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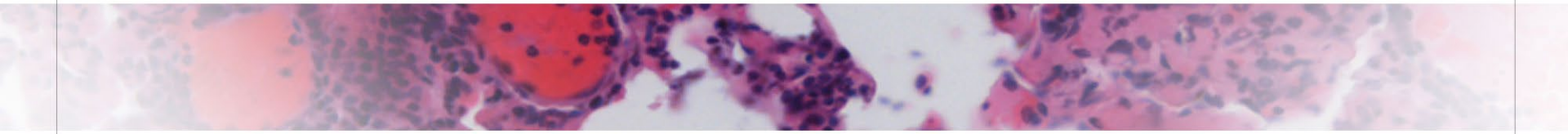

Pacritinib Is a Potent ACVR1 Inhibitor with Significant Anemia Benefit in Patients with Myelofibrosis

Session 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Towards Personalized Medicine in Myeloproliferative Neoplasms and Mastocytosis: New and Repurposed Drugs for Unmet Clinical Needs

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Anemia in Myelofibrosis

- Present in ~40% of MF patients at diagnosis[1]
- Develops in almost all MF patients over the course of disease[1]
- Associated with poor prognosis[2]
- Multifactorial[3]
  - Disease-related inflammation
  - Marrow fibrosis
  - Splenic sequestration
  - Drug-induced
- Other approved JAK2 inhibitors may exacerbate anemia within weeks of first dose[4,5]

JAK=Janus associated kinase; MF=myelofibrosis.

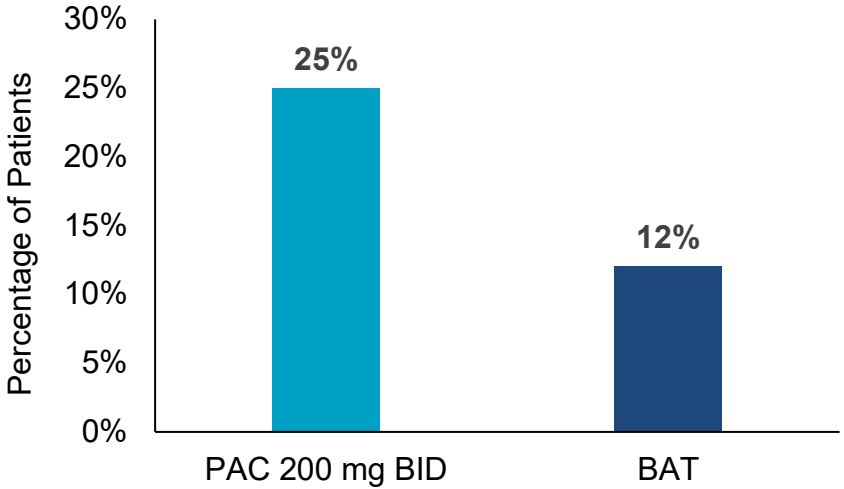
[1] Tefferi A, et al. *Mayo Clin Proc*. 2012;87(1):25-33. [2] Nicolosi M, et al. *Leukemia*. 2018;32:1254-58 [3] Naymagon L, Mascarenhas J. *Hemasphere*. 2017;1(1):e1. [4] Verstovsek S, et al. *Haematologica*. 2015;100(4). [5] Pardanani A, et al. *JAMA Oncology*. 2015;1(5):643-51.

Pacritinib in Cytopenic Myelofibrosis

- Approved in patients with MF who have a platelet count <50x10^9/L
- Able to be administered at the full approved dose (200 mg BID) regardless of cytopenias[1-3]
- Demonstrated hemoglobin improvement in randomized PERSIST-2 study[2]
- The mechanism behind / extent of anemia benefit has not been fully described

Clinical Improvement in Hemoglobin[2]

