Safety Analysis of Pacritinib in Patients With Myelofibrosis and Severe Thrombocytopenia

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John Mascarenhas,[1] Claire Harrison,[2] Aaron Gerds,[3] Josef Prchal,[4] Raajit Rampal,[5] Sarah Buckley,[6] Adam Craig,[6] Jennifer Smith,[6] John Volpone,[6] Karisse Roman-Torres,[6] Ruben Mesa[7]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Haematology Department, Guy's and St Thomas' NHS Trust, London, United Kingdom; [3]Leukemia Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH; [4]Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [5]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [6]CTI BioPharma, Seattle, WA; [7]Mays Cancer Institute at UT Health San Antonio MD Anderson, San Antonio, TX

INTRODUCTION

- Thrombocytopenia is a known adverse risk factor for patients with myelofibrosis (MF), which leads to decreased survival, increased risk of leukemia, increased risk of bleeding, increase in MF symptoms, and worse overall quality of life.[1-2]
- Patients with severe thrombocytopenia, or platelet count <50 × 10^9/L, were excluded from the pivotal studies for approved Janus kinase (JAK1/2) inhibitors, and continue to be excluded by most clinical trials; therefore, there is a serious unmet medical need for treatment of patients with myelofibrosis and severe thrombocytopenia.
- Pacritinib, an oral JAK2/interleukin-1 receptor-associated kinase 1 (IRAK1) inhibitor that does not inhibit JAK1[3], has demonstrated clinically significant activity in spleen volume and symptom reduction in patients with cytopenic MF, including those with severe thrombocytopenia, in phase 2 and 3 clinical studies.[4,5]
- Pacritinib has demonstrated clinical benefit at the full dose of 200 mg twice daily (BID) in patients with severe thrombocytopenia (platelet count <50 × 10^9/L) in the phase 2 dose finding PAC203 and phase 3 PERSIST-2 studies, but safety data have not been previously reported in this high-risk patient subset.[4,5]

OBJECTIVE

- To characterize the safety profile of pacritinib in patients with platelet count <50 × 10^9/L at the full dose of 200 mg BID, a retrospective analysis was performed on the data from the PAC203 and PERSIST-2 studies.

METHODS

- PAC203 was an open-label, randomized, dose finding phase 2 study of pacritinib in patients with MF previously treated with ruxolitinib (NCT04884191).[4]
  - PAC203 included patients who were intolerant of and/or resistant to ruxolitinib and who were randomized 1:1:1 to pacritinib 100 mg once daily (QD), 100 mg BID, or 200 mg BID.
  - Enhanced safety measures were incorporated in the study design to reduce the risk of high-grade bleeding and cardiac events.
- PERSIST-2 was a multicenter, randomized, phase 3 study of the safety and efficacy of pacritinib compared with best available therapy (BAT) in patients with MF and moderate-to-severe thrombocytopenia (platelet count ≤100 × 10^9/L; NCT02055781).[5]
  - In PERSIST-2, patients were randomized 1:1:1 to pacritinib 200 mg BID, pacritinib 400 mg QD, or BAT, including ruxolitinib or watch and wait; patients could be either JAK inhibitor naïve or have had prior exposure.
- In this analysis, patients with baseline platelet count <50 × 10^9/L treated with pacritinib 200 mg BID in PERSIST-2 and PAC203 or BAT in PERSIST-2 were included as the target population.
- Adverse events (AEs) were classified and graded according to the Common Terminology Criteria for Adverse Events; standardized Medical Dictionary for Regulatory Activities Query was used to assess bleeding and cardiac events.
- Major cardiac events were analyzed using major adverse cardiovascular events (MACE) classification.

RESULTS

Baseline Characteristics

- A total of 71 patients were analyzed as the pooled pacritinib 200 mg BID group (n=47 in PERSIST-2; n=24 in PAC203) and 42 patients in the PERSIST-2 BAT group.
- In addition to severe thrombocytopenia, patients in the pooled pacritinib group had profound anemia, with median hemoglobin 8.6 g/dL, and 34% were dependent on red blood cell transfusion at baseline (**Table 1**).

