Original Study

Consistency of Spleen and Symptom Reduction Regardless of Cytopenia in Patients With Myelofibrosis Treated With Pacritinib

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Abstract

Cytopenias are common in patients with myelofibrosis (MF). The efficacy of the JAK2/IRAK1/ACVR1 inhibitor pacritinib was analyzed by baseline platelet and hemoglobin levels using data from 2 Phase 3 studies in patients with MF. Pacritinib demonstrated spleen volume reduction and symptom responses across hemoglobin and platelet subgroups, indicating that pacritinib may provide benefit regardless of the presence of severe cytopenias.

Background: Pacritinib is a JAK2/IRAK1/ACVR1 inhibitor that is approved in the United States for the treatment of patients with myelofibrosis who have a platelet count $< 50 \times 109$/L. Phase 3 clinical studies of pacritinib included patients across a wide range of baseline platelet and hemoglobin levels. **Patients and Methods:** In order to assess the impact of baseline blood counts on pacritinib efficacy, an analysis of efficacy outcomes by baseline platelet and hemoglobin levels was performed using data pooled from 2 Phase 3 studies of pacritinib in patients with MF (PERSIST-1 and PERSIST-2). **Results:** Of 276 patients evaluable for spleen response, spleen volume reduction occurred consistently across platelet subgroups ($< 100 \times 109$/L or $\geq 100 \times 109$/L) and hemoglobin subgroups (< 8 g/dL, ≥ 8 to < 10 g/dL, or > 10 g/dL), with no diminution in treatment effect in patients with severe thrombocytopenia or anemia. Among 159 patients evaluable for symptoms response, improvement in total symptom score (TTS) was similar across platelet subgroups. A $\geq 50\%$ improvement of TSS occurred more frequently in patients with baseline hemoglobin < 8 g/dL compared with those with baseline hemoglobin ≥ 8 to < 10 g/dL or > 10 g/dL. Patients with baseline hemoglobin < 8 g/dL also experienced improved hemoglobin sustained over 24 weeks, whereas subgroups with less severe anemia had stable hemoglobin levels over time. Symptom improvement as assessed using the Patient Global Impression of Change instrument was generally consistent across platelet and hemoglobin subgroups. **Conclusion:** Pacritinib demonstrates consistent efficacy in patients with MF regardless of baseline platelet and hemoglobin counts.

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Keywords: Anemia, Hemoglobin, JAK2/IRAK1/ACVR1 inhibitor platelet, Thrombocytopenia

Introduction

In patients with myelofibrosis (MF), JAK inhibitor therapy can improve both splenomegaly and disease symptoms.[1,2] However, the JAK1/2 inhibitors ruxolitinib and fedratinib frequently cause or exacerbate cytopenias and therefore their dosing is commonly limited in patients with MF presenting with anemia or thrombocytopenia (cytopenic MF).[3-5] Furthermore, the efficacy of these

Abbreviations: Allo-HCT, allogeneic stem cell transplant; BID, twice daily; CI, confidence interval; FDA, Food and Drug Administration; IQR, interquartile range; JAK, Janus kinase; MF, myelofibrosis; PGIC, patients global impression of change; QD, daily; SVR, spleen volume response; TSS, total symptom score.

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JAK1/2 inhibitors diminishes with progressive cytopenias, possibly due to required dose reductions or higher-risk disease in patients with anemia and/or thrombocytopenia.[6-8]

Pacritinib is a JAK1-sparing inhibitor of JAK2 that also targets the IRAK1/NFkB pathway, a known driver of MF pathogenesis, and ACVR1, which has been linked to hepcidin reduction and anemia benefit.[6,9] Pacritinib received accelerated approval by the Food and Drug Administration (FDA) in the United States for the treatment of adults with MF who have a platelet count $< 50 \times 10^9$/L; however, Phase 3 clinical studies of pacritinib included patients across the cytopenic spectrum, including any range of baseline hemoglobin or platelets.

Here, we present data on spleen and symptom reduction in pacritinib-treated patients in 2 Phase 3 clinical studies grouped by baseline platelet and hemoglobin levels to assess consistency of response regardless of baseline cytopenia.

Patients and Methods

Details of PERSIST-1 (NCT01773187) and PERSIST-2 (NCT02055781) Phase 3 study designs have been published previously.[7,8] Both studies enrolled patients with intermediate or high-risk MF with palpable splenomegaly ≥ 5 cm below the left costal margin. Patients with any baseline platelet count were eligible in PERSIST-1 and patients with platelet count ≤ 100,000/μL during screening were eligible in PERSIST-2. Patients assigned to receive pacritinib were treated with a total daily dose of 400 mg (pacritinib 400 mg daily [QD] dose in PERSIST-1; pacritinib 400 mg QD or 200 mg twice daily [BID] in PERSIST-2). Both studies were approved by the institutional review boards at each participating institution and were conducted in accordance with the principles outlined in the Declaration of Helsinki. All patients provided written informed consent.

