Platelet Response in Pacritinib-Treated Patients with Cytopenic Myelofibrosis: a Retrospective Analysis of PERSIST-2 and PAC203 Studies

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CONCLUSIONS

- Platelet (PLT) improvement meeting International Working Group (IWG) criteria occurs in a subset of myelofibrosis patients treated with pacritinib and does not seem to be explained by changes in spleen volume.
- Further studies are warranted to assess the correlation between hematologic improvement and bone marrow fibrosis reduction with pacritinib.
- It is possible that pacritinib's unique mechanism of action as an IRAK1 inhibitor could result in modulation of the bone marrow microenvironment and thrombopoiesis.

BACKGROUND

- Myelofibrosis is a myeloid malignancy characterized by clonal hematopoisis, bone marrow fibrosis and ineffective extramedullary hematopoiesis, resulting in progressive cytopenias.
- Thrombocytopenia is both prognostic of poor outcomes and predictive of treatment intolerance with the JAK1/2 inhibitor ruxolitinib, which exacerbates cytopenias.
- Pacritinib is a JAK1-sparing inhibitor of JAK2/IRAK1/ACVR1[1,2] that can be administered at full dose to patients regardless of baseline PLT count.
- While prior studies have shown that pacritinib is associated with PLT stability in most patients, PLT improvement has not been described outside of a recently published case report.[3]

AIM

- Here, we report rates of hematologic improvement in PLTs (HI-P) with pacritinib across two clinical trials, the phase 3 PERSIST-2 and the phase 2 PAC203 studies.

METHODS

- Patients with baseline PLT ≤100 x 10^9/L on the pacritinib 200 mg twice daily (BID) arms of the phase 3 PERSIST-2 study (randomized ≥12 weeks prior to study termination) or the phase 2 dose-finding PAC203 study were included, as were patients on the best available therapy (BAT) arm of the PERSIST-2 study over the treatment period (end of study treatment).
- Rates of platelet improvement and efficacy outcomes were compared between HI-P responders (those who meet IWG criteria) vs non-responders (those who did not meet IWG criteria) and include reduction in spleen volume, symptom score reductions, and bone marrow fibrosis.

HI-P was defined per International Working Group criteria[4]:

- Baseline PLT <20 x 10^9/L: increase to >20 x 10^9/L and by at least 100%
- Baseline PLT 20-100 x 10^9/L: absolute increase of ≥30 x 10^9/L

No platelet transfusions sustained over any 8 weeks while on treatment

RESULTS

Table 1. Baseline patient characteristics

Baseline Characteristics	PAC 200 mg BID		BAT	
	HI-P Responder N=19	Non-responder N=98	HI-P Responder N=4	Non-responder N=73
Age, median	66	68	58	69
PLT count (x10^9/L), median	63	45	58	52
Hemoglobin (g/dL), median	10.3	8.8	9.1	9.4
JAK2V617F mutation, n (%)	15 (79)	73 (74)	2 (50)	53 (73)
Requires RBC transfusion, n (%)	2 (10.5)	26 (27)	1 (25)	20 (27)
Prior JAK2 inhibitor, n (%)	13 (68)	65 (66)	2 (50)	35 (48)

RESULTS

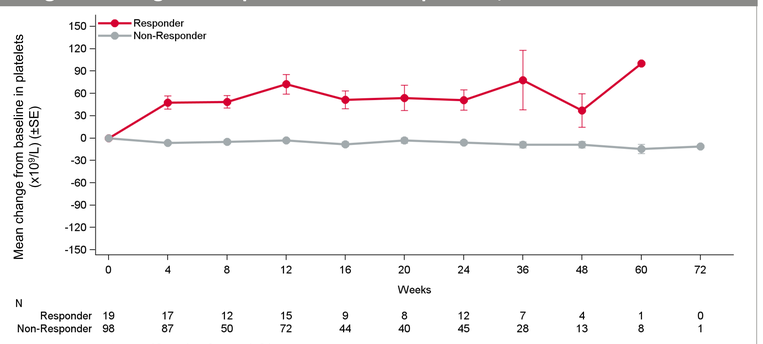
Baseline characteristics in HI-P responders and non-responders

- Of 117 patients randomized to pacritinib (75 from PERSIST-2, 42 from PAC203), 16% (n=19) experienced HI-P on study (as defined in methods; **Table 1**).
  - 14 of the 19 HI-P patients had sustained platelet improvement over ≥12 weeks.
- Among the HI-P responders, 32% of patients were ruxolitinib naïve (n=6), while the remaining 68% had prior ruxolitinib exposure (n=13), with a median dose of 10 mg BID.
- By contrast, only 5% (4/77) of patients on BAT achieved HI-P.