PERSIST-2, Week 24



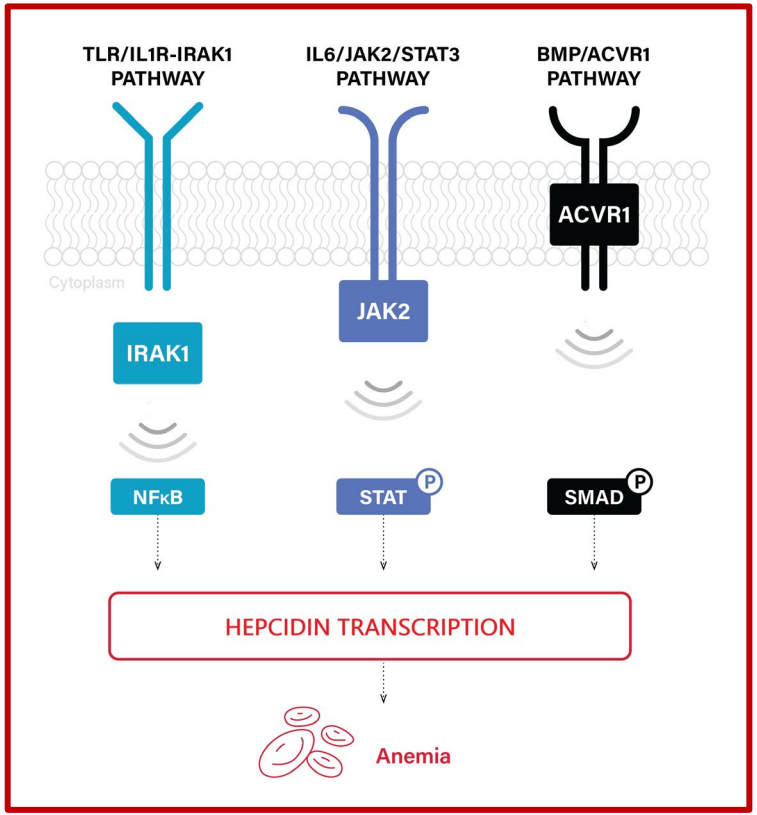
IWG criteria: among patients with baseline hemoglobin <10 g/dL, increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks

BAT=best available therapy; BID=twice daily; IWG= ; MF=myelofibrosis; RBC=red blood cell.

[1] Mesa R, et al. *Lancet Oncology*; 2017. [2] Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. [3] Gerds A, et al. *Blood Advances*. 2020;4(22):5825-35.

Aims

- **Aim 1**: 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[1,2]
- **Aim 2**: describe the impact of pacritinib 200 mg BID on RBC transfusion independence in the Phase 3 PERSIST-2 study



ACVR1= Activin A receptor type 1; BID=twice daily; JAK2=Janus associated kinase 2; IL6=interleukin-6; IRAK=interleukin receptor-associated kinase; RBC=red blood cell.
[1] Oh ST, et al. *Blood Advances*. 2020. [2] Asshoff M, et al. *Blood*. 2017.

Methods: Inhibition of ACVR1 *in vitro*

- Potency of JAK inhibitors (PAC, MMB, RUX, FED) against ACVR1 (ALK2) 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[1].
- Immunoblot of pSMAD (downstream of ACVR1) and qRT-PCR of hepcidin in HepG2 human liver cancer cells stimulated with BMP6 in the presence of JAK inhibitors (PAC, MMB, RUX, FED).

ACVR1= Activin A receptor type 1; BMP6=bone morphogenetic protein 6; C_{max}=highest concentration of a drug in the blood; FED=fedratinib; IC_{50}=half maximal inhibitory concentration; MMB=momelotinib; PAC=pacritinib; pSMAD=phospho-SMAD (downstream of ACVR1); RUX=ruxolitinib.

[1] Zheng et al. *Drug Meta Dispos*; 2018.

Pacritinib Is a Potent ACVR1 Inhibitor

- **Pacritinib is ~4x more potent** than momelotinib against 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
Replicate 1 ACVR1 IC_{50} (nM)	20.4	22.6	70.2	312.0	>1000
Replicate 2 ACVR1 IC_{50} (nM)	32.4	10.8	34.9	235.0	>1000
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