For this post-hoc analysis, efficacy data from patients with baseline and 24-week data (evaluable patients) treated with pacritinib in PERSIST-1 or PERSIST-2 were pooled and analyzed according to subgroups by baseline platelet count (< 100, $\geq 100 \times 10^9$/L) and hemoglobin (< 8, 8 to < 10, ≥ 10 g/dL). Groups were analyzed for depth and time of spleen volume reduction (SVR), total symptom score (TSS version 2.0 excluding tiredness) reduction, and patient global impression of change (PGIC). Analysis were also performed separately in those patients who received pacritinib 200 mg BID, the approved therapeutic dose.

Percent change in spleen volume and TSS over time was reported as median with inter-quartile range (IQR). The percentage of patients achieving a SVR, TSS, or PGIC response was presented with 95% confidence intervals (CIs) estimated using the Clopper-Pearson method. Median relative dose intensity (actual / planned dose per day, as a percentage) was also reported for each group, along with IQRs.

Results

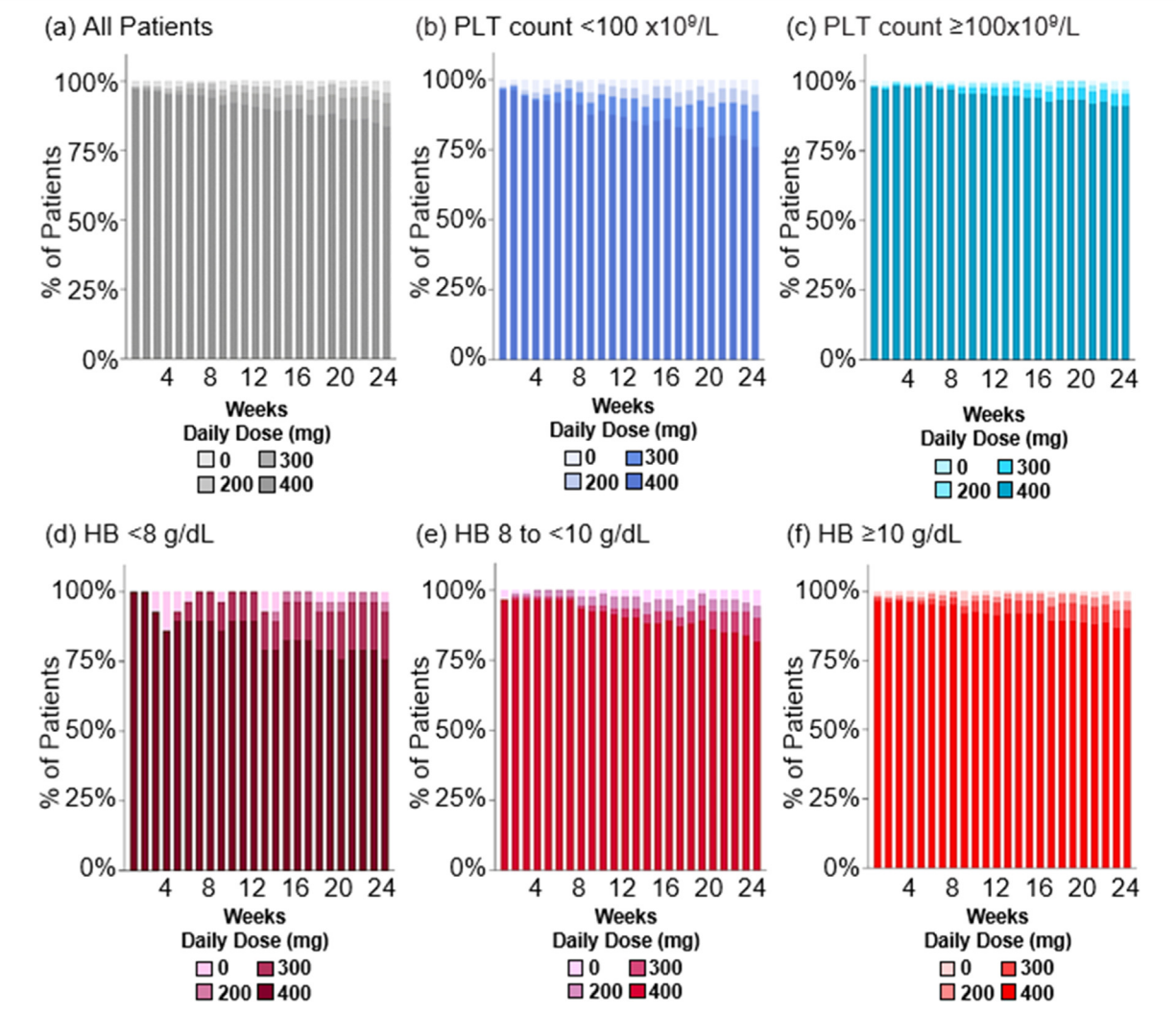
Data from 276 evaluable patients were included in the analysis. The median patient age was 67 years, 51.5% had grade 3 fibrosis, 70% had primary MF, and 16% had prior JAK2 inhibitor exposure. Equal numbers of patients had a baseline platelet count $< 100 \times 10^9$/L (50%) or $\geq 100 \times 10^9$/L (50%), whereas 29 (11%), 94 (34%) and 153 (55%) patients had a baseline hemoglobin count of < 8, 8 to < 10 or ≥ 10 g/dL, respectively. Baseline characteristics of patients by baseline platelet and hemoglobin subgroups are shown in Table 1. Patients with baseline platelet count $< 100 \times 10^9$/L and those with baseline hemoglobin < 8 g/dL were more likely to have prior JAK2 inhibitor exposure (29% and 41%, respectively, vs. 3%-15% in patients with higher baseline counts), reflecting PERSIST-2 study entry criteria, whereas PERSIST-1 did not restrict eligibility based on platelet count but prohibited prior JAK2 inhibitor exposure. Median pacritinib dose intensity was approximately 100% (400 mg total daily dose) across all platelet and hemoglobin strata in the SVR evaluable population (Figure 1). Of patients receiving a reduced pacritinib dose, the most common total daily dose was 300 mg.

