Pacritinib Is a Potent ACVR1 Inhibitor with Significant Anemia Benefit in Patients with Myelofibrosis

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BACKGROUND

- Anemia is present in approximately 40% of myelofibrosis (MF) patients at diagnosis, develops in almost all MF patients over the course of the disease,[1] and is associated with poor prognosis.[2]
- Anemia in MF is multifactorial with inflammation driven by aberrant cytokine production thought to be a primary cause.[3]
- Disease-related inflammation leads to increased hepcidin production which results in functional iron deficiency and impaired erythropoiesis.[4,5]
- It has been postulated that reducing hepcidin levels by inhibiting the hepcidin regulator activin A receptor, type 1 (ACVR1)/ activin receptor-like kinase-2 (ALK2),[6] could be a viable therapeutic strategy for improving anemia.
- Pacritinib is a JAK2/IRAK1 inhibitor[7] approved by the Food and Drug Administration (FDA) in the United States for patients with MF and thrombocytopenia which has demonstrated anemia benefit in these patients.
  - In the phase 3 PERSIST-2 study, patients on pacritinib 200 mg BID experienced higher rates of clinical improvement in hemoglobin (≥2 g/dL increase or RBC TI for ≥8 weeks) at week 24 compared to those treated with best available therapy (BAT).[8]
- The mechanism behind / extent of pacritinib's anemia benefit has not been fully described.

OBJECTIVES

- Assess pacritinib's in vitro potency against ACVR1 and its ability to reduce hepcidin
  - ACVR1 has been implicated in anemia of inflammation in patients with myelofibrosis[6,9]
- Describe the impact of pacritinib 200 mg BID on RBC transfusion independence in the Phase 3 PERSIST-2 study

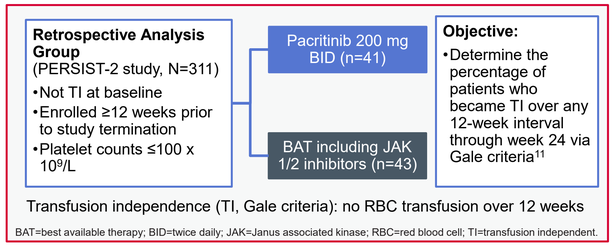
METHODS

- Potency of JAK2 inhibitors (pacritinib, momelotinib, fedratinib, and ruxolitinib) against ACVR1 assessed by in vitro HotSpot assay (Reaction Biology Corp)
  - IC_{50} calculated using 3-fold serial dilutions starting at 10 μM
  - Potency = ratio of clinical C_{max}: IC_{50}
- Compared IC_{50} to clinical drug concentration
  - Modeled concentration-time curves of free drug using R (v 4.1.1). For momelotinib, mean time-concentration data captured from medical literature and digitized, including the active M21 metabolite.[10]
- Immunoblot of pSMAD (downstream of ACVR1) and qRT-PCR of hepcidin in HepG2 human liver cancer cells stimulated with BMP6 in the presence of JAK2 inhibitors (pacritinib, momelotinib, fedratinib, and ruxolitinib).

PERSIST-2 Study Design

- In PERSIST-2, patients were randomized 1:1:1 to pacritinib 200 mg twice daily (BID), pacritinib 400 mg once daily (QD), or best available therapy (BAT).[8]
- Focus of this analysis was on the approved dose of pacritinib 200 mg BID and BAT.
  - Of these patients who were *not* transfusion independent (defined as any transfusion at baseline) and had enrolled ≥12 weeks prior to study termination were included in this retrospective analysis.

Figure 1. PERSIST-2 Analysis of Transfusion Independence



BAT=best available therapy; BID=twice daily; JAK=Janus associated kinase; RBC=red blood cell; TI=transfusion independent.

RESULTS

Pharmacodynamic Data

- Pacritinib is 4 times more potent than momelotinib against ACVR1 (**Table 1**).