Legend

Higher potency

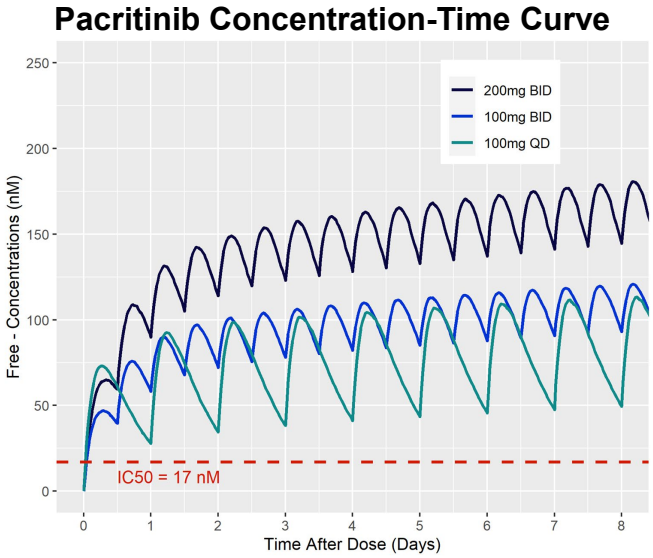
Lower potency

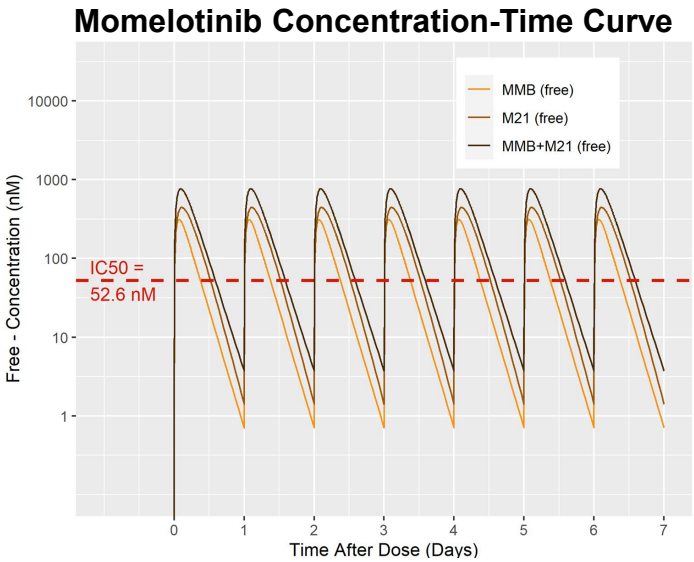
[a]LDN 193189 is an ACVR1 inhibitor.
[b]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

ACVR1= Activin A receptor type 1; FED=fedratinib; IC_{50}=half maximal inhibitory concentration; MOM=momelotinib; PAC=pacritinib; RUX=ruxolitinib.

Pacritinib Is a Potent ACVR1 Inhibitor

- Pacritinib concentration exceeds ACVR1 IC_{50} **100% of the time at all dose levels**
- Momelotinib concentration exceeds ACVR1 IC_{50} **55% of the time only** (accounting for both momelotinib and its metabolite [M21])