Table 1 Baseline Characteristics of Patients Evaluable for Spleen Response

	PLT < 100 *N = 136*	PLT ≥ 100 *N = 137*	HB < 8 *N = 29*	HB 8-9.99 *N = 94*	HB ≥ 10 *N = 153*
Age (years), median	68	65	68	68	66
Primary MF, % (n)	77% (105)	63% (86)	83% (24)	75.5% (71)	63% (97)
DIPSS high risk., % (n)	24% (33/136)	12% (16)	34.5% (10)	32% (30)	7% (11)
Hypocellular marrow, % (n/N)[a]	28% (38/134)	12% (17/137)	24% (7/29)	29% (27/94)	15% (23/151)
Grade 3 fibrosis, % (n/N)[a]	57% (76/134)	46% (63/137)	65.5% (19/29)	56% (53/94)	46% (69/151)
RBC-TD, % (n)	19% (26)	9% (12)	45% (13)	17% (16)	6% (9)
PLT-TD, % (n)	7% (9)	0	3% (1)	4% (4)	3% (4)
Prior JAK2 inhibitor, % (n)	29% (39)	3% (4)	41% (12)	15% (14)	12% (18)

[a] Denominator includes patients with baseline bone marrow assessment.
Abbreviations: DIPSS = dynamic international prognostic scoring system; HB = hemoglobin; PLT = platelet; RBC = red blood cell; TD = transfusion dependent (Gale criteria).

Figure 1 Pacritinib dose intensity by baseline blood counts (PERSIST-1 and PERSIST-2 patients on pacritinib). BL = baseline; HB = hemoglobin; PAC = pacritinib; PLT = platelet.

