The Oral JAK2/IRAK1 Inhibitor Pacritinib Demonstrates Spleen Volume Reduction in Myelofibrosis Patients Independent of JAK2 V617F Allele Burden

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BACKGROUND

JAK2 Allele Burden in Myelofibrosis

- In patients with primary JAK2-mutated MF, lower JAK2 allele burden is associated with poor prognosis and poor response to treatment.[1-3]
- Patients with low allele burden (variant allele frequency <50%) have[1,2]
  - More anemia and leukopenia
  - Shorter overall survival
  - 5.5-fold lower chance of achieving a spleen volume response (SVR) with ruxolitinib[3]
- Patients with low JAK2 allele burden represent an area of unmet medical need as they are high-risk and underserved by available therapies.

Pacritinib as Therapy for Myelofibrosis

- Pacritinib is an oral JAK2/IRAK1 inhibitor[5]
- Unlike other JAK2 inhibitors, pacritinib does not inhibit JAK1[5]
- Pacritinib leads to significant improvements in spleen volume response (SVR) compared to best available therapy (BAT) in two Phase 3 studies (PERSIST-1 and -2).[6,7]

PERSIST-1

Key Eligibility	Randomization		Primary Endpoint
• Primary or secondary MF • Any platelet count • No prior treatment with JAK2 inhibitors	• 2:1 pacritinib vs. BAT • N=327	Pacritinib 400mg QD BAT (excl. ruxolitinib)	• ≥35% SVR at Week 24

PERSIST-2

Key Eligibility	Randomization		Co-Primary Endpoints*
• Primary or secondary MF • Platelet count <100,000/µL • Prior JAK2 inhibitor therapy allowed	• 1:1:1 pacritinib vs. pacritinib vs. BAT • N=311 (211 completed 24 weeks on study)	Pacritinib 400mg QD Pacritinib 200mg BID BAT (including ruxolitinib)	• ≥35% SVR at Week 24 • ≥50% TSS reduction at Week 24

BAT, best available therapy; **SVR,** spleen volume response; **TSS**, total symptom score
* Primary analysis compared pooled pacritinib (400mg QD and 200mg BID) vs. BAT

Study Objective

- To evaluate the efficacy of pacritinib in patients with low (≤50%) vs. high (>50%) JAK2 V617F allele burden and in patients with JAK2-negative disease

METHODS

- A retrospective analysis of PERSIST-1 and PERSIST-2 was performed in which outcomes were stratified by JAK2 V617F mutation status and allele burden
- Baseline JAK2 V617F was quantified by PCR, and variant allele frequencies were binned by quartile
- The efficacy endpoint was the percentage of patients achieving ≥35% SVR (by MRI or CT scan) at Week 24 based on an intention-to-treat analysis
- Analysis was based on pooled results across the two studies for patients treated with pacritinib and those treated with BAT.

RESULTS

Baseline Characteristics

- Baseline characteristics were generally balanced between the pacritinib and BAT arms
- Patients with low JAK2 V617F allele burden had lower baseline platelet count, more severe anemia, smaller spleen size, and were more likely to have primary MF (**Table 1**).
- Patients who were JAK2 V617F negative were more similar at baseline to those with low allele burden, with more cytopenias, higher proportion of primary MF, and smaller spleen size. **(Table 1**).