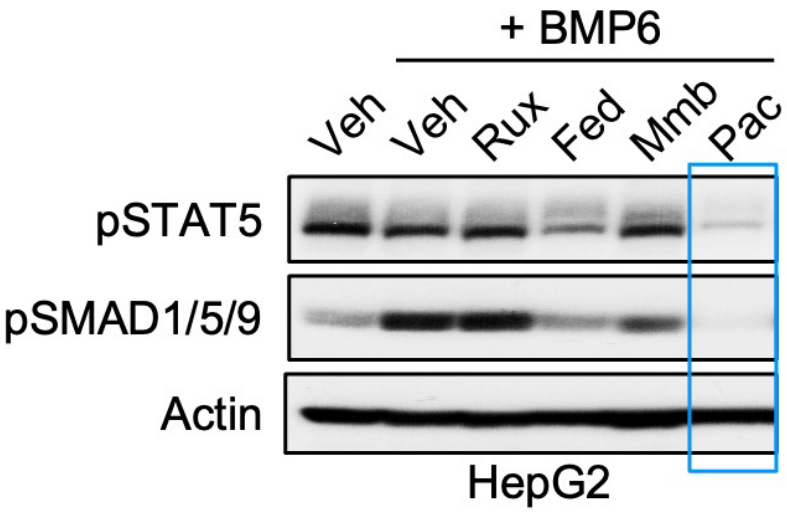




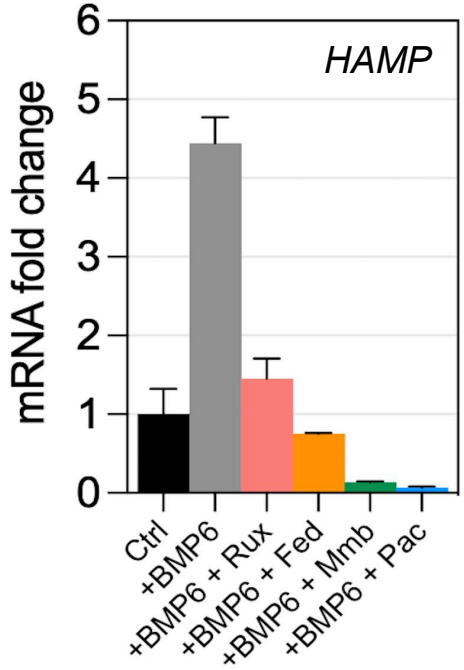
ACVR1= Activin A receptor type 1; BID=twice daily; IC_{50}=half maximal inhibitory concentration; MMB=momelotinib; QD=once daily.

Pacritinib Decreases Hepcidin Expression *in vitro*

- **Pacritinib decreases SMAD phosphorylation** (downstream of ACVR1)



- **Pacritinib decreases *HAMP* (hepcidin) mRNA levels**



Concentrations
BMP6: 10 ng/mL
JAK inhibitor: 1uM

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

Methods: Analysis of Transfusion Independence

- Evaluated pacritinib 200 mg BID (approved dose) and best available therapy (BAT) on PERSIST-2 study[1]

PERSIST-2 Population
- Myelofibrosis
- Platelets ≤100 x 10^9/L
- Prior JAK inhibitor therapy allowed

Randomization
- 1:1:1
- N=311

Pacritinib 200 mg BID

Pacritinib 400 mg QD

Best Available Therapy

Co-Primary Endpoints
- Spleen volume response
- Total symptom score response

- Among patients who were not TI at baseline and who were randomized ≥12 weeks prior to study termination, **what percentage became TI on study through week 24**?
  - TI (Gale criteria): no RBC transfusion over 12 weeks
  - TI (SIMPLIFY criteria): no RBC transfusion & no hemoglobin <8 g/dL over 12 weeks

BID=twice daily; QD-once daily; RBC=red blood cell; TI=transfusion independence.

[1] Mascarenhas et al. *JAMA Oncology*. 2018.

Baseline Patient Characteristics

PERSIST-2, Non-TI patients (Gale criteria)

Characteristic	Pacritinib 200 mg BID N=41	BAT N=43
Age in years, median	67	70
Primary myelofibrosis	83%	63%
Time since diagnosis in years, median	2.5	2.9
Prior JAK2 inhibitor	56%	58%
Platelet count $x10^9$/L, median	41	43
Hemoglobin in 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 composition

- **42% ruxolitinib**
  - Median 5 mg QD
- **26% erythroid support**
  - Danazol, ESAs, IMiDs, steroids
- **19% watch and wait only**

BAT=best available therapy; ESA=erythropoiesis-stimulating agents; IMiDs=immunomodulatory drugs; JAK=Janus associated kinase; QD=once daily; RBC=red blood cell; TI-transfusion independence.

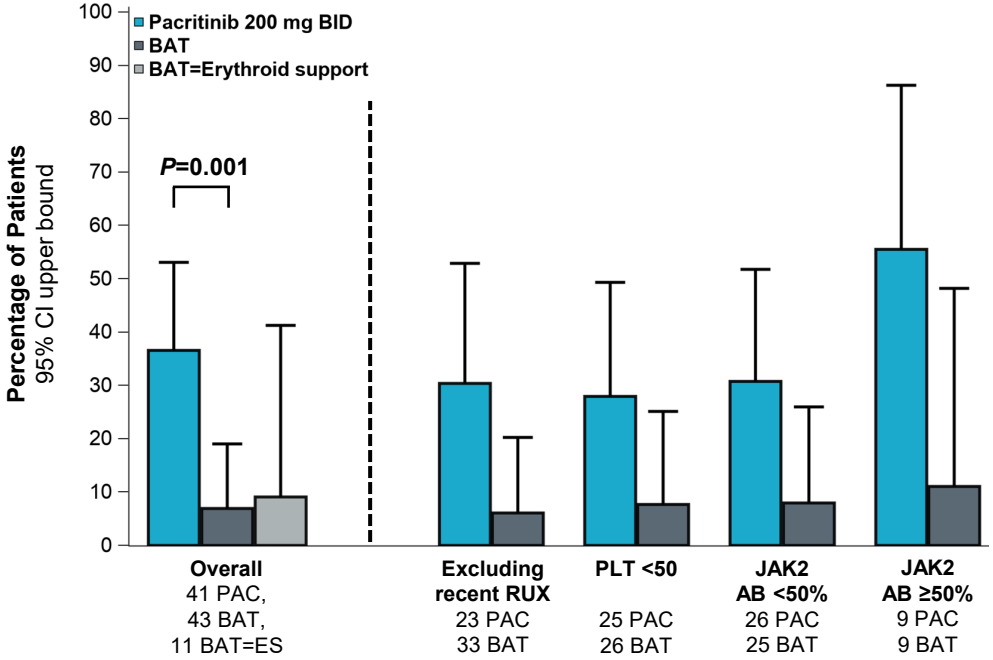
More Pacritinib Patients Achieved TI (Gale)

