Long-term treatment with pacritinib on a compassionate use basis in patients with advanced myelofibrosis

Pacritinib is an oral Janus kinase (JAK) 2/interleukin-1 receptor–associated kinase 1 (IRAK1)/ activin receptor type-1 (ACVR1) inhibitor that does not inhibit JAK1.[1,2] Pacritinib received accelerated approval in the US in February 2022 for the treatment of adults with intermediate- or high-risk myelofibrosis (MF) with a platelet count <50×10^9/L. Late-stage clinical studies of pacritinib include two randomized, controlled phase III trials (PERSIST-1 and PERSIST-2; *clinicaltrials gov. Identifier: NCT01773187* and *NCT02055781*) and a phase II dose-finding study (PAC203; *clinicaltrials gov. Identifier: NCT04884191*).[3–5] While pacritinib efficacy and safety was demonstrated across these studies, the phase III trials were terminated early due to a full clinical hold on February 8, 2016. The hold was removed on January 5, 2017 after submission of the final study reports, and patients who had benefited from pacritinib on trial were able to resume pacritinib on a compassionate use basis. In order to describe the long-term treatment experience with pacritinib, we analyzed data from 76 patients treated with pacritinib on a compassionate use basis after receiving pacritinib on a clinical trial, representing the longest-term data available. Most of these patients were thrombocytopenic and/or anemic, and most had received prior JAK2 inhibitor therapy. Pacritinib treatment duration was notable in this advanced population, with a median total duration (original study + compassionate use) of 21.1 months (range, 0.9-80.9 months). Similar treatment durations were observed regardless of baseline blood cell counts; however, median treatment duration was longer in patients who were JAK inhibitor naïve compared to those who had prior exposure. Reported serious adverse events (SAE) were consistent with those expected in an advanced MF patient population. Overall, these findings demonstrate that prolonged treatment with pacritinib is feasible in patients with advanced MF, including those with cytopenias.

Thrombocytopenia, occurring either as a result of disease progression or from treatment with myelosuppressive therapy, is a common complication in patients with MF and is associated with more advanced disease and shorter survival compared to patients with higher platelet counts.[6–9] The prevalence of severe thrombocytopenia (platelet count <50x10^9/L) in MF is estimated to be as high as 35%.[10] Outcomes are particularly poor in patients with prior JAK2 inhibitor therapy: median survival in MF after discontinuing ruxolitinib is 14 months overall and approximately 8 months if the platelet count was <100×10^9/L at discontinuation.[11]

The clinical studies of pacritinib are unique in the MF landscape, as they allowed enrollment of patients with severe cytopenias: the phase II PAC203 study and the phase III PERSIST-1 and PERSIST-2 studies all included patients with baseline platelet counts <50x10^9/L as well as those with higher platelet counts. By contrast, other approved JAK2 inhibitors have not been extensively studied in patients with severe thrombocytopenia. In this analysis, we reviewed treatment and safety data from patients who received pacritinib as part of a compassionate use program after participating in a clinical study. Upon study closure, patients enrolled in PERSIST-1, PERSIST-2, or PAC203 were eligible to continue pacritinib on a compassionate use basis if they had an unmet medical need and were experiencing benefit in the opinion of the investigator or patient. Patients were excluded if they had progressed to acute leukemia or experienced high-grade cardiac or bleeding events on study. Eighty-three patients were approved for compassionate use, and 76 received compassionate use pacritinib, of whom 42 were originally enrolled in the PERSIST-1/PERSIST-2 studies and 34 were enrolled in PAC203. Patient characteristics were available from the original study for 74 patients treated with compassionate use pacritinib (Table 1). Median age was 69 years. Most patients (70%) had received prior treatment with a JAK2 inhibitor. Over half (60%) had a baseline peripheral blast count ≥1%. Cytopenias were common, with 34% of patients having a platelet count <50×10^9/L and 69% having a platelet count <100×10^9/L; in addition, 50% had hemoglobin <10 g/dL. Between the original study enrollment and the transition to compassionate use, the percentage of patients requiring red blood cell transfusion decreased from 49% to 33%. Among 30 patients on PAC203 who had myeloid mutations assessed,[5] 67% had a non-driver mutation and 33% had a high-risk mutation (in *ASXL1, SRSF2, U2AF1* Q157*, TP53, EZH2, IDH1/2*, or *NRAS*).

