A Retrospective Head-to-Head Comparison Between Pacritinib and Ruxolitinib in Patients With Myelofibrosis and Moderate-to-Severe Thrombocytopenia

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INTRODUCTION

- Cytopenias are frequently encountered in patients with myelofibrosis (MF) and pose a challenge to treating physicians because approved Janus kinase (JAK) inhibitors can exacerbate both anemia and thrombocytopenia.[1-2]
- While lower doses of the approved JAK 1/2 inhibitor ruxolitinib have been commonly used for the treatment of patients with MF and thrombocytopenia, there is no recommended starting dose in the package insert for patients with platelet count <50 × 10^9/L. Instead, the package insert advises treatment should be interrupted when platelets fall below <50 × 10^9/L.[2]
  - The starting dose of ruxolitinib in patients with platelet count 50 to <100 × 10^9/L is markedly reduced, which may limit efficacy.
- Pacritinib, a JAK2/interleukin-1 receptor–associated kinase 1 (IRAK1) inhibitor that does not inhibit JAK1[3], is in development for use in patients with MF who have thrombocytopenia.
  - Pacritinib was studied in thrombocytopenic patients (platelet count ≤100 × 10^9/L) in the randomized phase 3 PERSIST-2 study, which showed pacritinib was more effective than best available therapy (BAT), including ruxolitinib, based on spleen volume reduction (SVR) and modified total symptom score (mTSS) response.[4,5]
  - While many patients in the BAT arm (45%) received ruxolitinib, a comparison between pacritinib and ruxolitinib has not been performed.

OBJECTIVE

- To conduct a retrospective head-to-head comparison of pacritinib versus ruxolitinib in "first-line" (ruxolitinib-naïve) patients treated in PERSIST-2.

METHODS

- In PERSIST-2, patients were randomized 1:1:1 to pacritinib 200 mg twice daily (BID), pacritinib 400 mg once daily (QD), or BAT.
- This analysis focuses on the 200 mg BID dosage, because the 400 mg QD dosage is no longer in development.
- The analysis is restricted to the subgroup of ruxolitinib-naïve patients in PERSIST-2.
- Patients who received ruxolitinib as BAT prior to week 24 were included; per the study protocol, ruxolitinib dosing was based on the package insert.
- Efficacy analyses included the percentage of patients who achieved ≥35% SVR or ≥50% mTSS response.
- Safety analyses were based on all treated patients; efficacy analyses were based on the intention-to-treat (ITT) population randomized at least 22 weeks prior to the end of the study treatment. Survival analysis was based on ITT for the PAC arm and on treated patients for the BAT=RUX group.
- Fisher's exact test was used to describe differences in response rates; logistic regression was used to adjust for differences in baseline characteristics.

RESULTS

Baseline Characteristics

- The safety analysis included 57 patients receiving pacritinib 200 mg BID and 12 receiving ruxolitinib; the efficacy analysis included 43 patients on pacritinib and 9 on ruxolitinib.
- Baseline characteristics were generally similar between the pacritinib and ruxolitinib groups (**Table 1**).

Table 1. Baseline Characteristics

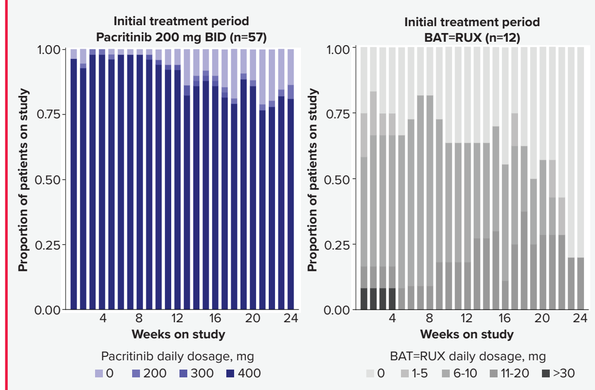
	Pacritinib (n=57)	Ruxolitinib (n=12)
Median age (range), years	67 (39-84)	72 (64-83)
Platelet count × 10^9/L, median (IQR)	51 (28-95)	49 (18-74)
Hemoglobin, g/L, median, (IQR)	97 (83-112)	100 (91-114)
Received red blood cell transfusion, %	37	33
DIPSS high risk, %	21	25
≥1% peripheral blasts, %	30	75
Primary MF, %	75	58
Secondary MF, %	25	42

DIPSS=Dynamic International Prognostic Scoring System; IQR=interquartile range; MF=myelofibrosis.

Dose Intensity

- The majority of patients treated with pacritinib were able to maintain full doses over time at weeks 12 and 24 (median dose = 400 mg/day).
- By contrast, patients on ruxolitinib received a median starting dose of 10 mg (interquartile range [IQR], 10-10 mg) daily at baseline, 10 mg (IQR, 0-10 mg) daily at week 12, and 10 mg (IQR, 0-20 mg) daily at week 24 (**Figure 1**).