Table 1. Inhibitory strength of ACVR1

	+ Control LDN 193189[a]	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
Mean ACVR1 IC_{50} (nM)	**26.4**	**16.7**	**52.6**	**273.5**	**>1000**
Potency[b] (C_{max}:IC_{50})	**N/A**	**12.7**	**3.2**	**1.0**	**<0.01**

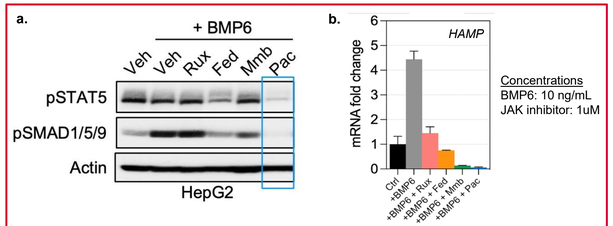
[a]LDN 193189 is an ACVR1 inhibitor.
[b]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

- Modeling concentration-time curves showed that pacritinib steady state drug concentration at the 200 mg BID dose exceeds ACVR1 IC_{50} for the entire day (24 hours); by contrast, momelotinib plasma concentration at the 200 mg QD dose exceeds IC_{50} for ~9 hours.
  - When accounting for momelotinib and M21 (active metabolite), exposure exceeds ACVR1 IC_{50} approximately 14 hours per day.

Pacritinib Decreases Hepcidin Expression In Vitro

- Pacritinib decreases SMAD phosphorylation (downstream of ACVR1) (**Figure 2a**)
- Pacritinib decreases HAMP (hepcidin) mRNA levels (**Figure 2b**)

Figure 2. Pacritinib Decreases Hepcidin Expression In Vitro



BMP6=bone morphogenic protein 6; Ctrl=control; Fed=Fedratinib; Mmb=momelotinib; Pac=pacritinib; Rux=ruxolitinib; Veh=vehicle.

Baseline Characteristics

- BAT was comprised of 42% ruxolitinib (median 5 mg QD), 26% erythroid support (including danazol, erythroid support agents, immunomodulatory drugs, and steroids) and 19% watch and wait only.
- Erythroid support agents were prohibited on the pacritinib arm.

Table 2. Baseline Characteristics of Non-Transfusion Independent Patients

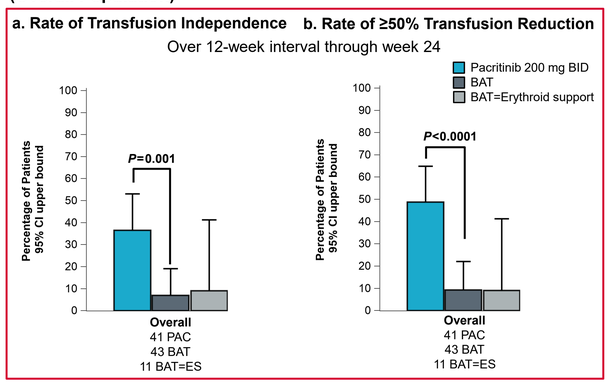
Characteristics	PAC 200 mg BID n=41	BAT n=43
Age (years), median	67	70
Primary MF	83%	63%
Time since MF diagnosis in years, median	2.5	2.9
Prior JAK2 inhibitor	56%	58%
Platelet count (x10^9/L), median	41	43
Hemoglobin (g/dL), median	8.7	8.6
RBC transfusions/month (prior 90 days), median	1.5	1.9
$JAK2^{V617F}$ mutation, n Allele burden <50%	35 74%	34 74%

BAT=best available therapy; JAK=Janus associated kinase; MF=myelofibrosis; PAC=pacritinib; RBC=red blood cell.

