PF1242

Efficacy of pacritinib versus momelotinib in patients with thrombocytopenic myelofibrosis: a matching adjusted indirect treatment comparison

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CONCLUSIONS

- **This matching adjusted indirect treatment comparison (MAIC) revealed a consistent, nominal trend toward pacritinib benefit across all efficacy endpoints and overall survival in patients with thrombocytopenic myelofibrosis, most of whom had moderate thrombocytopenia.**
- **When comparing therapies across disparate trials with differences in study design, it is essential to account for differences (including those of study populations) by adjusting for effect modifiers. Importantly, this analysis accounted for key baseline patient prognostic differences to ensure balanced analytic populations between the trials.**
- **Considering the limitations of not being a direct head-to-head comparison and the limited sample size, this MAIC provides evidence supporting pacritinib as a therapeutic option for patients with myelofibrosis and thrombocytopenia.**

INTRODUCTION

- Myelofibrosis is a clonal hematologic malignancy characterized by progressive bone marrow fibrosis, splenomegaly, and cytopenias.[1,2]
- Thrombocytopenia, often co-occurring with anemia, is a poor prognostic feature in myelofibrosis, associated with reduced survival and increased symptom burden.[1]
- Pacritinib is a Janus kinase 1 (JAK1)-sparing inhibitor of JAK2, interleukin-1 receptor-associated kinase 1 (IRAK1), and activin A receptor type 1 (ACVR1)[3] developed for patients with thrombocytopenic myelofibrosis.
- Momelotinib, a JAK1/JAK2/ACVR1 inhibitor was developed for patients with anemic myelofibrosis.[4]
- While comparative efficacy data for pacritinib and momelotinib would be valuable for informing evidence-based medicine,[5–9] no direct head-to-head evidence from randomized controlled trials (RCTs) is available.
  - Indirect treatment comparison is a pragmatic solution for the purpose of generating clinical evidence in the absence of gold-standard head-to-head RCTs.[10]

OBJECTIVES

This MAIC evaluated the efficacy of pacritinib versus momelotinib for treatment of patients with thrombocytopenic myelofibrosis, particularly in those patients with moderate thrombocytopenia.

METHODS

Data and trial selection

- Data were taken from three pivotal Phase 3 RCTs of pacritinib 200 mg twice daily and momelotinib 200 mg once daily; all studies had data available for patients with myelofibrosis and thrombocytopenia.[11]
  - Individual patient data from PERSIST-2 (NCT02055781) of the approved pacritinib 200 mg twice-daily dose in patients with a platelet (PLT) count of ≤100 × 10^9/L treated after a JAK1 inhibitor treatment washout period.[12]
  - Published *post-hoc* subgroup analysis[13] of the approved momelotinib 200 mg once-daily dose in patients with thrombocytopenic myelofibrosis and PLT count >24 to <100 × 10^9/L using pooled data from MOMENTUM (NCT04173494; following JAK inhibitor treatment washout period) and SIMPLIFY-1 (NCT01969838; in JAK inhibitor naïve)

Population harmonization

- To harmonize patients on pacritinib from PERSIST-2 with those from the momelotinib *post-hoc* analysis subgroup, only those pacritinib patients with baseline PLT count ≥24 to <100 × 10^9/L and Eastern Cooperative Oncology Group (ECOG) performance status grade 0–2 were included for analysis.

Matching

- The harmonized pacritinib population was matched on effect modifiers and prognostic factors (all selected based on expert medical opinion) to the momelotinib *post-hoc* patient subgroup (**Table 1**).
- Each outcome analyzed was matched on a universal set of baseline characteristics and an additional outcome-specific adjustment variable for each dependent variable (**Table 1**).

Table 1: Baseline variables used for matching

Universal baseline matching adjustment variables:	Additional outcome-specific baseline adjustment variables:	
	Outcome	Variable
Age (mean)	TSS-50	Baseline TSS (mean)
Male (%)	SVR-35	Baseline SV (mean)
Prior JAKi (%)	RBC-TI	NA
PLT count (mean)	OS	Baseline DIPSS high (%)[15]

DIPSS high, high-risk Dynamic International Prognostic Score; JAKi, JAK inhibitor; NA, none applied; OS, overall survival; PLT, platelet; RBC-TI, red blood cell transfusion independence; SVR-35, ≥35% spleen volume reduction; TSS-50, ≥50% total symptom score reduction.

Indirect comparison

- The indirect comparison evaluated:
  - Week 24 efficacy endpoints, the percentage of patients achieving:
    - ≥50% total symptom score reduction (**TSS-50**; Myeloproliferative Neoplasm Symptom Assessment Form TSS 2.0), calculated as the mean score for 10 items that focus on fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers[14])
    - ≥35% spleen volume reduction (**SVR-35**)
    - Red blood cell transfusion independence (**RBC-TI**)
  - Overall survival
- Weights for dichotomous variables (TSS-50, SVR-35, RBC-TI) were estimated using logistic regression and odds ratios.
- A hazard ratio for OS was estimated based on a weighted Cox proportional hazards model for time to event.
  - Kaplan–Meier survival curves were estimated; momelotinib data from the *post-hoc* analysis were digitalized using Inkscape® software.
- The recalculated outcomes for pacritinib were statistically compared with the published outcomes for momelotinib.

