Retrospective Analysis of Anemia Benefit of Pacritinib from the PERSIST-2 Trial

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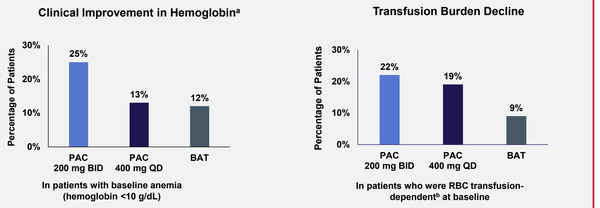
BACKGROUND

- Pacritinib (PAC) is an oral Janus kinase (JAK) 2/interleukin-1 receptor–associated kinase 1 (IRAK1) inhibitor, that does not inhibit JAK1.[1]
- Pacritinib is approved for patients with myelofibrosis (MF) who have severe thrombocytopenia (platelet count <50 x 10^9/L).
- The approved 200 mg twice daily (BID) dose of pacritinib was studied in a randomized Phase 3 study (PERSIST-2) showing improvements in spleen volume, symptom scores, as well as improvement in anemia and a decline in transfusion burden **(Figure 1)**.[2]
- Inhibition of Activin A receptor type 1 (ACVR1), also known as activin receptor-like kinase 2 (ALK2), which mediates hepcidin regulation, has been postulated as a mechanism for improving anemia in MF.[3,4]
- While pacritinib's anemia benefit has been attributed in part to IRAK1 inhibition, the role of ACVR1 inhibition has not previously been described.
- To date, only momelotinib is a known JAK2/ACVR1 inhibitor in development for MF.

Figure 1. Hematologic Benefits From Baseline to Week 24[2]



[a]International Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion-independence for ≥8 weeks prior.
[b]Gale criteria[5]: transfusion dependent defined as ≥2 RBC units/month in prior 90 days and transfusion independent as none.
BAT=best available therapy; BID=twice daily; BL=baseline; PAC=pacritinib; RBC=red blood cell.

OBJECTIVE

- To perform an *in vitro* analysis to explore pacritinib's inhibition of ACVR1.
- To assess pacritinib's impact on transfusion independence (TI) and hemoglobin among evaluable patients treated on the PERSIST-2 study.

METHODS

In Vitro Analysis

- The activity of pacritinib, the other JAK2 inhibitors momelotinib, fedratinib, ruxolitinib, and LDN193189 (a positive control), was assessed against ACVR1.
- Using the HotSpot assay from Reaction Biology Corporation a 10-dose IC_{50} (half maximal inhibitory concentration) assessment with 3-fold serial dilution starting at 10μM was performed.
- Kinase activity data were expressed as the percent remaining kinase activity in test samples compared to vehicle (dimethyl sulfoxide) reactions. IC_{50} values were obtained using Prism4 Software.

Study Design

- This analysis included patients with an available 24-Week visit (evaluable) from PERSIST-2 with platelet count ≤100x10^9/L randomized to PAC 200 mg BID, PAC 400 mg QD, or best available therapy (BAT).

METHODS

- Transfusion independence was defined as no red blood cell (RBC) transfusions and no hemoglobin level <8 g/dL; non-TI was defined as any RBC transfusions in 90 days prior to the first dose or a baseline hemoglobin <8 g/dL.
- Treatment comparisons were analyzed by the Fisher exact test. 95% confidence intervals were calculated using the Clopper Pearson method. Cumulative probabilities were estimated by the Kaplan-Meier method.

RESULTS

Pharmacodynamic Data

- On duplicate assays, pacritinib was shown to inhibit ACVR1 with an IC_{50} of 22.6 and 10.8 nM, with a mean IC_{50} of 16.7 nM (**Figure 2**).
  - Positive control LDN193189 had an IC_{50} of 20.4 and 32.4 nM respectively, with a mean IC_{50} of 26.4 nM.
  - Momelotinib's IC_{50} was 34.9 and 70.2 nM in the same respective assays.
  - Fedratinib had minimal activity; no activity was noted for ruxolitinib.

