 (0.5)	1 (0.5)
Ear hemorrhage	1 (0.5)	0
Vitreous hemorrhage	1 (0.5)	0
Eye hemorrhage	1 (0.5)	0
Eyelid bleeding	1 (0.5)	0
Gastric varices hemorrhage	1 (0.5)	0
Hemorrhoidal hemorrhage	1 (0.5)	0
Mouth hemorrhage	1 (0.5)	0
Vessel puncture site bruise	1 (0.5)	0
Traumatic hematoma	1 (0.5)	0
Pulmonary contusion	1 (0.5)	0
Traumatic intracranial hemorrhage	1 (0.5)	0
Hemorrhage intracranial	1 (0.5)	0
Hemoptysis	1 (0.5)	0
Ecchymosis	1 (0.5)	0
Nail bed bleeding	1 (0.5)	0
Skin hemorrhage	1 (0.5)	0
Bleeding varicose vein	1 (0.5)	0
Hemorrhage	1 (0.5)	0

Supplementary Table 22. Cardiac Events By SMQ Through Week 24

Cardiac events, n (%)	Pacritinib (n=220)		BAT (n=106)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Edema peripheral	18 (8.2)	1 (0.5)	13 (12.3)	1 (0.9)
Electrocardiogram QT prolonged	12 (5.5)	3 (1.4)	1 (0.9)	0
Cardiac failure	6 (2.7)	5 (2.3)	2 (1.9)	2 (1.9)
Atrial fibrillation	4 (1.8)	3 (1.4)	1 (0.9)	0
Cardiac failure congestive	3 (1.4)	3 (1.4)	0	0
Pulmonary edema	2 (0.9)	1 (0.9)	0	0
Syncope	1 (0.5)	1 (0.5)	2 (1.9)	2 (1.9)
Angina pectoris	1 (0.5)	1 (0.5)	1 (0.9)	0
Cardiac fibrillation	1 (0.5)	1 (0.5)	0	0
Sinus tachycardia	1 (0.5)	1 (0.5)	0	0
Portal vein thrombosis	1 (0.5)	1 (0.5)	0	0
Cerebrovascular accident	1 (0.5)	1 (0.5)	0	0
Arrhythmia	1 (0.5)	0	0	0
Atrial flutter	1 (0.5)	0	0	0
Cardio-respiratory arrest	1 (0.5)	0	0	0
Left ventricular dysfunction	1 (0.5)	0	0	0
Palpitations	1 (0.5)	0	0	0
Heart rate increased	1 (0.5)	0	0	0
Coronary artery disease	0	0	1 (0.9)	1 (0.9)
Splenic infarction	0	0	1 (0.9)	1 (0.9)
Angina unstable	0	0	1 (0.9)	1 (0.9)
Pulmonary embolism	0	0	1 (0.9)	1 (0.9)
Sick sinus syndrome	0	0	1 (0.9)	0
Bundle branch block left	0	0	1 (0.9)	0
Tachycardia	0	0	1 (0.9)	0
Transient ischemic attack	0	0	1 (0.9)	0
Arterial thrombosis	0	0	1 (0.9)	0

BAT, best available therapy.

Supplementary Table 23. Incidence of Cardiac Events By SMQ Over Time (Grade 3/4)

Time Interval	Pacritinib (n=220), n/n at risk (%)	BAT Initial Treatment (n=106), n/n at risk (%)	BAT Crossover (n=90), n/n at risk (%)
Week 1 – Week 8	8/220 (3.6)	2/106 (1.9)	1/90 (1.1)
Week 8 – Week 16	7/210 (3.3)	4/103 (3.9)	0/83
Week 16 – Week 24	6/195 (3.1)	0/100	3/75 (4.0)
Week 24 – Week 32	1/177 (0.6)	0/89	1/72 (1.4)
Week 32 – Week 40	2/157 (1.3)	0/33	0/65
Week 40 – Week 48	1/140 (0.7)	0/13	2/61 (3.3)
Week 48 – Week 56	2/131 (1.5)	0/7	1/55 (1.8)
Week 56 – Week 64	0/121	0/6	0/48
Week 64 – Week 72	0/114	0/6	1/38 (2.6)
Week 72 – Week 80	0/109	0/5	0/32
Week 80 – Week 88	1/103 (1.0)	0/5	0/19
Week 88 – Week 96	1/93 (1.1)	0/5	0/13
Week 96 – Week 104	1/73 (1.4)	0/4	0/7
Week 104 – Week 112	0/60	0/3	0/5
Week 112 – Week 120	0/49	0/3	0/2
Week 120 – Week 128	1/41 (2.4)	0/3	0/1
Week 128 – Week 136	0/24	0/1	0
Week 136 – Week 144	0/13	0/1	0
Week 144 – Week 152	0/6	0	0
Week 152 – Week 160	0/1	0	0
Week 160 – Week 168	0	0	0