TI Conversion Rate

Pacritinib N=41	BAT N=43	*P*-value
37%	7%	0.001

- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
  - Erythroid support agents were prohibited on the pacritinib arm

Rate of TI (Gale criteria) through Week 24



AB=allele burden; BAT=best available therapy; ES=erythroid support; JAK=Janus associated kinase; PAC=pacritinib; PLT=platelets; recent RUX=no ruxolitinib in prior 30 days; TI=transfusion independence.

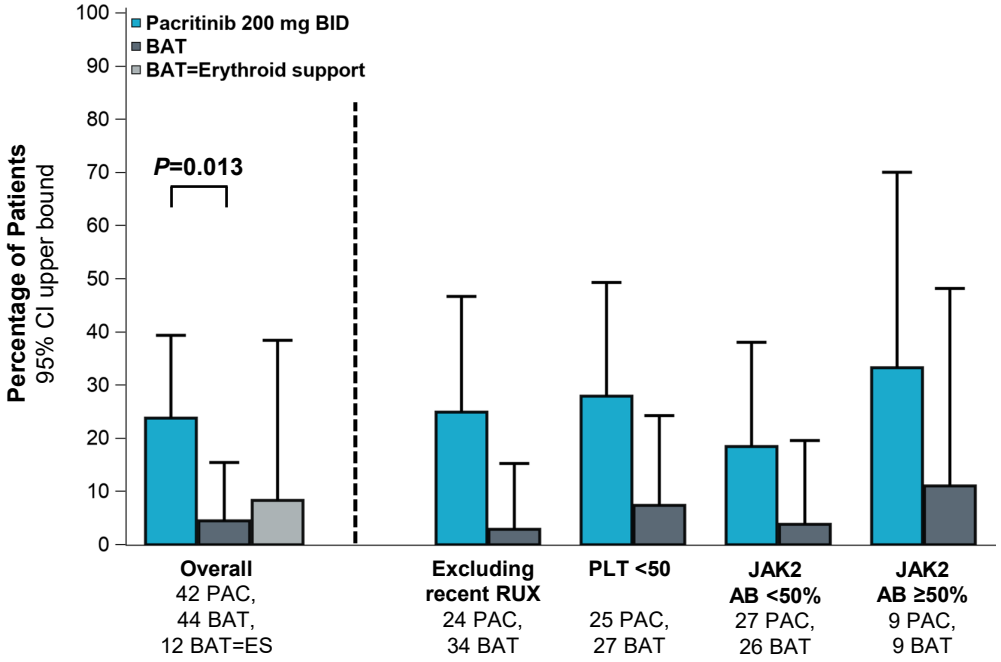
More Pacritinib Patients Achieved TI (SIMPLIFY)