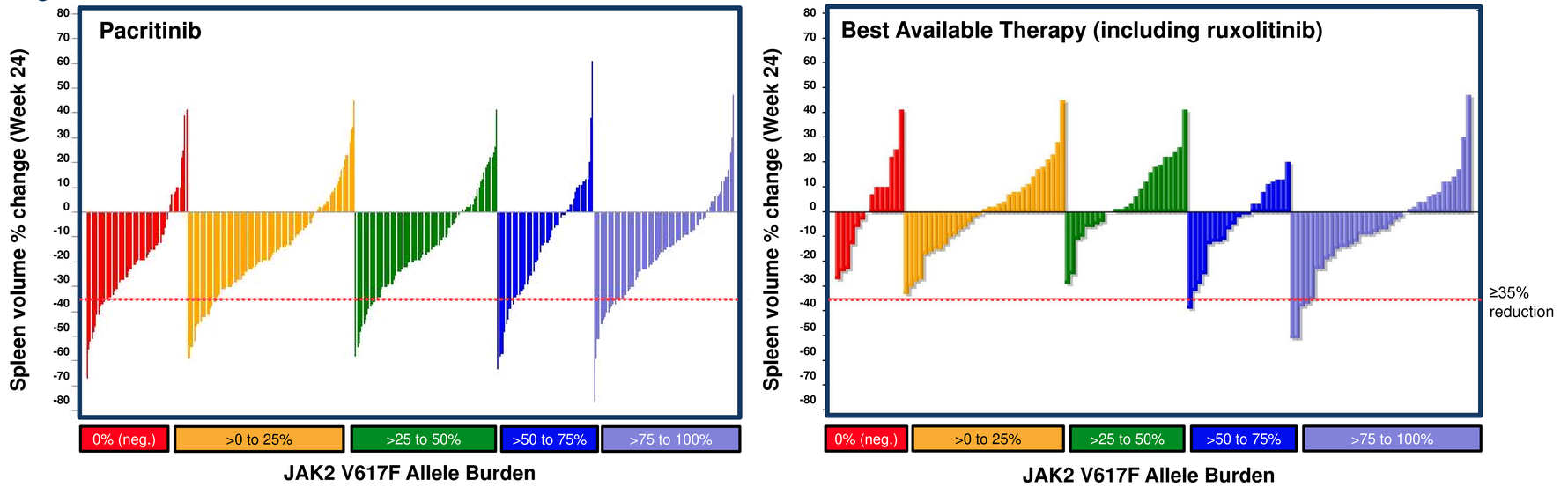
Table 1: Baseline Characteristics by JAK2 Mutation Status and Allele Burden

	JAK2 V617F negative N=80	Allele burden <50% N=256	Allele burden ≥50% N=200
Age (median, range)	66.0 (33-84) years	67.0 (23-87) years	67.0 (27-85) years
Platelets (median, IQR)	97,000 (41-187,000) /µL	75,000 (41-180,000)/µL	127,000 (55-315,000)/µL
Platelets <50,000/µL (%)	33%	31%	22%
Hemoglobin <10g/dL (%)	61%	53%	35%
RBC transf. dependent (%)	23%	22%	10%
Spleen length (median)	10.0 cm	10.5 cm	15.0 cm
Spleen volume (median)	1817 cm^3	1904 cm^3	2583 cm^3
Primary myelofibrosis (%)	76%	80%	37%

Spleen volume response observed in pacritinib-treated patients regardless of JAK2 allele burden

- Pacritinib was associated with similar SVR response at all levels of allelic burden as shown in **Figure 1**.
- No SVR response was observed for patients treated with BAT (including ruxolitinib) who had low JAK2 allele burden or JAK2 V617F-negative disease.
- Pacritinib was associated with higher rates of SVR response than BAT among patients will low JAK2 allele burden (<50%):
  - Allele burden >0 to 25% response rate for pacritinib vs. BAT = 21% vs. 0% (P<0.001)
  - Allele burden >25 to 50% response rate for pacritinib vs. BAT = 15% vs. 0% (P=0.02)

Figure 1: Percent Change in Spleen Volume (Week 24) on Pacritinib vs. BAT Stratified by JAK2 Mutation Status and Allele Burden Quartile



CONCLUSIONS

- Pacritinib demonstrated clinical efficacy regardless of JAK2 allele burden or JAK2 mutation status
- No SVR response was observed for patients treated with best available therapy (including ruxolitinib) who had low JAK2 allele burden or JAK2-negative disease
- Patients with low JAK2 allele burden and JAK2-negative disease may have non-JAK2 mediated disease. Pacritinib's efficacy in this population may be mediated by a JAK2-independent mechanism (e.g., through inhibition of IRAK1).

REFERENCES

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POSTER INFORMATION

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PosterCast