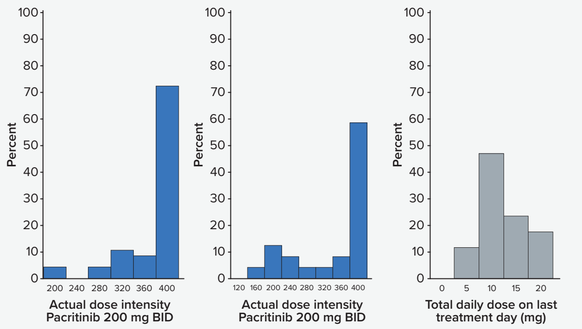
Table 1. Baseline Characteristics of Target Population[a] in PERSIST-2 and PAC203

	PERSIST-2		PAC203	Total (pooled)
	Pacritinib 200 mg BID (n=47)	BAT (n=42)	pacritinib 200 mg BID (n=24)	pacritinib 200 mg BID (N=71)
Median platelet count × 10^9/L	32	27	28	30
Median hemoglobin count, g/dL	9.2	9.4	8.1	8.6
Had prior JAK2 therapy, n (%)	21 (45)	21 (50)	24 (100)	45 (63)
Red blood cell transfusion dependent, n (%)	13 (28)	16 (38)	11 (46)	24 (34)
Platelet transfusion dependent, n (%)	7 (15)	7 (17)	6 (25)	13 (18)

[a]Based on the Common Terminology Criteria for Adverse Events grading criteria (platelet count <50 × 10^9/L is defined as grade 3 thrombocytopenia, and hemoglobin <10 g/dL is defined as grade 2 anemia), the majority of patients were deemed to have higher-grade thrombocytopenia and anemia at baseline.
BAT=best available therapy; BID=twice daily.

- Sustained dose intensity was observed for the pacritinib group, with median dose of 400 mg/day in PERSIST-2 and 396 mg/day in PAC203.
- In the BAT subgroup from PERSIST-2, among the patients who received ruxolitinib (n=17), the median post-titration dose was 10 mg/day (**Figure 1**).

Figure 1. Dose at Week 24 for Patients With Platelet Count <50 × 10^9/L



BAT=best available therapy; BID=twice daily.

- A total of 44% of patients treated with pacritinib and 21% treated with BAT had drug exposure ≥6 months.

Safety Analysis

- All-grade treatment-emergent AEs (TEAEs) and those leading to study drug discontinuation were observed at similar rates in the pooled pacritinib and BAT groups (**Table 2**).
- The patients in the pooled pacritinib group had a higher incidence of grade ≥3 and serious TEAEs compared with those receiving BAT, which included patients on supportive care strategies.
- The frequency of patients experiencing fatal TEAEs was lower in the pooled pacritinib group than in the BAT subgroup from PERSIST-2.

Table 2. Overview of Adverse Events in the Target Population in PERSIST-2 and PAC203

	PERSIST-2		PAC203	Total (pooled)
AE, n (%)	Pacritinib 200 mg BID (n=47)	BAT[a] (n=42)	pacritinib 200 mg BID (n=24)	pacritinib 200 mg BID (N=71)
TEAE (all grades)	46 (98)	38 (91)	24 (100)	70 (99)
Grade ≥3 TEAE	39 (83)	26 (62)	23 (96)	62 (87)
Treatment-emergent serious AE	28 (60)	16 (38)	16 (67)	44 (62)
Grade ≥3 treatment-emergent serious AE	25 (53)	15 (36)	14 (58)	39 (55)
TEAE leading to study drug discontinuation	10 (21)	7 (17)	4 (17)	14 (20)
TEAE with an outcome of death	6 (13)	8 (19)	3 (13)	9 (13)

[a]The most common BAT was ruxolitinib (40%) and watch and wait (31%).
AE=adverse event; BAT=best available therapy; BID=twice daily; TEAE=treatment-emergent adverse event.

- In the pooled pacritinib group, all-grade TEAEs were mostly driven by thrombocytopenia (32%) and gastrointestinal events, which included low-grade nausea (30%) and diarrhea (41%), which was manageable with over-the-counter antidiarrheals and resolved without leading to drug discontinuation (**Table 3**).
- The most common grade ≥3 AEs in the pooled pacritinib group included thrombocytopenia (32%) and anemia (27%).
- Rates of other commonly reported AEs in both trials were lower in the pooled pacritinib group compared with BAT including epistaxis and peripheral edema.

