

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 ruxolitinib³
- 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 inhibitor⁵
- Unlike other JAK2 inhibitors, pacritinib does not inhibit JAK1⁵
- 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 | Pacritinib 400mg QD | Primary Endpoint |
| <ul style="list-style-type: none"> Primary or secondary MF Any platelet count No prior treatment with JAK2 inhibitors | <ul style="list-style-type: none"> 2:1 pacritinib vs. BAT N=327 | BAT (excl. ruxolitinib) | |
| | | | <ul style="list-style-type: none"> ≥35% SVR at Week 24 |

PERSIST-2

| | | | |
|--|--|--------------------------------|--|
| Key Eligibility | Randomization | Pacritinib 400mg QD | Co-Primary Endpoints* |
| <ul style="list-style-type: none"> Primary or secondary MF Platelet count <100,000/μL Prior JAK2 inhibitor therapy allowed | <ul style="list-style-type: none"> 1:1:1 pacritinib vs. pacritinib vs. BAT N=311 (211 completed 24 weeks on study) | Pacritinib 200mg BID | |
| | | | <ul style="list-style-type: none"> ≥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

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

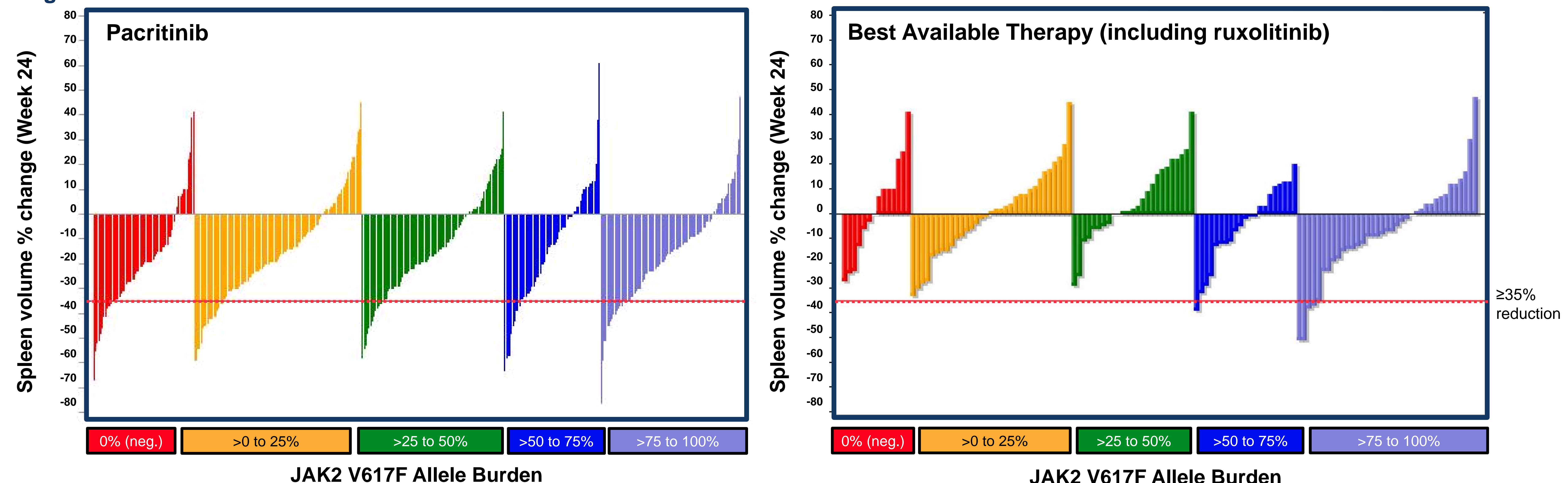
| | JAK2 V617F negative N=80 | Allele burden <50% N=256 | Allele burden ≥50% N=200 |
|---------------------------|-----------------------------|-----------------------------|-----------------------------|
| Age (median, range) | 66.0 (33-84) years | 67.0 (23-87) years | 67.0 (27-85) years |
| Platelets (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% |

- 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**).

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 with 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

This poster was presented at the 2019 American Society of Hematology Annual Meeting.



PosterCast