Pacritinib dosing data was collected as part of the compassionate use program and was available for 70 of 76 patients. The allowed dosing regimens for pacritinib were 200 mg twice daily (BID), 100 mg BID, and 100 mg daily. For patients treated at lower doses during the original studies, dose escalation up to 200 mg BID was permitted at the discretion of the medical monitor and treating physician. Among the 70 patients with available dosing data at the start of the compassionate use program, 68% received pacritinib at a starting dose of 200 mg BID, 26% received 100 mg BID, and 6% received 100 mg daily. Nearly all patients (97% [66/68]) received the same dose or a higher dose than they had received on-study.

Table 1. Baseline characteristics[a] of patients receiving compassionate use pacritinib.

Characteristic	Patients receiving pacritinib (N=76)	
Prior study participation, % (N) PERSIST-1 PERSIST-2 PAC203	 8 (6/76) 47 (36/76) 45 (34/76)	
Sex, % (N) Male Female	 59 (44/74) 41 (30/74)	
Age in years at start of original study, median (range)	69 (37-84)	
Peripheral blasts ≥1%, % (N)	60 (38/63)	
Prior JAK inhibitor, % (N) Yes No	 70 (52/74) 30 (22/74)	
Blood cell counts	**At original study start**	**Prior to compassionate use**
Median PLT count x10^9/L, (IQR) PLT <50x10^9/L, % (N) PLT <100x10^9/L, % (N) PLT ≥100x10^9/L, % (N) Median WBC x10^9/L, (IQR) Median ANC x10^9/L, (IQR) Median Hb g/dL, (IQR) Hb <10 g/dL, % (N)	74 (40-117) 34 (24/71) 69 (49/71) 31 (22/71) 7.4 (3.7-16.4) 4.3 (2.1-10.5) 9.9 (8.3-11.2) 50 (37/74)	61 (32-105) 40 (29/73) 74 (54/73) 26 (19/73) 6.8 (3.5-12.0) 4.4 (1.9-8.7) 9.8 (8.2-11.8) 53 (39/74)
Platelet transfusion within the past 90 days, % (N)	12.2 (9/74)	9.5 (7/74)
RBC transfusion within the past 90 days, % (N)	48.6 (36/74)	32.4 (24/74)
Myeloid mutations (PAC203)[b], % (N) Non-driver mutation ≥2 non-driver mutations High-risk mutation[c] Driver mutation Driver allele burden <50% Driver allele burden ≥50%	 67 (20/30) 27 (8/30) 33 (10/30) 100 (30/30) 50 (13/26 with baseline VAF data) 50 (13/26 with baseline VAF data)	

[a]Characteristics as of the time of original study enrollment unless otherwise noted; denominators are based on N with available data. [b]Mutation analysis was performed in the PAC203 study only; mutation status is based on N=30 patients with available baseline data. [c]High risk includes *ASXL1, SRSF2, U2AF1* Q157, *TP53, EZH2, IDH1/2, NRAS. JAK*: Janus associated kinase; IQR: interquartile range; PLT: platelet count; Hb: hemoglobin; WBC: white blood cell; ANC: absolute neutrophil count; RBC: red blood cell; VAF: variant allele frequency.

Prolonged pacritinib treatment was feasible in patients in the compassionate use program (Figure 1). Overall, the median total duration of treatment with pacritinib (original study + compassionate use) was 21.1 months (range, 0.9-80.9 months) (Table 2), including a median treatment duration of 7.7 months on the original study and 11.6 months in the compassionate use program. At the time of this analysis (data cut-off February 28, 2022), 15 patients continued to receive compassionate use pacritinib with a median total treatment duration of 41 months (range, 33-79 months).