^aFrom the time of crossover; BAT, best available therapy.

Supplementary Table 24. Cardiac Events By SMQ With Pacritinib at Any Time on Study

Cardiac events, n (%)	Pacritinib (n=220)	
	All Grade	Grade 3/4
Edema peripheral	25 (11·4)	1 (0·5)
Electrocardiogram QT prolonged	12 (5·5)	3 (1·4)
Cardiac failure	9 (4·1)	6 (2·7)
Atrial fibrillation	8 (3·6)	4 (1·8)
Cardiac failure congestive	4 (1·8)	4 (1·8)
Pulmonary edema	3 (1·4)	2 (0·9)
Syncope	2 (0·9)	2 (0·9)
Cardiac failure acute	2 (0·9)	0
Angina pectoris	1 (0·5)	1 (0·5)
Acute myocardial infarction	1 (0·5)	1 (0·5)
Cardiac fibrillation	1 (0·5)	1 (0·5)
Right ventricular failure	1 (0·5)	1 (0·5)
Sinus tachycardia	1 (0·5)	1 (0·5)
Portal vein thrombosis	1 (0·5)	1 (0·5)
Ejection fraction decreased	1 (0·5)	1 (0·5)
Cerebrovascular accident	1 (0·5)	1 (0·5)
Deep vein thrombosis	1 (0·5)	1 (0·5)
Supraventricular tachycardia	1 (0·5)	0
Tachycardia	1 (0·5)	0
Arrhythmia	1 (0·5)	0
Atrial flutter	1 (0·5)	0
Cardiac arrest	1 (0·5)	0
Cardio-respiratory arrest	1 (0·5)	0
Left ventricular dysfunction	1 (0·5)	0
Myocardial infarction	1 (0·5)	0
Myocardial ischemia	1 (0·5)	0
Palpitations	1 (0·5)	0
Sudden death	1 (0·5)	0
Heart rate increased	1 (0·5)	0

BAT, best available therapy.

Supplementary Table 25. Changes in Leukocyte and Neutrophil Counts From Baseline to Week 24.

Parameter	Pacritinib (n=220)		BAT (n=106)	
	Baseline	Week 24	Baseline	Week 24
Median leukocytes, $\times 10^9/L$ (range)	n=220	n=160	n=105	n=64
	9·9	8·1	11·7	10·1
	(1·2-169·6)	(1·1-249·3)	(1·9-85·0)	(2·0-44·4)
Median neutrophils, $\times 10^9/L$ (range)	n=201	n=129	n=99	n=54
	7·2	5·6	8·3	6·1
	(0·2-84·8)	(0·2-65·9)	(1·3-52·7)	(1·2-39·2)

BAT, best available therapy.