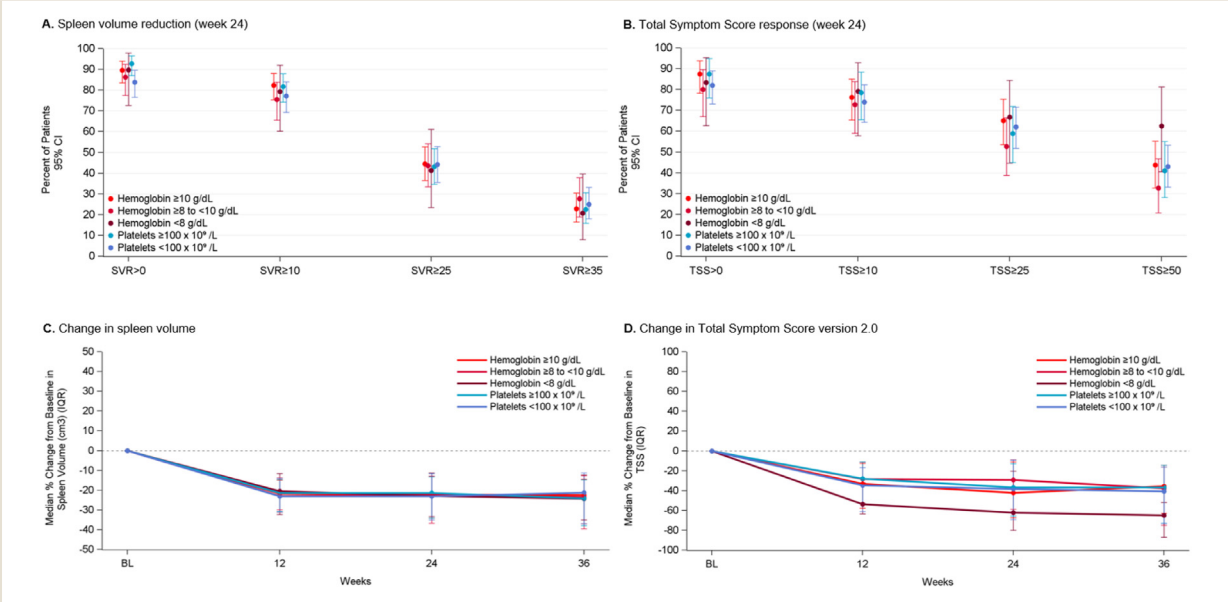


Overall, 88% of evaluable patients had clinical improvement (any reduction: SVR > 0) in spleen volume from baseline to week 24, including 80% with ≥ 10% reduction (SVR ≥ 10%), 44% with SVR ≥ 25%, and 24% with SVR ≥ 35%, respectively. Spleen reduction occurred consistently across platelet and hemoglobin strata, with no diminution in treatment effect in patients with severe thrombocytopenia or anemia (Figure 2A). The timing of spleen volume reduction was consistent across all platelet and hemoglobin strata, with responses occurring by week 12 and maintained steadily over the course of the study (Figure 2C).

Among 159 patients evaluable for TSS response, clinical improvement in TSS (TSS reduction > 0) from baseline to week 24 was noted in 84% of patients, including 75.5% with TSS reduction ≥ 10%, 61% with TSS reduction ≥ 25%, and 43% with TSS reduction ≥ 50%. Improvement in TTS was similar across all platelet subgroups; however, among hemoglobin subgroups, a reduction of TSS ≥ 50% occurred most frequently in patients with baseline hemoglobin < 8 g/dL (Figure 2B). While most symptom reduction occurred by week 12, ongoing improvement was also noted through week 24 (Figure 2D), particularly among patients with baseline hemoglobin < 8 g/dL, who experienced a median 54% decrease in total score at week 12 and a 62% decrease at week 24. Similar trends were observed for the "tiredness" symptom, which was measured as part of the TSS but not included in the total score: patients with hemoglobin < 8 g/dL experienced the greatest reductions in 'tiredness' severity at week 12 (median 31% decrease from baseline) and week 24 (median 29% decrease from baseline) compared to patients with higher hemoglobin (median decrease of ~15% and ~15% at weeks 12 and 24, respectively).

Outcomes for SVR and TSS among the 57 patients treated specifically with the approved pacritinib 200 mg BID dose (PERSIST-2 only) are provided in Figure 3. Similar to the overall popula-

Figure 2 Depth and timing of response. Panels A and B show the percentage of evaluable patients with any, ≥ 10%, ≥ 25%, and ≥ 35% spleen volume reduction (A) and any, ≥ 10%, ≥ 25%, and ≥ 50% improvement in Total Symptom Score (B) at Week 24. Panels C and D show the median percent change from baseline in spleen volume (C) and TSS (D) by baseline strata. Note: clinical improvement refers to > 0% SVR, > 0% TSS reduction. Abbreviations: CI = confidence interval; IQR = interquartile range; SVR = spleen volume reduction; SVR35 ≥ 35% reduction; SVR10 / TSS10 = ≥ 10% reduction; SVR25 / TSS25 = ≥ 25% reduction; TSS = total symptom score (version 2.0, excluding tiredness); TSS50 = ≥ 50% reduction.



tion presented above, improvements in SVR and TSS were consistent across the cytopenic spectrum, though the depth of spleen and symptom response was greater at this approved dose than in the pooled pacritinib population.

Symptom improvement was also assessed using the PGIC instrument.[10] Among 235 patients evaluable for PGIC, symptom improvement was noted in 78%, including 48.5% who reported that their disease symptoms were "much" or "very much" improved. Importantly, similar to TSS, PGIC response was consistent across the cytopenic spectrum, but most prominent in more severely cytopenic patients (Figure 4).