TI Conversion Rate

Pacritinib N=42	BAT N=44	*P*-value
24%	5%	0.013

- Similar results based on SIMPLIFY criteria for TI

Rate of TI (SIMPLIFY criteria) through Week 24

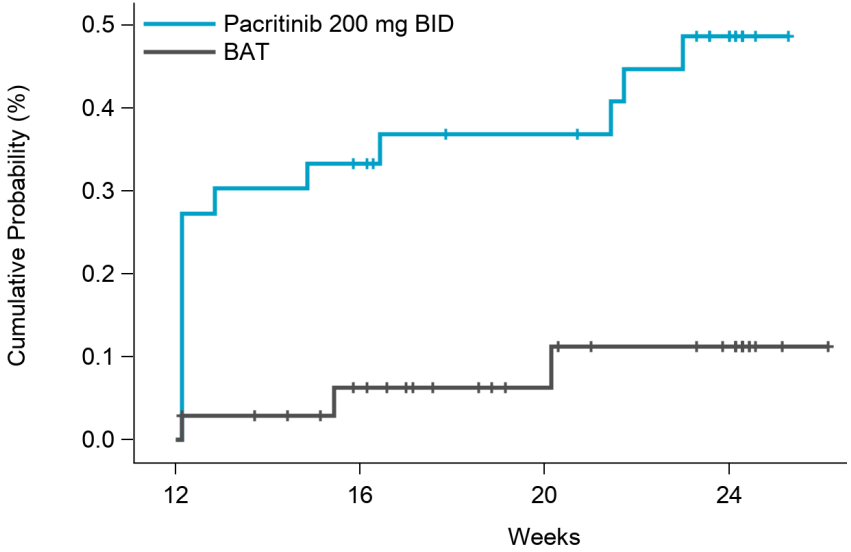


AB=allele burden; BAT=best available therapy; ES=erythroid support; JAK=Janus associated kinase; PAC=pacritinib; PLT=platelets; recent RUX=no ruxolitinib in prior 30 days; TI=transfusion independence.

TI Conversion Can Occur Late in Treatment

- Many responses occurred early during treatment
- Some responses occurred after several months on treatment

Cumulative Incidence of TI (Gale criteria)



Number of Subjects				
Pacritinib 200 mg BID	33	21	17	10
BAT	34	27	19	14

BAT=best available therapy; BID=twice daily; TI=transfusion independence.

More PAC Patients Had ≥50% Transfusion Reduction

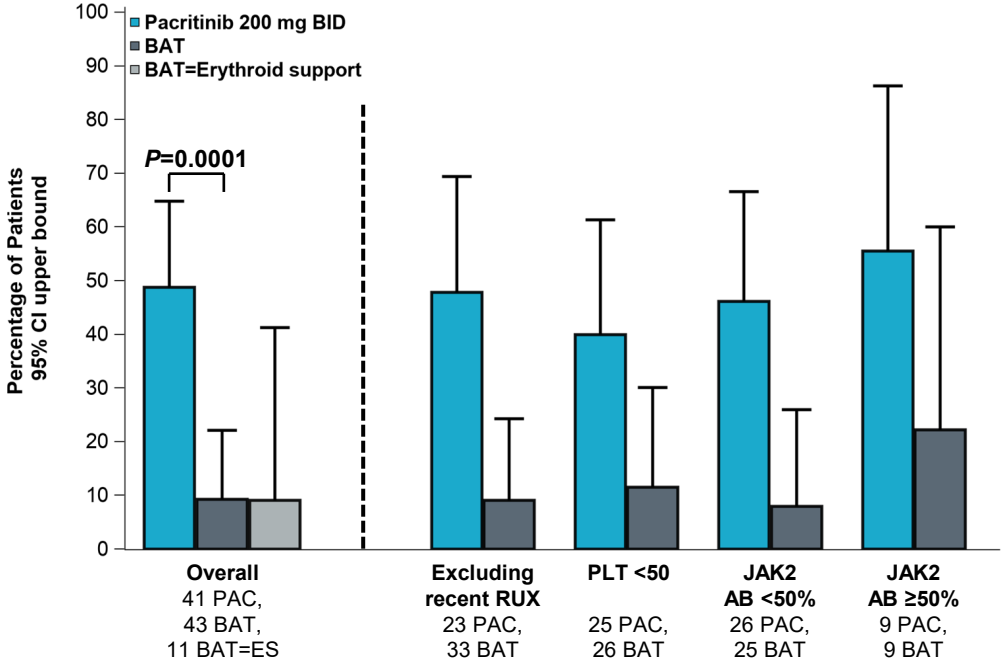
Transfusion Reduction

Pacritinib N=41	BAT N=43	*P*-value
49%	9%	0.0001

- Clinically significant reduction in transfusion burden more common on pacritinib