Figure 2. Inhibitory Strength of ACVR1[a]

	+ Control LDN 193189	PAC	MOM	FED	RUX
ACVR1 IC_{50} (nM) Replicate 1	20.4	22.6	70.2	312	>1000
ACVR1 IC_{50} (nM) Replicate 2	32.4	10.8	34.9	235	>1000
ACVR1 IC_{50} (nM) Mean	26.4	16.7	52.5	273	>1000

Legend: Higher potency → Lower potency

[a]Darker blue indicates higher potency (lower IC_{50})
ACVR1= Activin A receptor type 1; FED=fedratinib; MOM=momelotinib; PAC=pacritinib; RUX=ruxolitinib.

Baseline Characteristics

- Two study populations were analyzed:
  - Evaluable patients who were non-TI (had any transfusions or had hemoglobin <8 g/dL) at baseline.
  - Evaluable patients who had baseline hemoglobin <10 g/dL.
- Key baseline characteristics for these study populations are shown in Table 1.

Table 1. Key Baseline Characteristics

	Pacritinib 200 mg BID	Pacritinib 400 mg QD	BAT
Patients with any transfusions or hemoglobin <8 g/dL (non-TI)[a], n	**26**	**24**	**19**
Median age (IQR), years	66.5 (62.0 - 71.0)	68.5 (62.5 - 76.5)	70.0 (62.0 - 76.0)
Platelet count x 10^9/L, median (IQR)	48.0 (36.0 - 72.0)	55.0 (30.0 - 91.0)	56.0 (35.0 - 75.0)
Hemoglobin, g/dL, median (IQR)	8.5 (7.6 - 9.7)	8.4 (7.0 - 9.0)	8.6 (7.9 - 8.7)
RBC transfusions (unit/month), median (IQR)	1.6 (0.8 - 3.2)	1.7 (1.1 - 3.2)	1.7 (1.0 - 3.2)
Patients with hemoglobin <10 g/dL, n	**33**	**30**	**28**
Median age (IQR), years	65.0 (57.0 - 69.0)	69.0 (66.0 - 77.0)	66.5 (62.5 - 73.5)
Platelet count x 10^9/L, median (IQR)	58.0 (40.0 - 74.0)	47 (31.0 - 69.0)	59.0 (35.0 - 76.0)
Hemoglobin, g/dL, median (IQR)	8.5 (7.7 - 9.5)	8.6 (7.7 - 8.9)	8.6 (8.3 - 9.3)
RBC transfusions (unit/month), median (IQR)	1.6 (0.7 - 4.0)	1.6 (1.1 - 2.3)	1.6 (1.0 - 3.2)

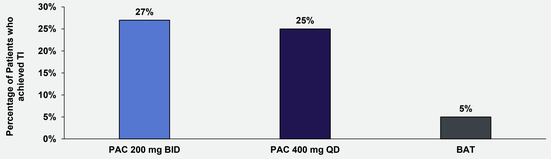
[a]Patients randomized 12 week prior to the clinical hold.
BAT=best available therapy; BID=twice daily; IQR=interquartile range; QD=once daily; RBC=red blood cell; TI=transfusion independence.

RESULTS

Transfusion Independence in Non-TI Patients at Baseline

- Among evaluable non-TI patients, the percentage who achieved TI over any 12-week intervals through week 24 was greater on pacritinib than BAT (**Figure 3**).

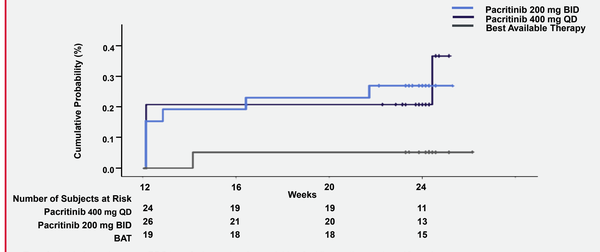
Figure 3. Patients Achieving Transfusion Independence (12-week Intervals)



BAT=best available therapy; BID=twice daily; PAC=pacritinib; QD=once daily.