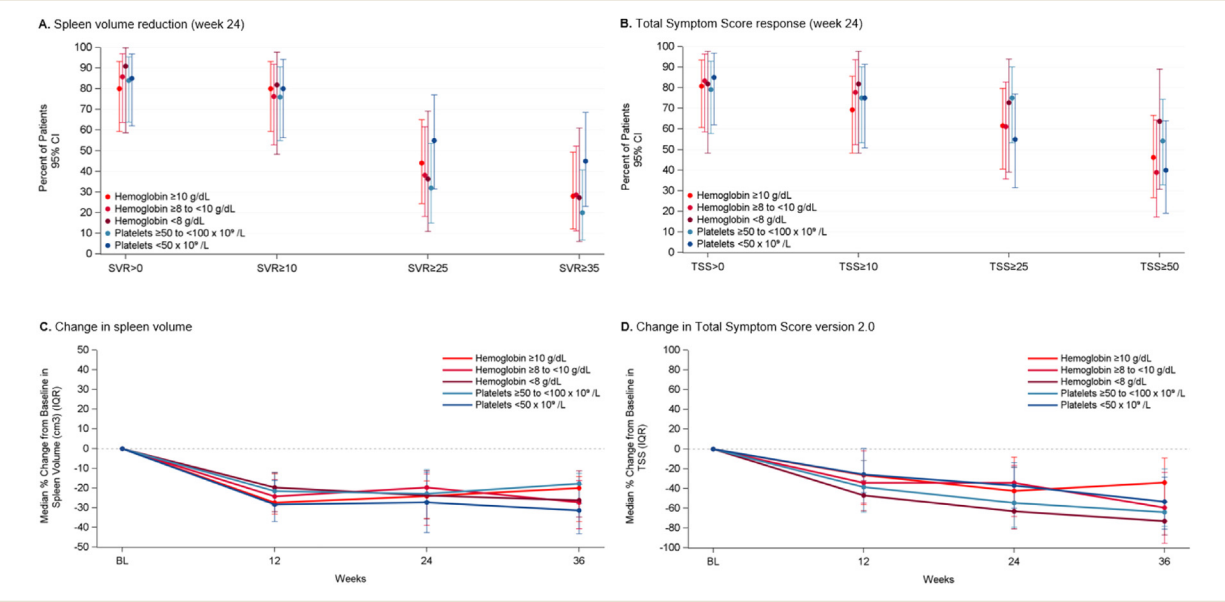
In line with symptom results, the subgroup of patients with baseline hemoglobin < 8 g/dL experienced improved hemoglobin on study sustained over 24 weeks; subgroups with less severe anemia at baseline had stable hemoglobin levels over time (Figure 5). Of the 29 patients with baseline hemoglobin < 8 g/dL, 90% (n = 26) were receiving RBC transfusions at baseline. Among these 26 patients, 35% (n = 9) became transfusion independent on study, defined as zero RBC transfusions over any 12-week period. Among the 13 patients with hemoglobin < 8 g/dL who met Gale criteria for transfusion dependence at baseline, 23% (n = 3) became transfusion independent on study. A moderate correlation between percent improvement in hemoglobin and percent decrease in tiredness from baseline to week 24 was observed: r - 0.33, $P = .15$ in patients with hemoglobin < 8.

Discussion

Pacritinib demonstrates consistent efficacy for spleen and symptom response regardless of baseline cytopenia in patients with MF. This consistency may be related to pacritinib's ability to be delivered at full dose regardless of baseline hemoglobin level or platelet count. It is also possible that pacritinib's unique mechanism of action results in enhanced efficacy in patients with severe cytopenia who generally pose greater treatment challenges. For example, recent data indicate that an innate immune dysregulation involving the IRAK-NFkB axis favors a more cytopenic phenotype in MF patients,[11] and thus pacritinib's role as an IRAK1 inhibitor could boost the observed effects in patients with severe anemia or thrombocytopenia.

Of note, pacritinib showed consistent responses even in patients with severe anemia at baseline, resulting in more rapid and deeper reductions in MF symptom burden on pacritinib compared to less severely anemic or nonanemic patients. As pacritinib has been identified as a potent inhibitor of the hepcidin regulator ACVR1,[6,12] we hypothesized that some of the benefit experienced by these patients may have been related to improvement in anemia. Indeed, these patients reported greater improvements in "tiredness", a common symptom associated with anemia, compared to less anemic patients, and experienced increases in hemoglobin, decreases in transfusion burden, and – in a subset – transfusion independence on study. Overall, this highlights that pacritinib may be able to

Figure 3 Depth and timing of response for pacritinib 200 mg BID. Panels A and B show the percentage of evaluable patients with any, ≥ 10%, ≥ 25%, and ≥ 35% spleen volume reduction (A) and any, ≥ 10%, ≥ 25%, and ≥ 50% improvement in Total Symptom Score (B) at Week 24. Panels C and D show the median percent change from baseline in spleen volume (C) and TSS (D) by baseline strata. Note: clinical improvement refers to > 0% SVR, > 0% TSS reduction. Abbreviations: CI = confidence interval; PGIC = patient global impression of change; SVR = spleen volume reduction; SVR10 / TSS10 = ≥ 10% reduction; SVR25 / TSS25 = ≥ 25% reduction; SVR35 ≥ 35% reduction; TSS = total symptom score (version 2.0, excluding tiredness); TSS50 = ≥ 50% reduction.