Treatment duration was similar in patients with baseline thrombocytopenia or anemia compared with the 21.1-month duration in the overall population: median treatment duration was 20.7 months in patients with platelet count <50×10^9/L (n=24) and 19.8 months in patients with hemoglobin <10 g/dL (n=37). Among patients who had previously been enrolled in PAC203 and had mutational analysis data (n=30), the median total treatment duration was 28.7 months in patients with high-risk mutations (n=10) and 22.6 months in patients without high-risk mutations (n=20), indicating the feasibility of long-term pacritinib treatment regardless of molecular risk status. Median treatment duration was longer in patients who were JAK inhibitor naïve (29.4 months, n=22) compared to those with prior JAK inhibitor exposure (17.9 months, n=52). Among patients with prior JAK inhibitor exposure, the median time between prior JAK inhibitor and the start of pacritinib was only 18 days, and the median time from prior JAK inhibitor discontinuation to last day of treatment with compassionate use pacritinib was 27.3 months (range, 7.3-79.4 months). This observed total time from prior JAK in-

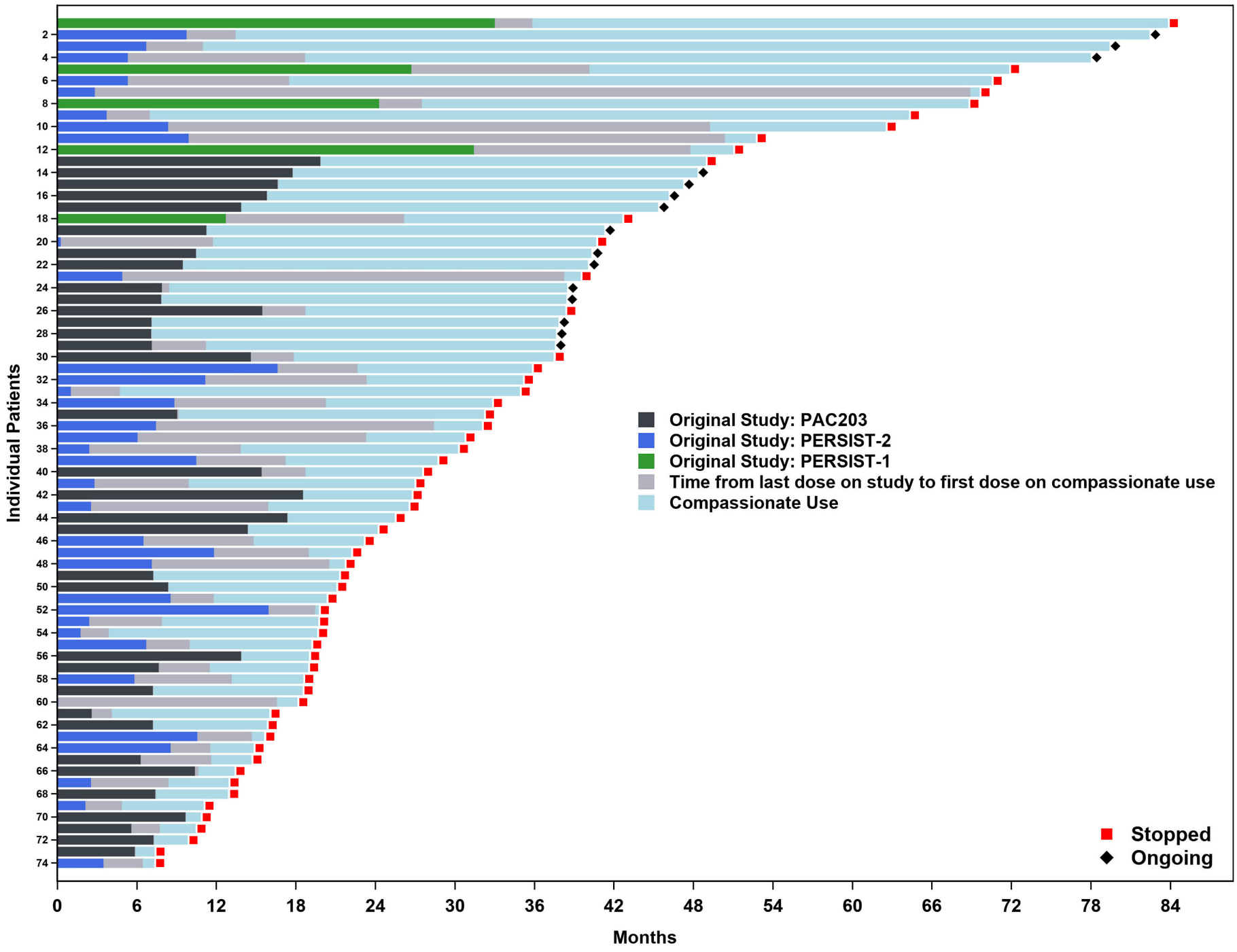

Figure 1. Time on pacritinib in compassionate use population. Patients ordered by length of time on treatment. Ongoing patients at time of data cut-off February 28, 2022.