Rates of Transfusion Independence and Reduction

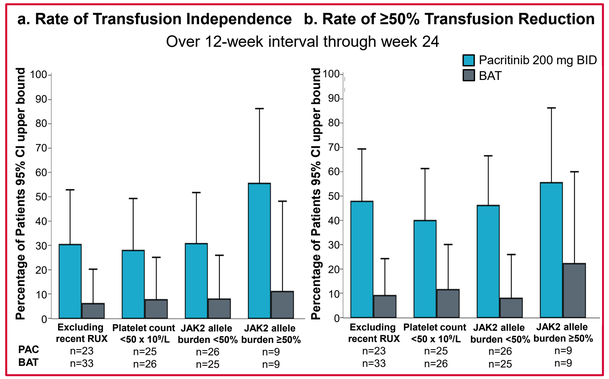
- A significantly greater proportion of patients on pacritinib 200 mg BID achieved TI (37%) compared to BAT (7%) over any 12-week interval through week 24 (*P*=0.001) (**Figure 3a**).
  - Among patients who received erythroid supportive agents as BAT, the TI conversion rates were similar to the overall BAT group (9%).
- The percentage of patients who achieved a ≥50% reduction in transfusion rate over any 12-week interval was significantly higher on pacritinib (49%) compared to BAT (9%; *P*<0.0001) and BAT=erythroid support (9%) (**Figure 3b**).

Figure 3. Rate of Transfusion Independence and Reduction (Overall Population)



- The effect of pacritinib on TI conversion (**Figure 4a**) and transfusion reduction (**Figure 4b**) was maintained in patients who had not received ruxolitinib within 30 days prior to treatment initiation.
- Similar trends were seen in the subgroup of patients with baseline platelet counts <50 x 10^9/L, as well as in those with both low and high JAK2V617F allele burden (**Figure 4a** and **4b**).

Figure 4. Rate of Transfusion Independence and Reduction (in Subgroups)



Survival Trend on Pacritinib

- Among patients who were not transfusion independent at baseline, hazard ratio (HR) = 0.61 (95% confidence interval [CI]: 0.22-1.68) (**Figure 5**).
- After adjusting for baseline transfusion rate HR_{adj} = 0.64 (95% CI: 0.23-1.76)

Figure 5. Overall Survival

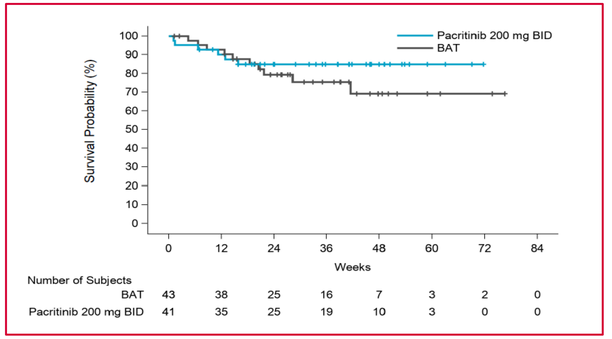
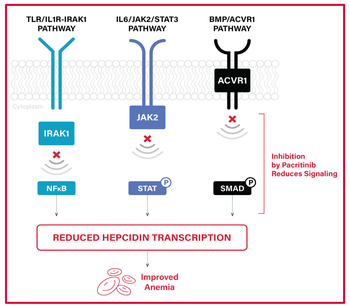


Figure 6. Proposed Pacritinib Mechanism of Action



- 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.
- Hepcidin reduction ameliorates anemia of inflammation that occurs in myelofibrosis.
- Potent, 24-hour inhibition of ACVR1 may function in conjunction with IRAK1 and JAK2 inhibition to reduce level of sequestered iron for erythropoiesis.

CONCLUSIONS

- Pacritinib is a potent ACVR1 inhibitor (~4x greater potency than momelotinib).
- Pacritinib is the only known JAK2 inhibitor that provides full-day inhibition of ACVR1 at full approved dose.
- Pacritinib reduces hepcidin levels in vitro.
- Pacritinib therapy results in transfusion independence in patients with myelofibrosis who require red blood cell transfusions.
- Due to its unique mechanism of action as a JAK2/IRAK1/ACVR1 inhibitor, pacritinib may provide a therapeutic option that affords spleen, symptom, and anemia benefit for patients with myelofibrosis.

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