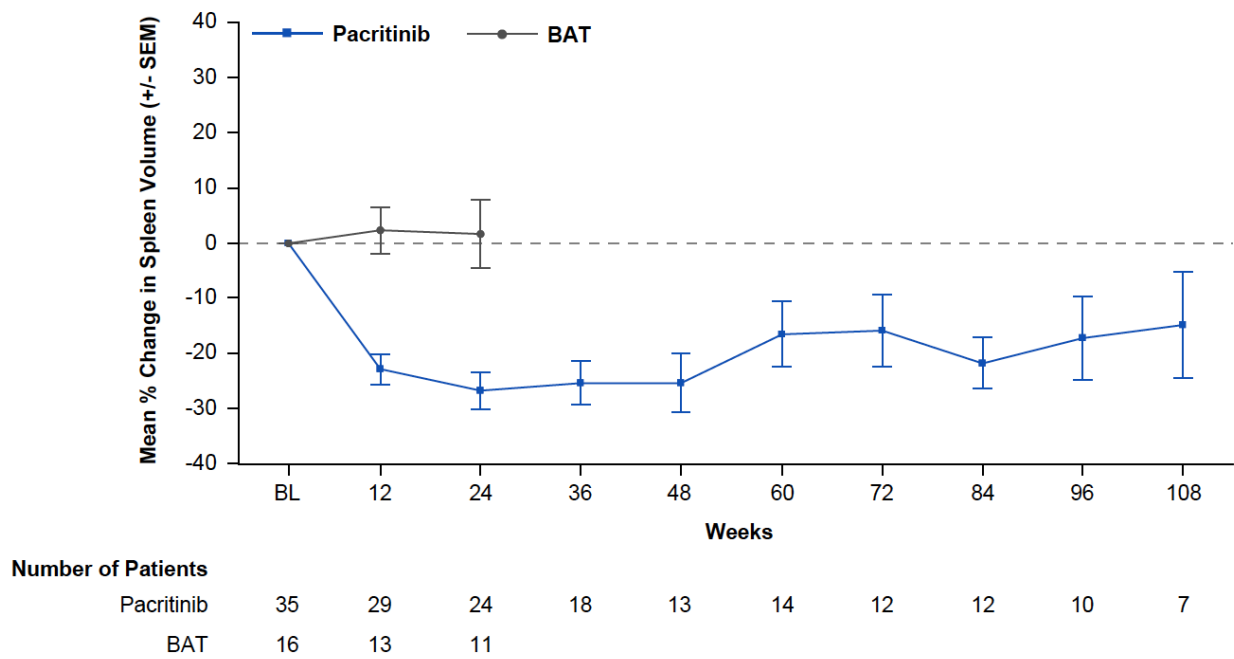
Supplementary Table 26. Discontinuations Due to Adverse Events Through Week 24.

Adverse Event, n (%)	Pacritinib (n=220)	BAT (n=106)
Patients with ≥ 1 AE leading to study drug discontinuation	22 (10.0)	3 (2.8)
Diarrhea	3 (1.4)	0
Thrombocytopenia	2 (0.9)	0
Anemia	1 (0.5)	0
Abdominal pain	1 (0.5)	0
Diverticular perforation	1 (0.5)	0
Splenomegaly	1 (0.5)	0
Thrombocytosis	1 (0.5)	0
Platelet count decreased	1 (0.5)	0
Cardiac failure	1 (0.5)	0
Cardiac failure, congestive	1 (0.5)	0
Portal vein thrombosis	1 (0.5)	0
Peritonitis	1 (0.5)	0
Pneumonia	1 (0.5)	0
Traumatic intracranial hemorrhage	1 (0.5)	0
Hyponatremia	1 (0.5)	0
Bone pain	1 (0.5)	0
Non-small cell lung cancer	1 (0.5)	0
Cerebral hemorrhage	1 (0.5)	0
Cerebrovascular accident	1 (0.5)	0
Coma	1 (0.5)	0
Parkinson's disease	1 (0.5)	0
Azotemia	1 (0.5)	0
Hematuria	1 (0.5)	0
Ocular rosacea	0	1 (0.9)
Septic shock	0	1 (0.9)
Parasthesia	0	1 (0.9)
Renal failure	0	1 (0.9)
Acute respiratory distress syndrome	0	1 (0.9)