hibitor discontinuation compares favorably to the median survival of 14 months (95% confidence interval: 10-18) previously reported in patients discontinuing ruxolitinib,[11] although the possibility of selection bias during enrollment in the compassionate use program should be noted.

SAE reporting was required on the compassionate use program. Among the 76 patients treated with compassionate use pacritinib, 35 (46%) experienced an SAE (*Online Supplementary Table S1*). SAE considered possibly related to pacritinib were reported in 16 patients (21%). Most SAE were considered unlikely related to pacritinib and were expected in an end-stage MF population, including bleeding events in 15 patients (20%), infection in ten patients (13%), and heart failure in three patients (4%). Among the infections reported, only one was considered atypical or potentially opportunistic: a case of actinomyces pneumonia in a patient with baseline neutropenia, which resolved with administration of antibiotics. In addition to heart failure, other cardiac events were reported in four patients (5%) and consisted of QT prolongation in two patients, and myocardial infarction and atrial enlargement in one patient each. There was one reported SAE of skin cancer, which was a case of invasive squamous cell carcinoma in a patient with a history of recurrent squamous cell carcinomas prior to treatment. Transformation to AML was reported in one patient.

Most SAE were grade 3 or 4 (48 events in 28 patients). There were ten fatal (grade 5) SAE reported in nine patients, including infection (n=3), heart failure (n=2), bleeding events (retroperitoneal hemorrhage, subdural hematoma, and hematemesis [n=1 each]), acute kidney injury (n=1) and disease progression (n=1). In the case of fatal subdural hematoma, the patient had been off pacritinib for >1 month at the time of death. In the case of fatal hematemesis, the patient had been on concomitant venetoclax plus decitabine prior to the event. Both events were con-

Table 2. Duration of treatment for patients receiving compassionate use pacritinib.

	Median pacritinib treatment duration, months (range)		
	Original study[a]	Compassionate use	Total
All patients (N=75)	7.7 (0-33.0)	11.6 (0.3-69.0)	21.1 (0.9-80.9)
PLT <50×10^9/L (N=24)	8.7 (2.3-24.2)	11.6 (1.2-57.3)	20.7 (6.1-65.5)
PLT 50-100×10^9/L (N=25)	7.1 (1.0-19.8)	13.2 (0.7-68.4)	24.1 (3.5-75.1)
PLT >100×10^9/L (N=22)	7.5 (0.2-33.0)	11.6 (0.9-69.0)	22.7 (4.3-80.9)
Hb <10 g/dL (N=37)	7.3 (1.0-24.2)	10.6 (0.3-68.4)	19.8 (3.5-75.1)
PLT <50×10^9/L and Hb <10 g/dL (N=15)	8.5 (2.3-24.2)	13.3 (2.5-57.3)	21.9 (9.7-65.5)
With high-risk mutation (N=10)[b]	12.1 (7.2-17.3)	16.2 (2.5-31.4)	28.7 (9.7-46.0)
Without high-risk mutation (N=20)[b]	7.5 (5.5-16.6)	12.6 (1.1-30.7)	22.6 (7.2-47.1)
Prior JAK inhibitor (N=52)	7.5 (1.7-19.8)	9.5 (0.3-31.4)	17.9 (3.5-48.8)
No prior JAK inhibitor (N=22)	8.5 (0.2-33.0)	16.4 (0.9-69.0)	29.4 (8.2-80.9)

[a]Data on the original study is based on N=73 patients with available baseline data from original study. [b]Mutation analysis was performed in the PAC203 study only; mutation status is based on N=30 patients with available baseline data. Hb: hemoglobin; PLT: platelet count; JAK: Janus associated kinase.