Table 3. Most Common and Grade ≥3 TEAEs of Interest in Myelofibrosis

	PERSIST-2				PAC203	Total (pooled)
AE, n (%)	Pacritinib 200 mg BID (n=47)	BAT[a] (n=42)	BAT=RUX (n=17)	BAT=Watch and wait (n=9)	pacritinib 200 mg BID (n=24)	pacritinib 200 mg BID (N=71)
All grade (≥25%)						
Thrombocytopenia	13 (28)	10 (24)	3 (18)	2 (22)	10 (42)	23 (32)
Anemia	14 (30)	7 (17)	2 (12)	1 (11)	6 (25)	20 (28)
Diarrhea	24 (51)	7 (17)	1 (6)	3 (33)	5 (21)	29 (41)
Nausea	15 (32)	7 (17)	4 (23)	3 (33)	6 (25)	21 (30)
Peripheral edema	11 (23)	11 (26)	4 (23)	4 (44)	5 (21)	16 (23)
Fatigue	7 (15)	6 (14)	2 (12)	2 (22)	9 (38)	16 (23)
Epistaxis	7 (15)	11 (26)	5 (29)	4 (44)	8 (33)	15 (21)
Grade ≥3						
Thrombocytopenia	13 (28)	10 (24)	3 (18)	2 (22)	10 (42)	23 (32)
Anemia	14 (30)	6 (14)	2 (12)	1 (11)	5 (21)	19 (27)
Diarrhea	1 (2)	0	0	0	1 (4)	2 (3)
Nausea	1 (2)	1 (2)	0	1 (11)	0	1 (1)
Peripheral edema	1 (2)	0	0	0	1 (4)	2 (3)
Fatigue	1 (2)	3 (7)	1 (6)	1 (11)	2 (8)	3 (4)
Epistaxis	4 (9)	0	0	0	1 (4)	5 (7)

[a]The most common BAT agents were ruxolitinib and watch and wait.
BAT=best available therapy; BID=twice daily; RUX=ruxolitinib; TEAE=treatment-emergent adverse event.

- The incidences of serious and grade ≥3 bleeding AEs were lower with pacritinib 200 mg BID in PAC203 than those reported with pacritinib 200 mg BID or BAT in PERSIST-2, likely attributable to the additional safety measures in PAC203 (**Table 4**).
- The incidence of cardiac events of any grade and those grade ≥3 were lower in the pooled pacritinib group compared with the BAT group; no patients in the pooled pacritinib group and 2 in the BAT group (1 fatal) had a MACE event.

Table 4. Summary of Hemorrhage AEs, Cardiac AEs, and MACE in the Target Population in PERSIST-2 and PAC203

	PERSIST-2		PAC203	Total (pooled)
AE, n (%)	Pacritinib 200 mg BID (n=47)	BAT[a] (n=42)	pacritinib 200 mg BID (n=24)	pacritinib 200 mg BID (N=71)
Treatment-emergent hemorrhage AEs (SMQ)[b]				
Any-grade bleeding AEs	23 (49)	26 (62)	18 (75)	41 (58)
Serious bleeding AEs	6 (13)	4 (10)	2 (8)	8 (11)
Grade ≥3 bleeding AEs	8 (17)	5 (12)	3 (13)	11 (16)
Treatment-emergent cardiac AEs (SMQ)[b]				
Any-grade cardiac AEs	16 (34)	19 (45)	13 (54)	29 (41)
Serious cardiac AEs	4 (9)	9 (21)	3 (13)	7 (10)
Grade ≥3 cardiac AEs	4 (9)	8 (19)	2 (8)	6 (9)
MACE category[c]				
MACE	0 (0)	2 (5)	0 (0)	0 (0)
MACE death (Grade 5)	0 (0)	1 (2)	0 (0)	0 (0)

[a]The most common BAT agents were ruxolitinib and watch and wait. [b]Bleeding and cardiac events defined by SMQ include the preferred terms in hemorrhage and cardiac arrhythmias, cardiac failure, ischemic heart disease, and embolic and thrombotic events, respectively.
[c]The MACE category: patients who experienced any of the following TEAEs: (1) fatal (grade 5) cardiac event; (2) ischemic stroke of any grade, based on the Preferred Term "cerebral infarction"; and (3) myocardial infarction of any grade.
AEs=adverse events; BAT=best available therapy; BID=twice daily; MACE=major adverse cardiac event; SMQ=standardized Medical Dictionary for Regulatory Activities query; TEAE=treatment-emergent adverse event.

CONCLUSIONS

- In this analysis of patients with cytopenic MF, including those who have severe thrombocytopenia, the safety profile of pacritinib 200 mg BID was comparable to BAT, which included supportive care and watch and wait.
- This analysis suggests that pacritinib 200 mg BID may represent the first fully dosed therapeutic option for patients with cytopenic MF, including severe thrombocytopenia.

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Presenting Author: John Mascarenhas, john.mascarenhas@mssm.edu