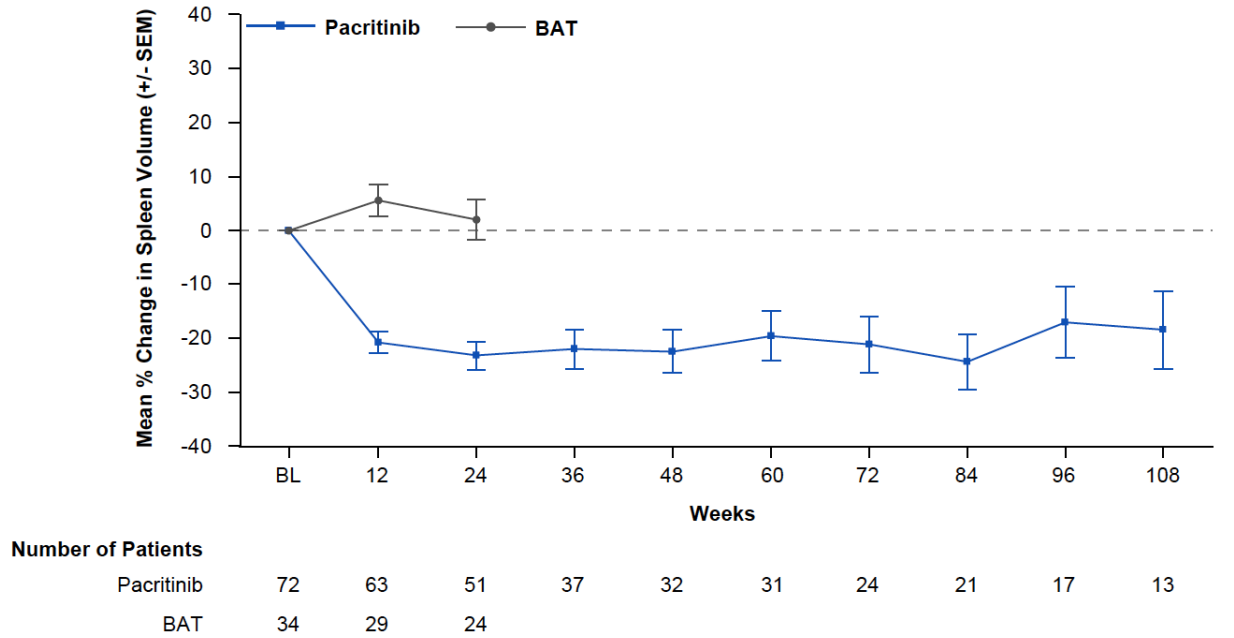
AE, adverse event; BAT, best available therapy.

Supplementary Figure 1. Mean percentage change in spleen volume over time for evaluable patients.
(A) patients with baseline platelet count <50,000/ μ L, (B) patients with baseline platelet count <100,000/ μ L