- Among evaluable non-TI patients, the cumulative probability of TI was greater for both pacritinib 200 mg BID and 400 mg QD compared to BAT (**Figure 4**).

Figure 4. Cumulative Probabilities of Transfusion Independence[a]

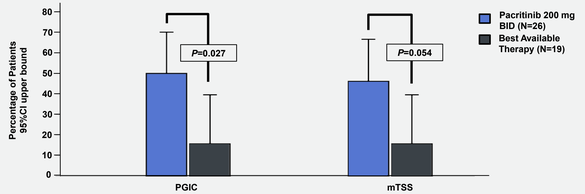


[a]Transfusion independence: no RBC transfusion and no hemoglobin <8 g/dL over the previous 12 weeks.
BAT=best available therapy; BID=twice daily; QD=once daily; RBC=red blood cells.

Symptom Improvement in Non-TI Patients at Baseline

- A greater proportion of evaluable non-TI patients reported "much improved" or "very much improved" symptoms with pacritinib 200 mg BID (FDA approved dose) compared to BAT (50% vs 16%; *P*=0.027; **Figure 5**).

Figure 5. Symptom Improvement at Week 24



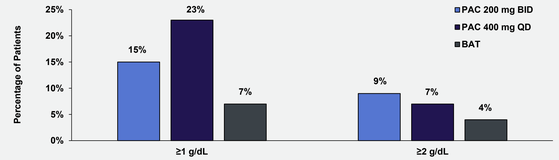
BID=twice daily; mTSS=modified total symptom score; PGIC=Patient's Global Impression of Change.

- More evaluable non-TI patients who received 200 mg BID of pacritinib experienced a notable ≥50% reduction in modified total symptom score (mTSS) compared to those who received BAT (46% vs 16%; *P*=0.054; **Figure 5**).

Hemoglobin Improvement in Patients with Baseline Anemia

- Among evaluable patients with baseline hemoglobin <10 g/dL, the percentage who achieved ≥1 g/dL or ≥2 g/dL improvement at any time through week 24 was higher in pacritinib groups than BAT **(Figure 6)**.

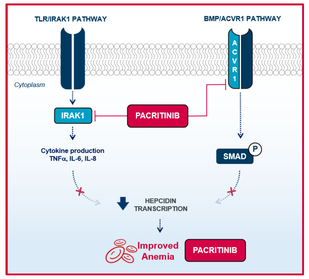
Figure 6. Hgb Improvement Among Patients with Baseline Hgb <10 g/dL



BAT=best available therapy; BID=twice daily; Hgb=hemoglobin; PAC=pacritinib; QD=once daily.

Figure 7. Hypothesized Mechanism of Action of Pacritinib

ACVR1 is a receptor kinase that controls the expression of the peptide hormone hepcidin. Inhibition of ACVR1 reduces production of hepcidin, which leads to increased iron availability for erythropoiesis. In parallel, inhibition of IRAK1 contributes to the reduction of downstream cytokines, particularly interleukin-6, which also impacts hepcidin expression. The unique kinase inhibition profile of pacritinib provides a dual mechanism for the improvement of anemia.



CONCLUSIONS

- **Pacritinib is a highly potent inhibitor of ACVR1 with greater potency than other JAK2 inhibitors.**
- **In evaluable non-TI patients, pacritinib therapy improved transfusion-independence and symptoms of myelofibrosis.**
- **The anemia benefit of pacritinib is potentially related to inhibition of ACVR1 and IRAK-1.**
- **These data suggest an important role for pacritinib in addressing anemia in patients with myelofibrosis.**

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