Spleen volume reduction (SVR) predicts overall survival (OS) in myelofibrosis (MF) patients on pacritinib (PAC) but not best available therapy (BAT): PERSIST-2 landmark OS analysis

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BACKGROUND

- Myelofibrosis (MF) is a life-limiting malignancy characterized by marrow fibrosis, splenomegaly, and progressive cytopenias.
- Pacritinib (PAC) is a JAK1-sparing inhibitor of JAK2/IRAK1/ACVR1[1,2] that demonstrated spleen volume response (SVR) benefit vs best available therapy (BAT; including ruxolitinib [RUX]) in MF patients with platelets ≤100×10^9/L in the PERSIST-2 study.[3]
- JAK2 inhibitors can reduce spleen volume, which is considered a surrogate for disease response.
- The relationship between SVR and overall survival (OS) in MF patients with thrombocytopenia is unknown.

OBJECTIVE

- To assess whether SVR on PAC or on BAT (including RUX) is associated with prolonged survival in MF patients with thrombocytopenia.

METHODS

- This analysis includes PERSIST-2 patients who were alive and on study at the start of the week 12 SVR window (study week 10) on PAC 200 mg twice daily (BID) and on BAT.
- Week 12 SVR was evaluated using various volume reduction thresholds: ≥35%, ≥20%, ≥10%, and >0%.
- OS was evaluated among SVR responders vs. non-responders at each threshold based on landmark analysis methodology. Survival was compared using the log-rank test. The impact of baseline imbalances between groups was assessed using Cox modeling.

RESULTS

- Among all tested SVR response thresholds, SVR ≥10% demonstrated the greatest separation in OS curves between responders vs. non-responders on PAC, but not on BAT (**Figure 1**).
- Compared to SVR ≥10% responders, non-responders had smaller spleen volumes and were more likely to require red blood cell (RBC) transfusions at baseline, shown in **Table 1**.

Table 1. Characteristics of SVR ≥10% Responders and Non-Responders

Baseline characteristics	PAC 200 mg BID		BAT	
	R N=65	N-R N=24	R N=28	N-R N=56
Age, median	66	67	66	69
DIPSS high risk	18.5%	46%	21%	25%
PLT count (x10^9/L), median	58	67	68	47
Hemoglobin (g/dL), median	9.7	9.3	10.0	9.6
Requires RBC transfusion	38%	58%	32%	54%
Prior JAK2 inhibitor	45%	50%	64%	45%
Spleen volume (cm^3), median	2573	2094.5	2907	2393
Palpable spleen length (cm), median	15.00	12.75	12.00	14.50

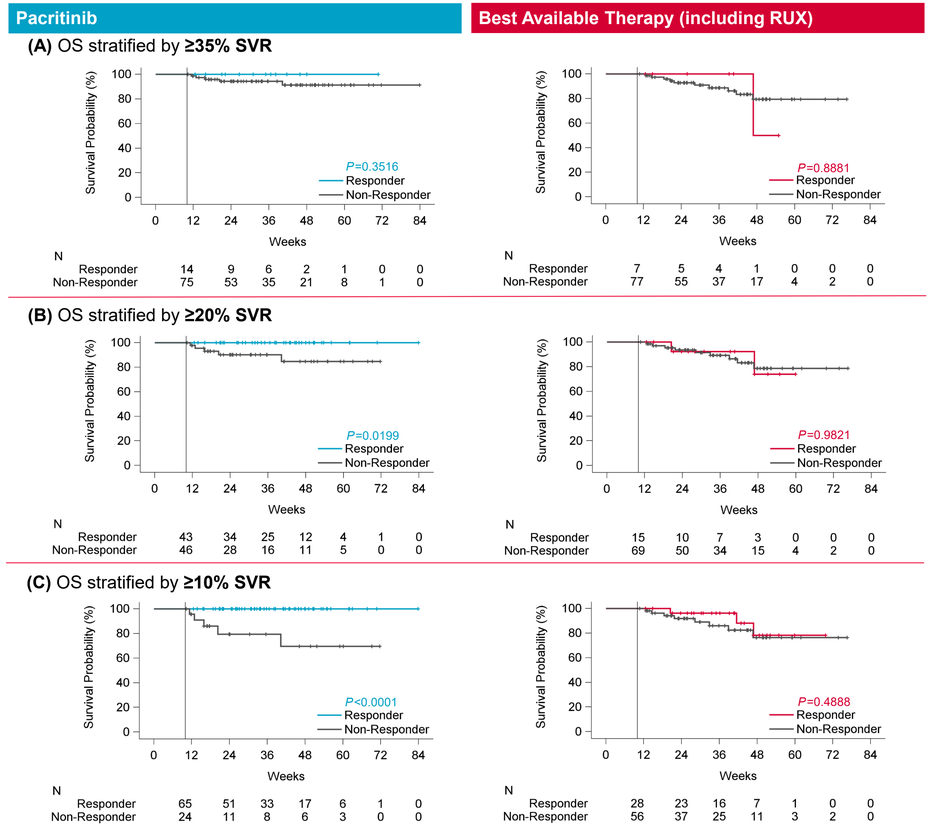
BAT, best available therapy; BID, twice daily; N-R, non-responder; PAC, pacritinib; PLT, platelet; R, responder; RBC, red blood cell.