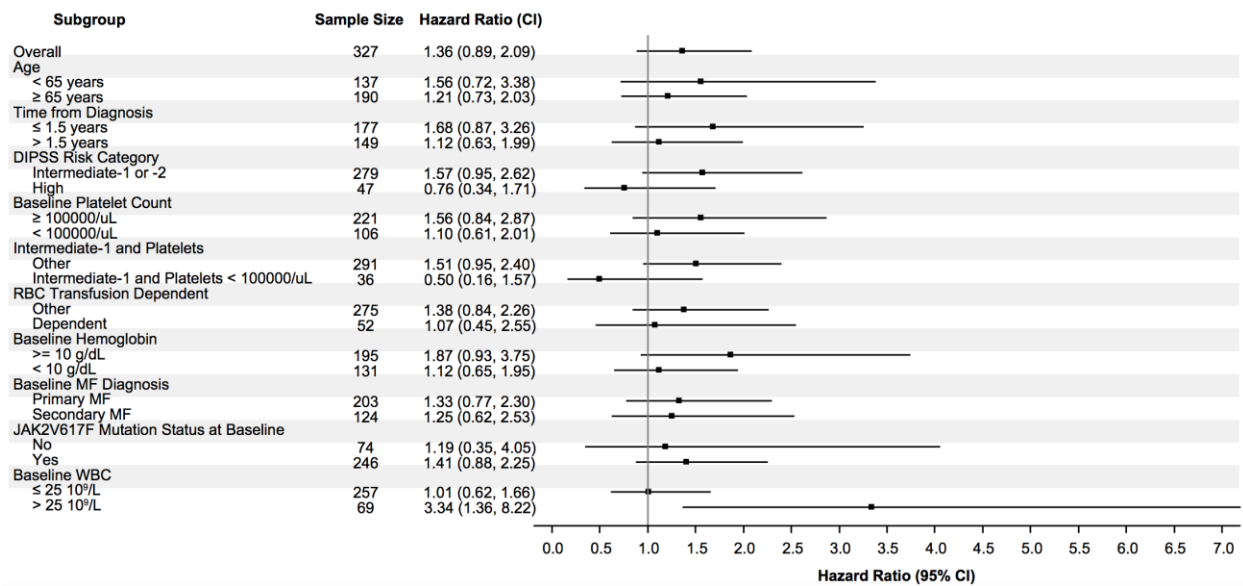
A



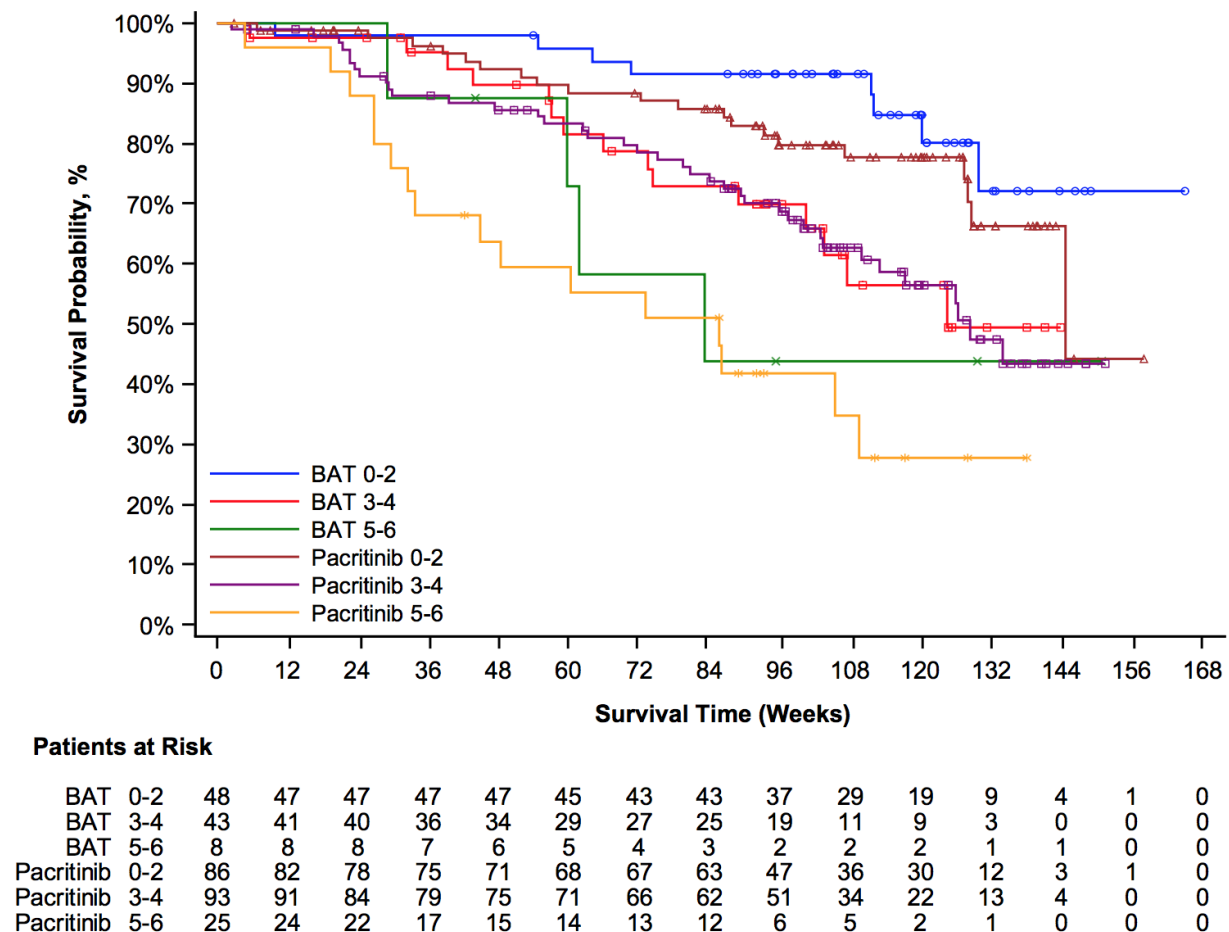
B



Supplementary Figure 2. Forest Plot of Hazard Ratio for OS Estimates by Subgroup.