Rate of ≥50% Transfusion Reduction

Over 12-week interval through week 24

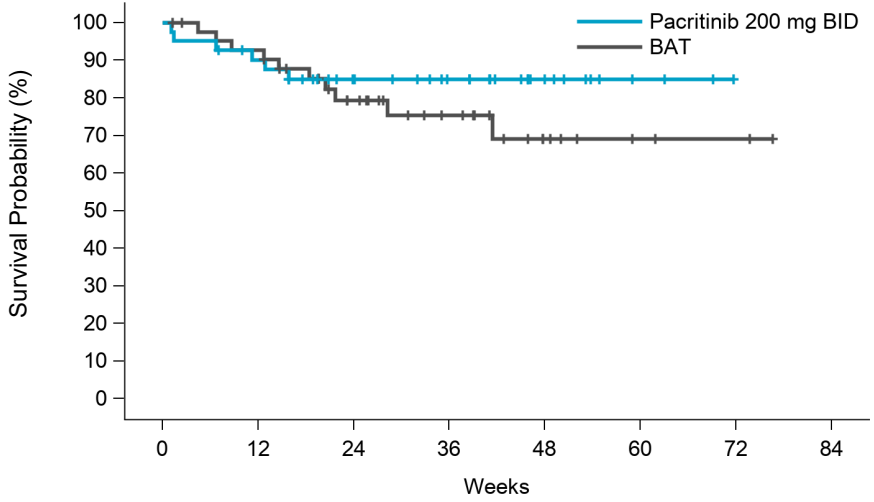


AB=allele burden; BAT=best available therapy; ES=erythroid support; JAK=Janus associated kinase; PAC=pacritinib; PLT=platelets; recent RUX= no ruxolitinib in prior 30 days; TI=transfusion independence.

Survival Trend on Pacritinib

- Among patients who were not transfusion independent at baseline:
  - **HR = 0.61** (95% CI: 0.22-1.68)
- After adjusting for baseline transfusion rate:
  - HR_{adj} = 0.64 (95% CI: 0.23-1.76)

Overall Survival



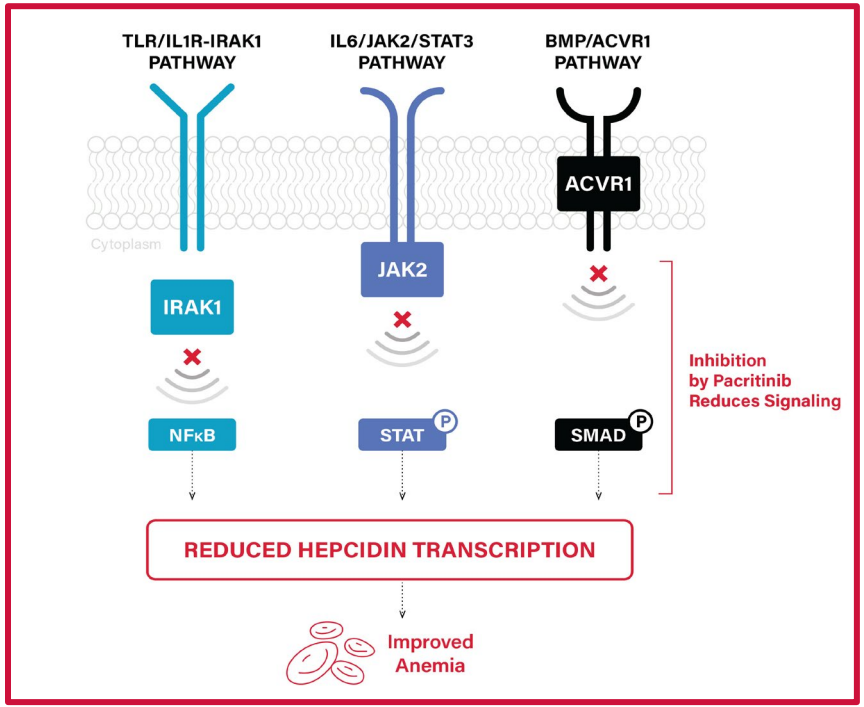
Number of Subjects								
BAT	43	38	25	16	7	3	2	0
Pacritinib 200 mg BID	41	35	25	19	10	3	0	0

BAT=best available therapy; BID=twice daily; CI=confidence interval; HR=hazard ratio; HR_{adj}=adjusted HR.

Hypothesized Mechanism of Anemia Benefit

- **Potent, 24-hour inhibition of ACVR1** may function in conjunction with IRAK1 and JAK2 inhibition to reduce levels of hepcidin

- Hepcidin reduction ameliorates anemia of inflammation that occurs in myelofibrosis



ACVR1= Activin A receptor type 1; JAK2=Janus associated kinase 2; IL6=interleukin-6; IRAK=interleukin receptor-associated kinase.

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 all doses
- 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