Platelet improvement in HI-P responders

- Platelet improvement was noted within the first 12 weeks in most HI-P responders treated with pacritinib, whereas platelet count remained stable, on average, among non-responders (**Figure 1**).

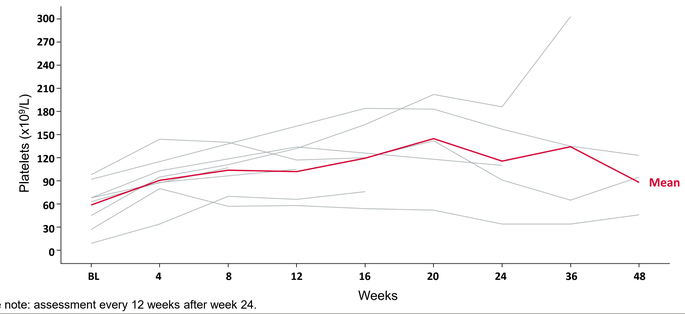
Figure 1. Mean change in platelet count from baseline over time on pacritinib 200 mg BID among HI-P responders vs non-responders, PERSIST-2 & PAC203



Please note: assessment every 12 weeks after week 24.

- A subset of patients with ruxolitinib exposure in previous 30 days (11/19) were analyzed to evaluate if the recent ruxolitinib exposure and washout of drug was responsible for HI-P.
  - Mean PLT count increased from 56 to 141 x 10^9/L at week 12 among these responders.
- In the remaining 8 patients without recent ruxolitinib exposure, PLT count increased from 59 to 102 x 10^9/L at week 12 (**Figure 2**).

Figure 2. Change in platelets over time, PERSIST-2 & PAC203, PAC 200 mg BID



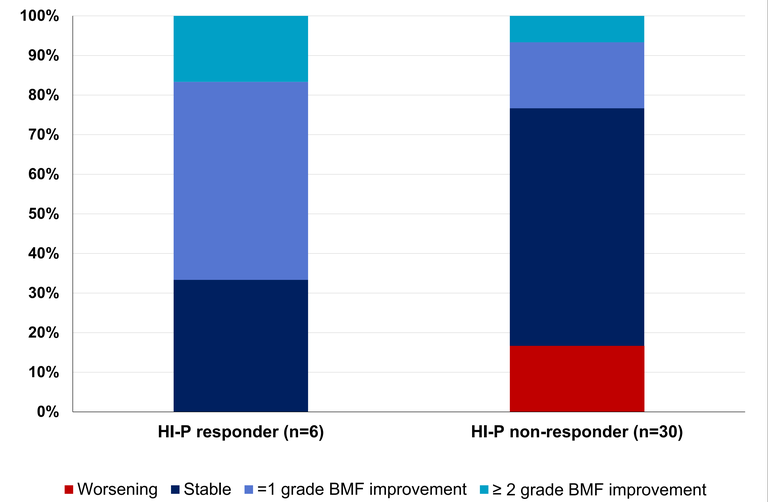
Please note: assessment every 12 weeks after week 24.

- There was no difference noted in the magnitude of spleen volume or symptom score reduction in HI-P responders vs non-responders.

Association between PLT increase and improvement in bone marrow fibrosis

- Among the 36 patients on pacritinib with available bone marrow data from baseline and week 24, HI-P responders were numerically more likely to have bone marrow fibrosis reduction (67%, n=4/6) compared to non-responders (23%, n=7/30, *P*=0.057, **Figure 3**).

Figure 3. Change in bone marrow fibrosis in HI-P responders vs non-responder, PERSIST-2 & PAC203, pacritinib 200 mg BID



Safety similar between HI-P responders and non-responders

- There was no difference in the rate of hemorrhagic events (by standardized MedDRA queries) in HI-P responders vs non-responders (47% vs 46%), though grade ≥3 bleeding was observed at lower frequency in responders compared to non-responders (10.5% vs 16%).
- Other commonly reported adverse events with pacritinib occurred at similar frequency between HI-P responders and non-responders.

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ABBREVIATIONS: BID, twice daily; BL, baseline; BMF, bone marrow fibrosis; HI-P, hematologic improvement in platelets; PAC, pacritinib; PLT, platelets; SE, standard error

REFERENCES: **1.** Singer et al. *J Exp Pharmacol*. 2016;8:11-19. **2.** Oh, et al. Blood Adv. 2023;7:5835–5842. **3.** Yacoub A, et al. *JCO Precis Oncol*. 2023;7:e2200523. **4.** Tefferi A, et al. *Blood.* 2013;122(8):1395–1398.

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