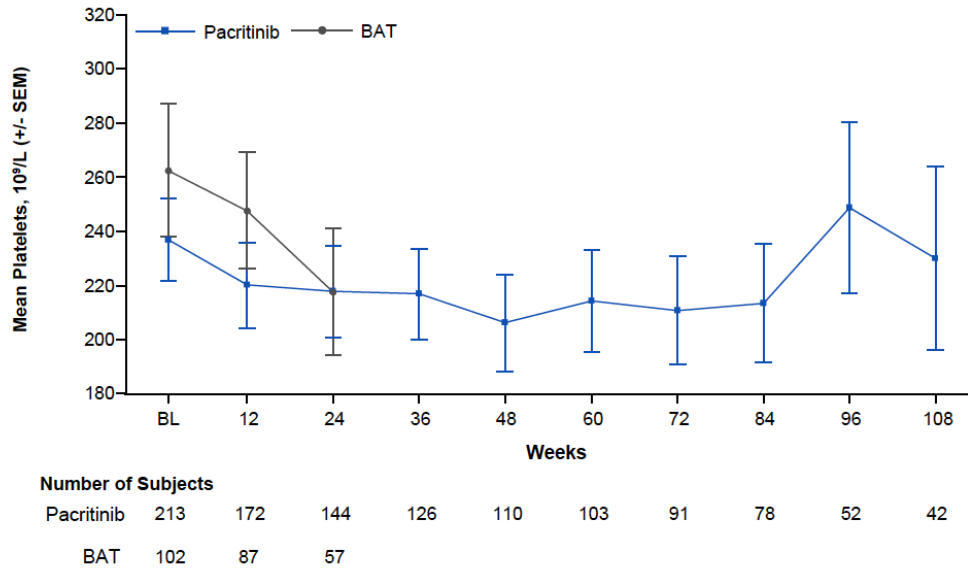


Supplementary Figure 3. OS by Number of Risk Factors in Patients Randomized to Pacritinib (PAC) or BAT.