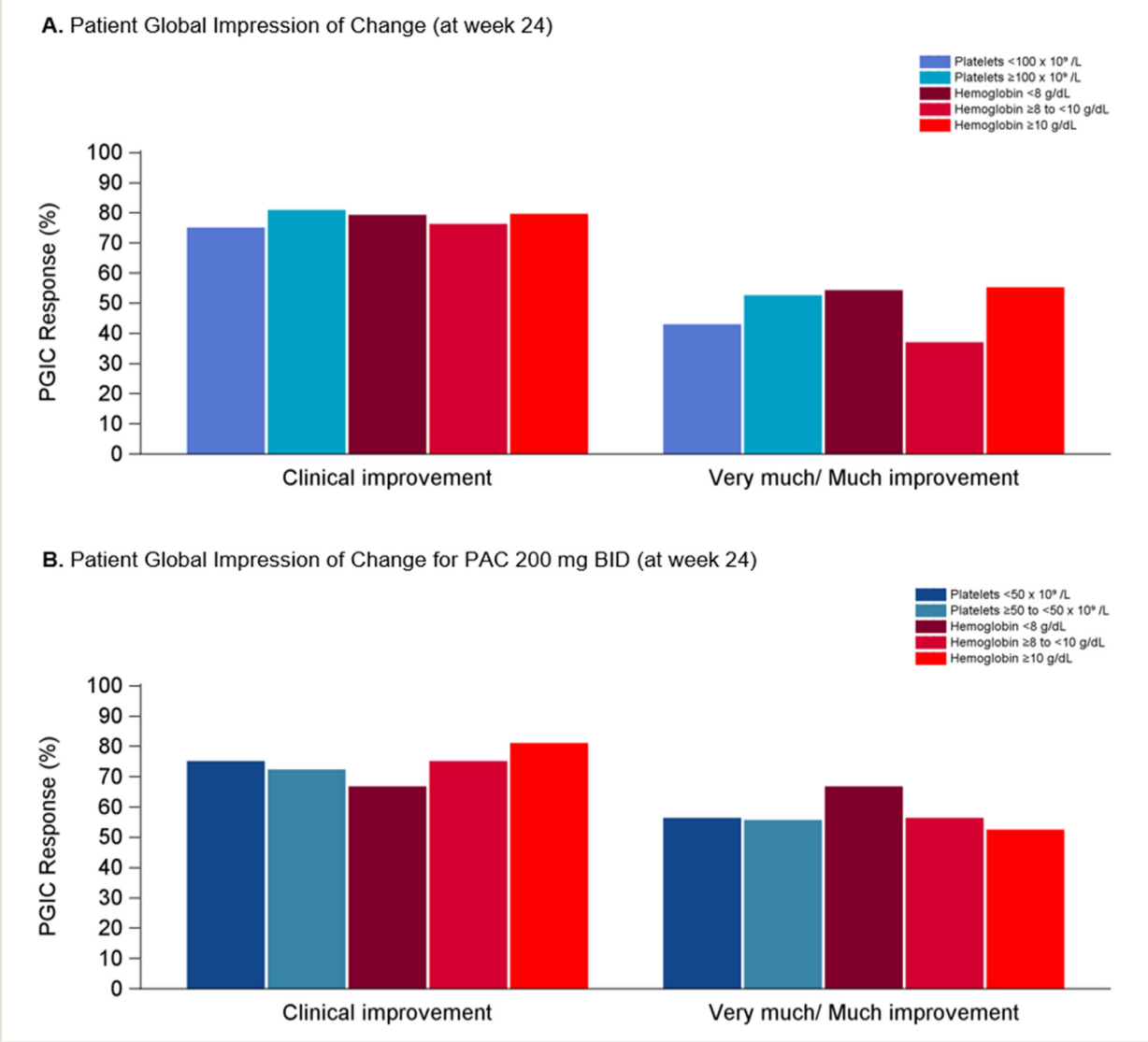


successfully improve patients' underlying disease and general condition even in severe cases, which might enable them, if eligible, to undergo potentially curative treatment with allo-HCT.