sidered unlikely related to pacritinib by the investigator. This analysis provides unique evidence supporting the feasibility of prolonged treatment with pacritinib, even in patients with cytopenias. While standard clinical trial endpoints were not available on the compassionate use program, the duration of therapy in this advanced MF population suggests that patients were experiencing benefit and tolerating treatment. The duration of therapy in patients with prior JAK2 inhibitor exposure was favorable compared to the expected survival in MF after ruxolitinib discontinuation. The SAE profile of pacritinib on compassionate use was consistent with that previously observed with pacritinib and with the end-stage treatment setting. These data support the use of pacritinib for long-term treatment of patients with MF, including those with cytopenias.

Authors

Claire Harrison,[1] Abdulraheem Yacoub,[2] Bart Scott,[3] Adam Mead,[4] Aaron T. Gerds,[5] Jean-Jacques Kiladjian,[6] Ruben Mesa,[7] Miklos Egyed,[8] Christof Scheid,[9] Valentin Garcia Gutierrez,[10] Jennifer O'Sullivan,[4] Sarah Buckley,[11] Kris Kanellopoulos[11] and John Mascarenhas[12]

[1]Guy's and St Thomas' NHS Foundation Trust, London, UK; [2]The University of Kansas Cancer Center, Kansas City, KS, USA; [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [4]University of Oxford, Oxford, UK; [5]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [6]Hôpital Saint-Louis, Université Paris Cité, Paris, France; [7]Mays Cancer Center at UT Health San Antonio, San Antonio, TX, USA; [8]Somogy County Mór Kaposi General Hospital, Kaposvár, Hungary; [9]Universitätsklinikum Köln (AöR), Cologne, Germany; [10]Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain; [11]CTI BioPharma Corp, Seattle, WA, USA and [12]Icahn School of Medicine at Mount Sinai, New York, NY, USA

Correspondence:
C. HARRISON - Claire.Harrison@gstt.nhs.uk

https://doi.org/10.3324/haematol.2022.282089

Received: September 30, 2022.
Accepted: December 21, 2022.
Early view: January 5, 2023.

Disclosures

CH has received Honoria from AbbVie, CTI BioPharma, Geron, Janssen, and Novartis; has acted in a consulting or advisory role for AOP, Celgene/BMS, Constellation Pharmaceuticals, CTI BioPharma, Galecto, Geron, Gilead, Janssen, Keros, Promedior, Roche, Shire, Sierra Oncology, and Novartis; has participated in speakers bureaus

for AbbVie, BMS, CTI BioPharma, Geron, Sierra Oncology, and Novartis; and has received research funding from BMS, Constellation Pharmaceuticals, and Novartis. AY has acted in a consulting or advisory role for AbbVie, Acceleron Pharma, Apellis, CTI BioPharma, Gilead, Incyte, Notable Labs., Novartis, Pfizer, PharmaEssentia, and Servier. BS has acted in a consulting or advisory role for Acceleron Pharma, Celgene, and Novartis; has participated in speakers bureaus for Alexion Pharmaceuticals, Celgene, Jazz Pharmaceuticals, and Novartis; has received honoraria from BMS, Incyte, and Taiho Oncology; and has received funding to their institution from Celgene. AM has received honoria for consulting or speakers' fees from AbbVie, BMS/Celgene, CTI BioPharma, Galecto, Gilead, Incyte, Karyopharm, Novartis, Pfizer, Sensyn, and Sierra Oncology; has received funding to their institution from BMS/Celgene, Galecto, and Novartis, and is a co-founder and equity holder in Alethiomics Ltd, a spin-off company of the University of Oxford. AG has acted in a consulting or advisory role for AbbVie, BMS, Constellation Pharmaceuticals, CTI BioPharma, Novartis, PharmaEssentia, and Sierra Oncology. JJK has acted in a consulting or advisory role for AbbVie, BMS, Incyte, Novartis, and PharmaEssentia. RM has acted in a consulting or advisory role for Constellation Pharmaceuticals, LaJolla Pharmaceutical, Novartis, and Sierra Oncology; has received research support from AbbVie, Celgene, Constellation Pharmaceuticals, CTI BioPharma, Genotech, Incyte, Promedior, and Samus; and has received grants from Mays Cancer Center P30 Cancer Center Support Grant from National Cancer Institute (CA054174). CS has acted in a consulting or advisory role from Amgen, BMS, Janssen, and Roche; has received travel and accommodation expenses from Amgen, BMS, Janssen; has received honoraria from Amgen, BMS, Janssen, Novartis, Pfizer, and Takeda; and has received funding to their institution from Janssen, Novartis, and Takeda. VGG has participated in speakers bureaus, received research funding, and acted in a consulting or advisory role for Incyte, Novartis, and Pfizer; has received travel and accommodation expenses reimbursed from BMS, Incyte, Novartis, and Pfizer. SB and KK are employed by, have stock ownership in, and have travel and accommodation expenses reimbursed by CTI BioPharma. JM has acted in a consulting or advisory role for AbbVie, BMS, Celgene, Constellation Pharmaceutical, CTI BioPharma, Galecto, Geron, Incyte, Kartos, Karyopharm, Novartis, PharmaEssentia, and Sierra Oncology; and has received funding to their institution from AbbVie, BMS, Celgene, CTI BioPharma, Geron, Incyte, Kartos, Merck, Novartis, PharmaEssentia, and Roche. ME and JO'S have no conflicts of interest to disclose.