Figure 1. Total Daily Dose Distribution for Patients Receiving Pacritinib (Left) or Ruxolitinib (Right) in the PERSIST-2 Study

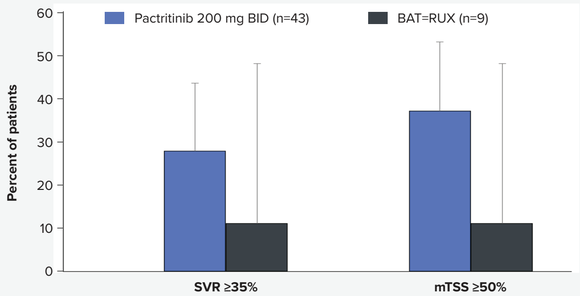


BAT=best available therapy; BID=twice daily; RUX=ruxolitinib.

Efficacy

- Patients treated with pacritinib had numerically higher rates of SVR (28% vs 11%) and mTSS response (37% vs 11%) compared with patients treated with ruxolitinib (**Figure 2**).

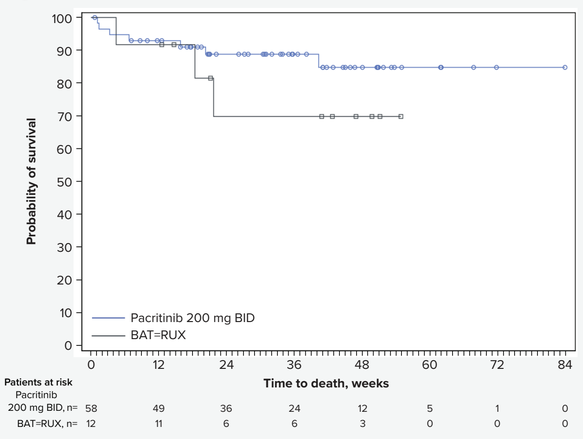
Figure 2. Percent of Patients Meeting SVR and mTSS Thresholds



Data in patients randomized prior to September 7, 2015, based on ITT truncated on the day of the FDA clinical hold. Differences between groups were not significant. Error bars are the 95% confidence interval upper bound.
BAT=best available therapy; BID=twice daily; FDA=US Food and Drug Administration; ITT=intention-to-treat; mTSS=modified total symptom score; RUX=ruxolitinib; SVR=spleen volume reduction.

- The hazard ratio for overall survival for pacritinib versus ruxolitinib was 0.49 (95% confidence interval, 0.13-1.92) (**Figure 3**).
  - There was no diminution of treatment effect observed for SVR, TSS, or survival after adjusting for baseline Dynamic International Prognostic Scoring System high risk, platelet count, and primary versus secondary MF.

Figure 3. Overall Survival



Circles represent censored data. BAT=best available therapy; BID=twice daily; RUX=ruxolitinib.

Adverse Events

- The percentages of any adverse event, cytopenias, hemorrhagic events, and cardiac events were similar between the pacritinib and ruxolitinib groups.
- Rates of diarrhea were higher in the pacritinib group, though these were almost exclusively grade 1-2 events.
- Rates of infection were higher in the pacritinib group, but rates of grade ≥3 infection were higher in the ruxolitinib group.
- Fatal adverse events occurred more commonly in the ruxolitinib group.

Table 2. Adverse Events for the Pacritinib and Ruxolitinib Treatment Groups

	Pacritinib, % (n=57)	BAT=RUX, % (n=12)
Any adverse event	93	100
Diarrhea (all grades)	47	8
Diarrhea (grade ≥3)	1.8	0
Thrombocytopenia	33	33
Anemia	30	25
Hemorrhagic events (all grades)	44	58
Hemorrhagic events (grade ≥3)	19	17
Cardiac events (all grades)	26	33
Cardiac events (grade ≥3)	5	17
Infection (all grades)	47	33
Infection (grade ≥3)	11	17
Fatal adverse events	7	25

BAT=best available therapy; RUX=ruxolitinib.

CONCLUSIONS

- Patients with moderate or severe thrombocytopenia were able to maintain full dose intensity with pacritinib.
- Full-dose pacritinib yielded higher response rates and a similar safety profile compared with lower doses of ruxolitinib in "first-line" patients with cytopenic MF.
- Pacritinib may address the unmet medical need of patients with cytopenic MF who cannot tolerate full doses of JAK1/2 inhibitors such as ruxolitinib.

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ACKNOWLEDGMENTS: This study was supported by CTI BioPharma. Medical writing and editorial assistance was provided under the direction of the authors by MedThink SciCom, and funded by CTI BioPharma.

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