Pacritinib was shown to have an acceptable safety profile in phase 3 clinical studies that enrolling patients with a wide range of baseline platelet and hemoglobin levels.[7,8] Furthermore, a post-hoc risk-adjusted safety analysis demonstrated that the overall incidence of treatment-emergent adverse events and the incidence of specific adverse events of interest (e.g., bleeding, cardiac, and infection events) was comparable or favorable with pacritinib 200 mg BID versus best available therapy, confirming the feasibility of treatment with pacritinib regardless of cytopenias.[13]

Allo-SCT remains the only definitively disease-modifying treatment option currently available to patients with MF, and positioning patients for successful HCT is an important treatment goal.[14,15] In patients with MF, bulky splenomegaly prior to allo-HCT is a risk factor for worse post-transplant outcomes, including delayed engraftment, poor graft function, and especially increased risk for relapse.[16,17] Some studies have suggested an association between splenomegaly and post-transplant mortality,[18,19] however these studies may be prone to bias, given that spleen size evaluation over the disease course including before allo-HCT remains heterogenous in quality. Furthermore, spleen and symptom control are challenging in patients with cytopenic MF, especially when undergoing intensive treatment, suggesting center effect,[20] with more experienced centers showing significantly better outcomes for patients with high symptom burden and splenomegaly. Few studies have examined the efficacy and safety of JAK inhibitor therapy in the pretransplant setting. In a preliminary report of findings from a phase 2 study of ruxolitinib given pre, during, and post-HCT in patients with MF, rates of graft-versus-host-disease-free, relapse-free survival (GRFS), progression-free survival (PFS), and overall survival (OS) at 1 year post-HCT were 74%, 79%, and 86%, respectively, while grade 3/4 thrombocytopenia, anemia, and neutropenia were observed in 32%, 27%, and 25% of patients, respectively.[21] In a retrospective study, treatment with fedratinib pretransplant reduced spleen size and symptoms; however, post-transplant follow-up was limited.[22] While both phase 3 pacritinib studies excluded transplant-eligible MF patients, recent data from the Phase II HOVON-134 study found pacritinib to be safe and effective at reducing spleen size and symptom burden pretransplant.[23] The data shown here suggests that pacritinib may be a treatment option for pretransplant disease optimization in MF patients regardless of cytopenias. As ruxolitinib and fedratinib may worsen cytopenia and are therefore often dose-reduced or held in this setting,[24] our findings suggest that pacritinib may be an effective option for pretransplant disease control, facilitating patients to undergo potentially curative treatment together with adequate transplant-specific risk evaluation.[25] This may lead to more access to and improved PFS and OS outcomes after allo-HCT in patients with MF regardless of cytopenias. These data warrant further evaluation in transplant-eligible MF patients.

Figure 4 Patient-reported improvement in disease symptoms at week 24 shown by baseline strata for (A) evaluable patients who received pacritinib (any dose) and (B) evaluable patients who received pacritinib 200 mg BID.



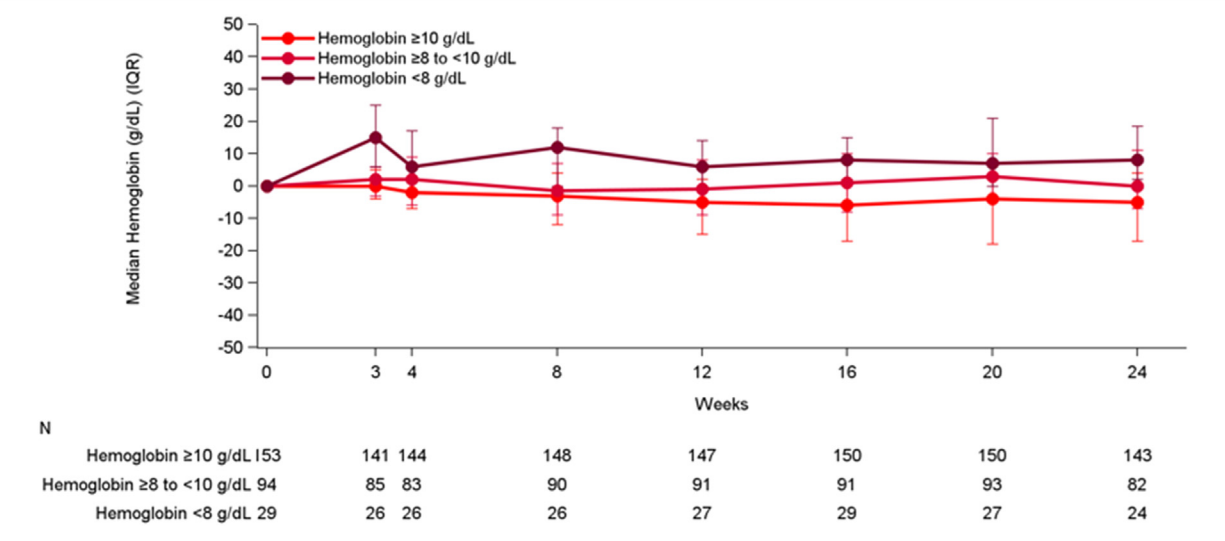
Conclusion

In this post-hoc analysis of data pooled from 2 Phase 3 studies, pacritinib demonstrated consistent efficacy in patients with MF regardless of baseline platelet and hemoglobin counts. These findings suggest that pacritinib may be able to successfully improve underlying disease and general condition in severe cytopenic cases and potentially in pretransplant settings to avoid the risk of drug-induced exacerbation of cytopenia associated with ruxolitinib and fedratinib.