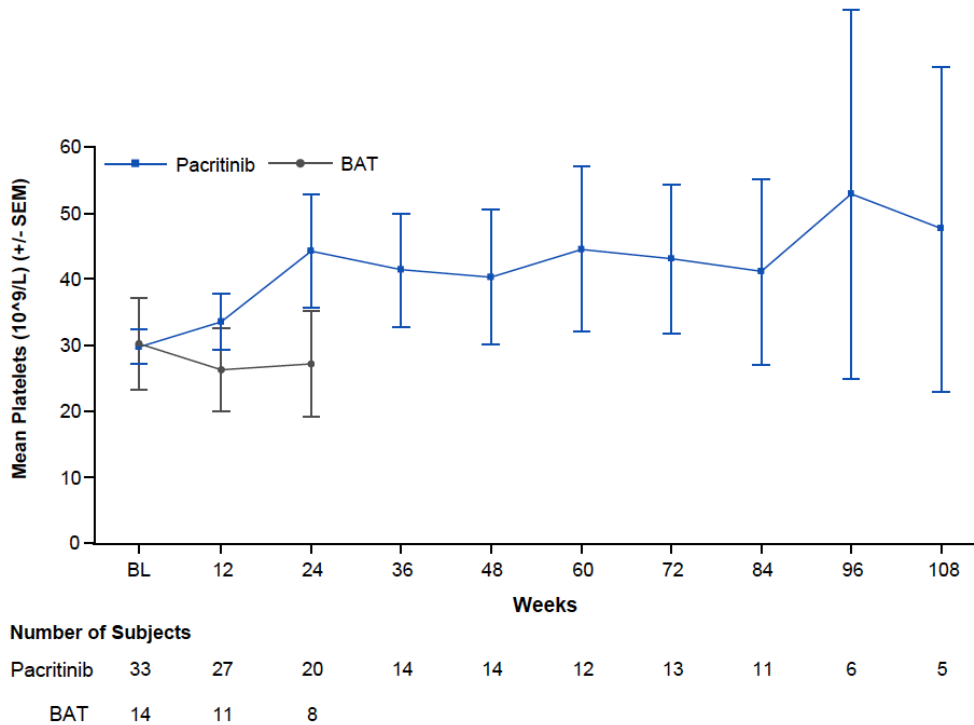


Supplementary Figure 4. Changes in Platelet Counts and Hemoglobin Levels During Treatment. Mean platelet counts over time (\pm SEM) from baseline in (A) all patients and (B) patients with baseline platelets $<50,000/\mu\text{L}$. (C) Mean percentage change in platelets (\pm SEM) in patients with baseline platelets $<50,000/\mu\text{L}$. (D) Mean hemoglobin levels (\pm SEM) from baseline in pacritinib- and BAT-treated patients. (E) Mean hemoglobin levels (\pm SEM) in patients with baseline hemoglobin <10 g/dL, including patients who received red blood cell transfusions.