RESULTS

SVR is associated with survival benefit on PAC, but not on BAT

- On the PAC arm, SVR ≥10% was prognostic for survival (**Figure 1C**). More stringent SVR thresholds (≥20%, ≥35%) were also prognostic, but led to less separation between responder and non-responder survival curves (**Figure 1A, B**).
  - Adjusting for baseline spleen volume and requirement for RBC transfusion (in a univariate analysis) did not impact the survival benefit seen with SVR ≥10% on the PAC arm.
- Achieving any degree of spleen volume reduction (SVR >0%) was also associated with improved survival on PAC (hazard ratio [HR]=0.08 [95% confidence interval [CI]: 0.01, 0.51], *P*=0.0007), though the separation between responder and non-responder survival curves was not as great as at the SVR ≥10% threshold.
- SVR did not predict survival on BAT, regardless of SVR threshold. (**Figure 1**)
  - 11% (3/28) of patients on BAT who achieved SVR ≥10% died compared to a similar percent (14%, 8/56) of non-responders.

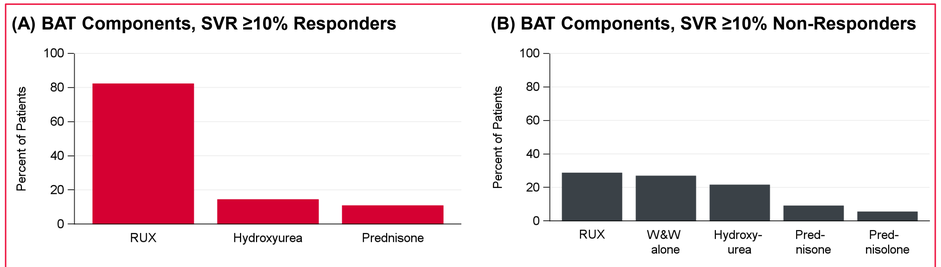
Figure 1. Overall Survival Stratified by SVR, Data shown on PAC (left) and BAT (right)



Low-dose ruxolitinib led to SVR≥10% on BAT, but not survival benefit

- On the PAC arm, median dose intensity through week 12 was 100% (200 mg BID) among SVR ≥10% responders and non-responders.
- Of the 28 patients on BAT who achieved SVR ≥10%, 23 (82%) were treated with RUX prior to the week 12 SVR assessment. Of these 23 patients on RUX:
  - 78% were on RUX ≤10 mg BID at the time of the landmark analysis
  - 43% on RUX ≤5 mg BID at the time of the landmark analysis
- Breakdown of BAT treatments stratified by SVR ≥10% response are shown in **Figure 2**.

Figure 2. BAT Treatments in SVR ≥10% Responders and Non-Responders

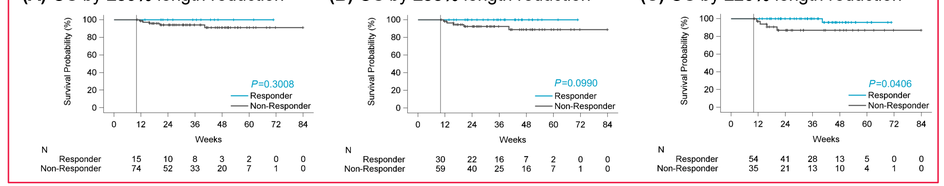


Agents used in ≥5% of patients shown. As patients may have been on multiple agents, percentages do not sum to 100%.

Spleen length reduction (by palpation) is not as prognostic as SVR (by imaging) on PAC

- Achieving ≥20% reduction in palpable spleen length on PAC is associated with OS benefit (HR=0.14 [95% CI: 0.02-1.26], **Figure 3**), but separation of curves is not as great as prognostication based on SVR.

Figure 3. Overall Survival Stratified by Spleen Length Reduction (by Palpation), PAC arm only



CONCLUSIONS

- In MF patients with thrombocytopenia (platelets ≤100×10^9/L), achieving SVR ≥10% at week 12 on full-dose PAC was associated with significant OS benefit.
- By contrast, this association was not found with BAT, including patients on RUX (most at doses of 10 mg BID or less).
- As PAC can be given at full dose regardless of platelet count, it is possible that PAC may offer a unique survival advantage for MF patients with moderate or severe thrombocytopenia who achieve ≥10% spleen reduction.

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ABBREVIATIONS: BAT, best available therapy; BID, twice daily; PAC, pacritinib; OS, overall survival; RUX, ruxolitinib; SVR, spleen volume response; W&W, watch and wait.

REFERENCES: 1. Singer et al. *J Exp Pharmacol*. 2016;8:11-19. **2.** Oh et al. *Clin Lymphoma Myeloma Leuka*. 2022;S:327 **3.** Mascarenhas et al. *JAMA Oncol*. 2018;4:652-659.

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