Clinical Practice Points

Pacritinib is approved for the treatment of adults with MF who have a platelet count < 50 × 109/L; however, clinical studies of pacritinib have included patients across a wide range of baseline platelet and hemoglobin levels. In this analysis of data pooled from 2 Phase 3 studies, pacritinib demonstrated consistent efficacy for spleen volume reduction and symptom response in patients with MF regardless of baseline cytopenic status. Of interest, pacritinib showed greater reduction in symptoms in patients with severe anemia at baseline, resulting in more rapid and deeper reductions in MF symptom burden compared with results in less severely anemic or nonanemic patients. These findings suggest that pacritinib may be able to successfully improve underlying disease and general condition even in severe cases, which might enable such patients to undergo potentially curative treatment with allo-HCT, if eligible. In contrast, ruxolitinib and fedratinib may worsen cytopenia and are therefore often dose-reduced or held in cytopenic patients. Thus, pacritinib may be an effective option for pretransplant disease

Figure 5 Change in median hemoglobin over time. Change in median hemoglobin over time is shown by baseline hemoglobin group. Abbreviation: IQR = interquartile range.



control, improving access to potentially curative treatment together. These data support further evaluation of pacritinib treatment in patients with MF who are transplant-eligible.

Disclosure

Nico Gagelmann: has consulted for Morphosys and Kite/Gilead; and has received travel support from Kite/Gilead, Janssen, and Neovii.

Prithviraj Bose: has consulted for or received honoraria from AbbVie, Blueprint, BMS, Cogent, CTI BioPharma Corp., a Sobi company, Disc Medicine, GSK, Incyte, Ionis, Jubilant, Karyopharm, Morphic, MorphoSys, Novartis, PharmaEssentia, and Sumitomo; and has received research funding from Blueprint, BMS, Cogent, CTI BioPharma Corp., a Sobi company, DISC Medicine, Geron, Incyte, Ionis, Janssen, Kartos, Karyopharm, MorphoSys, Sumitomo, and Telios.

Vikas Gupta: has consulted for AbbVie, BMS-Celgene, CTI BioPharma Corp., a Sobi company, GSK, Imago, Incyte, Karyopharm, MorphoSys, Novartis, Pfizer, Roche; has received research funding from Novartis, Incyte; has participated in advisory boards for AbbVie, BMS- Celgene, Constellation, CTI BioPharma Corp., a Sobi company, GSK, Incyte, Novartis, Pfizer.

Donal P. McLornan: has received speakers fees from AbbVie, BMS/Celgene, Jazz Pharmaceuticals and Novartis; has received research funding from BMS/Celgene and Jazz Pharmaceuticals; and has participated on advisory boards and received travel assistance from Jazz Pharmaceuticals.

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Haris Ali: has received research/ grant support from Incyte, has consulted for Karyopharm, GSK, and PharmaEssentia, and has participated in speakers bureaus for BluePrint and BMS.

Philipp Treskes: consults for Sobi Inc.

Sarah Buckley: is employed by Sobi Inc. and has received payment of unvested equity awards from CTI BioPharma Corp., a Sobi company, following its acquisition in June 2023 by the Swedish Orphan Biovitrum AB (publ).

Karisse Roman-Torres: is employed by Sobi Inc. and has received payment of unvested equity awards from CTI BioPharma Corp., a Sobi company, following its acquisition in June 2023 by the Swedish Orphan Biovitrum AB (publ).

Bart Scott: has participated on the data and safety monitoring board for Nektar and Johnson and Johnson; has participated in advisory panels for BMS, Celgene, Jazz Pharmaceuticals, and Novartis; has consulted for Alexion, Celgene, BMS, and Incyte; has received honoraria from Celgene, and BMS; and has received research funding from BMS and Novartis.

CRediT authorship contribution statement

Nico Gagelmann: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization. **Prithviraj Bose:** Writing – review & editing. **Vikas Gupta:** Writing – review & editing, Investigation, Formal analysis. **Donal P. McLornan:** Writing – review & editing, Writing – original draft, Supervision, Methodology. **Pankit**

Vachhani: Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Haifa-Kathrin Al-Ali:** Writing – review & editing, Conceptualization. **Haris Ali:** Writing – review & editing, Supervision, Data curation. **Philipp Treskes:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Sarah Buckley:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Karisse Roman-Torres:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Bart Scott:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

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