Contributions

CH, SB, and JM were involved in conception and design of the study; all authors participated in analysis and interpretation of the data; medical writer JL drafted the manuscript; all authors critically revised the manuscript and provided final approval for submission and publication.

Acknowledgments

Medical writing and editorial assistance was provided under the direction of the authors by Janis Leonoudakis, PhD and funded by CTI BioPharma Corp.

Funding

This study was supported by CTI BioPharma Corp.

Data-sharing statement

No shared data are available.

References

1. Singer JW, Al-Fayoumi S, Ma H, Komrokji RS, Mesa R, Verstovsek S. Comprehensive kinase profile of pacritinib, a nonmyelosuppressive janus kinase 2 inhibitor. J Exp Pharmacol. 2016;8:11-19.
2. Oh S, Mesa R, Harrison C, et al. Retrospective analysis of anemia benefit of pacritinib from the PERSIST-2 trial. Clin Lymphoma Myeloma Leuk. 2022;22(Suppl 2):S327.
3. Mesa R, Vannucchi A, Mead A, et al. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial. Lancet Haematol. 2017;4(5):e225-e236.
4. Mascarenhas J, Hoffman R, Talpaz M, et al. Pacritinib vs best available therapy, including ruxolitinib, in patients with myelofibrosis: a randomized clinical trial. JAMA Oncol. 2018;4(5):652-659.
5. Gerds AT, Savona MR, Scott BL, et al. Determining the recommended dose of pacritinib: Results from the PAC203 dose-finding trial in advanced myelofibrosis. Blood Adv. 2020;4(22):5825-5835.
6. Scotch A, Kosiorek H, Scherber R, et al. Symptom burden profile in myelofibrosis patients with thrombocytopenia: lessons and unmet needs. Leuk Res. 2017;63:34-40.
7. Hernández-Boluda JC, Correa JG, Alvarez-Larrán A, et al. Clinical characteristics, prognosis and treatment of myelofibrosis patients with severe thrombocytopenia. Br J Haematol. 2018;181(3):397-400.
8. Masarova L, Alhuraiji A, Bose P, et al. Significance of thrombocytopenia in patients with primary and postessential thrombocythemia/polycythemia vera myelofibrosis. Eur J Haematol. 2018;100(3):257-263.
9. Sastow D, Mascarenhas J, Tremblay D. Thrombocytopenia in patients with myelofibrosis: pathogenesis, prevalence, prognostic impact, and treatment. Clin Lymphoma Myeloma Leuk. 2022;22(7):e507-e520.
10. Masarova L, Mesa RA, Hernández-boluda JC, Taylor JA. Severe thrombocytopenia in myelofibrosis is more prevalent than previously reported. Leuk Res. 2020;91:106338.
11. Newberry K, Patel K, Masarova L, et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. Blood. 2017;130(9):1125-1131.