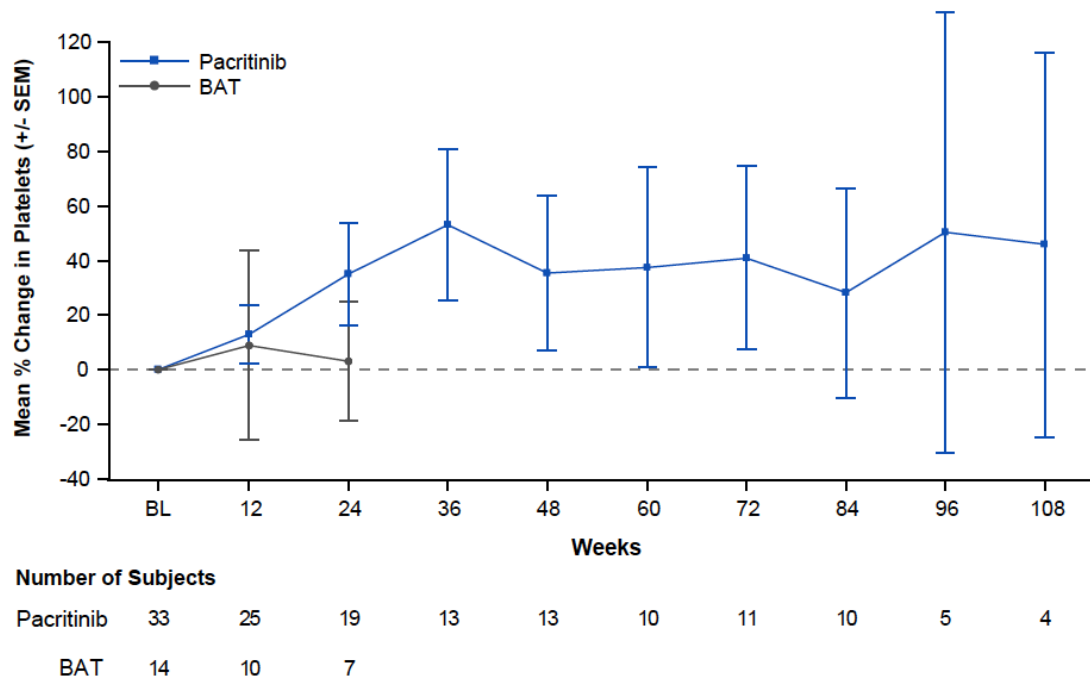
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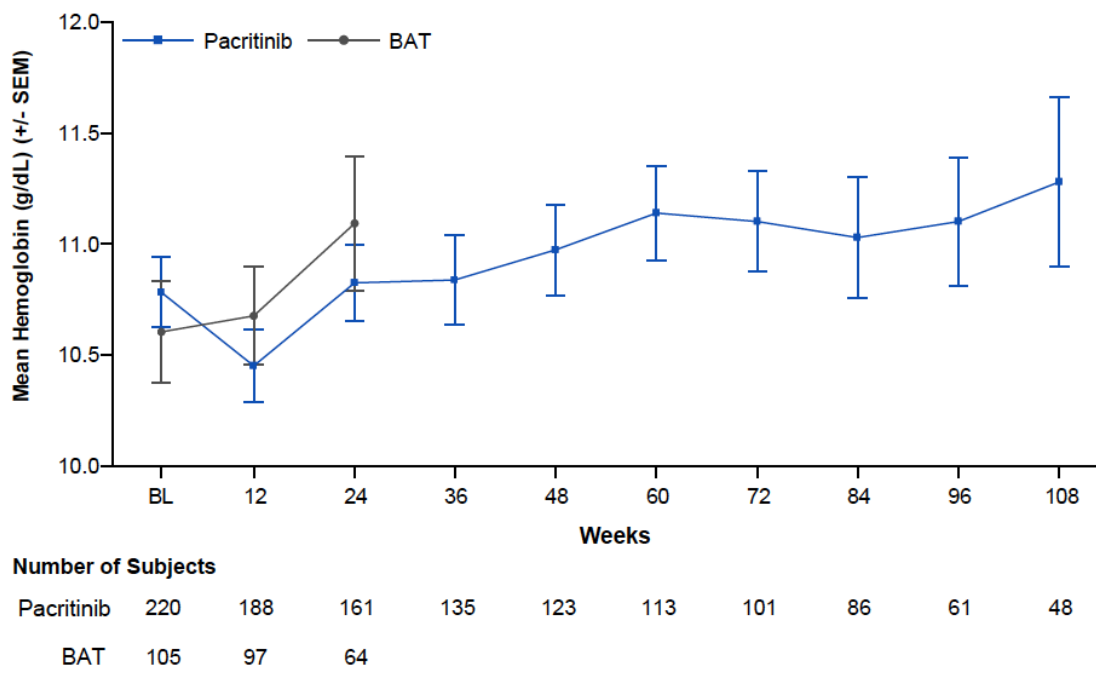
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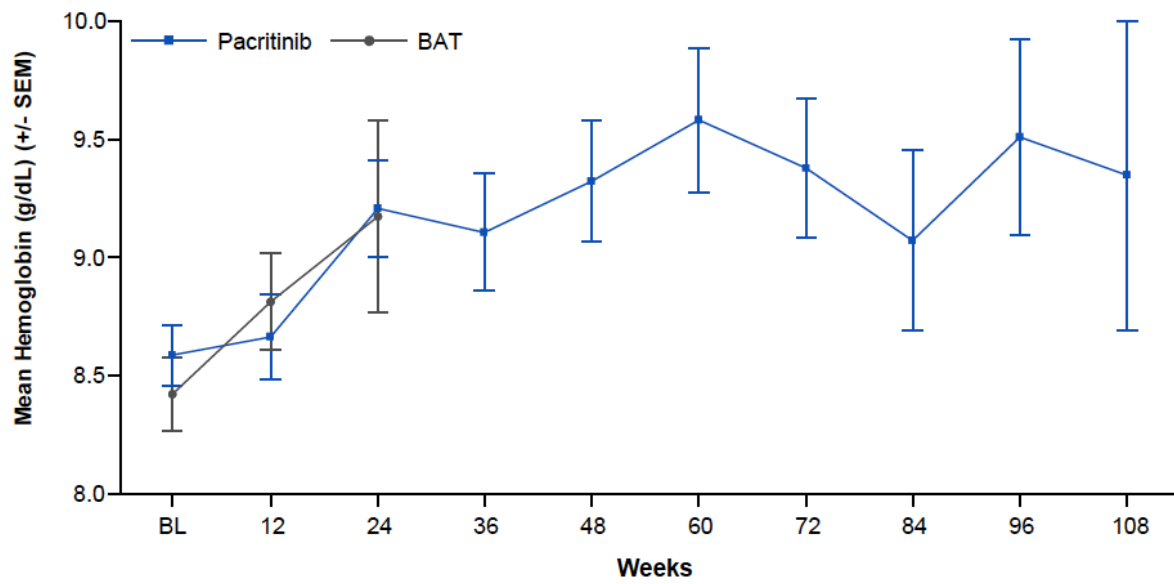
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D



E



Number of Subjects

Pacritinib	84	71	56	44	41	33	28	23	15	13
BAT	46	40	24							