RESULTS

- After matching, baseline characteristics were generally balanced (**Table 2**).
  - Between 79% to 83% of pacritinib patients had moderate thrombocytopenia (PLT count 50–99 × 10^9/L).
  - The effective sample sizes for endpoints ranged between 36% and 47% of the full PERSIST-2 study population.

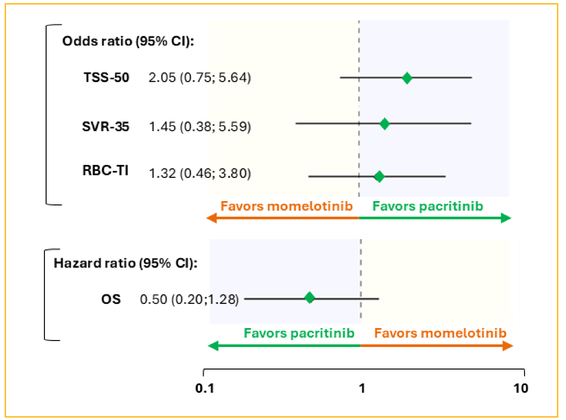
Table 2: Comparison of baseline characteristics before and after matching

Variable	Before matching			After matching	
	Pacritinib (n=47)	Momelotinib (n=84)	Pacritinib vs momelotinib	Pacritinib (ESS=20–25)	Pacritinib vs momelotinib
	Estimate		*P* value	Estimate	*P* value
Age (mean)	66.57	69.79	0.03	69.79	1.00
Male (%)	53.19	61.90	0.43	61.90	1.00
Prior JAKi (%)	55.32	78.57	0.01	78.57	1.00
PLT count (mean)	57.96	68.43	<0.01	68.43	1.00
TSS (mean)	25.06	25.86	0.73	25.86	1.00
SPV (mean)	2761.61	2327.44	0.10	2327.46	1.00
DIPSS high (%)	22.39	40.48	0.03	40.48	1.00

DIPSS high, high-risk Dynamic International Prognostic Score; ESS, effective sample size; ITT, intent to treat; JAKi, JAK inhibitor; OS, overall survival; SVR, spleen volume reduction; TSS total symptom score.

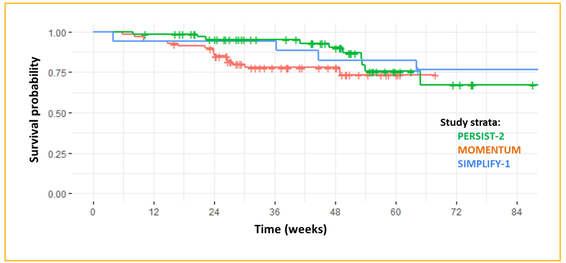
- The MAIC did not indicate statistically significant differences between pacritinib and momelotinib for any of the outcomes evaluated, but nominally favored pacritinib.
  - For all efficacy endpoints, ORs (95% CI) (**Figure 1**) were:
    - TSS-50: 2.05 (0.75; 5.64)
    - SVR-35: 1.45 (0.38; 5.59)
    - RBC-TI: 1.32 (0.46; 3.80)
  - For OS, the HR (95% confidence interval [CI]) was 0.50 (0.20; 1.28) for pacritinib versus momelotinib (**Figure 1**); with the Kaplan–Meier survival estimates from the three trials plotted on **Figure 2**.

Figure 1: Forest plot (logarithmic scale) of efficacy outcomes and overall survival



CI, confidence interval OS, overall survival; RBC-TI, red blood cell transfusion independence; SVR-35, ≥35% spleen volume reduction; TSS-50, ≥50% total symptom score reduction.

Figure 2: Kaplan–Meier overall survival curves



Study strengths and limitations

- This MAIC included harmonized patient populations and considered important prognostic covariates/effect modifiers in the weighting model to avoid bias in the results.
- Compared with a previously presented analysis that included momelotinib patients that were not comparable with patients in pacritinib trials,[16] the harmonized populations and selection of registration trials only in the present study added to the robustness of the findings.

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Acknowledgements

This study was funded and reviewed by Sobi. Writing support, under the guidance of the authors, was provided by Gauri Saal, MA CMPP, Neulumic Consulting, Birmingham, UK, edited by Max Thomas, Brighton, UK, and funded by Sobi in accordance with Good Publication Practice (GPP) guidelines (Ann Intern Med. 2022 Sep;175(9):1298–1304). Sobi reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content.

Disclosures

NP: Consulting/scientific advisory/speaking: AbbVie, BMS, CTI BioPharma, GSK, Immunogen, INCYTE , JNJ, Karyopharm, Menarini-Stemline Group, Morphosys, OPNA, Pacylex, Protagonist, Sobi, Takeda; research grant: Sager Strong Foundation, US Dept of Defence; board of directors: Dan's House of Hope.
AL: Declared relationships with MorphoSys, Amgen, Grifols, Novartis, Sanofi, Protagonist, Sobi, Pfizer, Incyte, and BMS
SO: Consulting for Sobi Inc.
JM: Research funding paid to my institution from Incyte, Novartis, Ajax, SOBI, BMS, Geron, Kartos, Karyopharm, PharmaEssentia, Italfarmco Spa, Disc therapeutics, MorphoSys, AbbVie and consulting fees from Incyte, Novartis, SOBI, Geron, Kartos, Karyopharm, PharmaEssentia, Italfarmco Spa, Galecto, Disc therapeutics, MorphoSys, AbbVie, Keros, Merck, Roche, BMS, Blueprint Medicines, and GSK.
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