Indirect treatment comparison of momelotinib vs pacritinib safety and anemia outcomes in patients with myelofibrosis

Lucia Masarova,[1] Srdan Verstovsek,[1] Francesca Palandri,[2] Ruben Mesa,[3] Claire Harrison,[4] Balázs Dobi,[5] Boris Gorsh,[6] Zhaohui Wang,[6] Catherine Ellis,[6] Dwaipayan Patnaik,[6] Venediktos Kapetanakis[7]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [3]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [4]Guy's and St Thomas' NHS Foundation Trust, London, UK; [5]Evidera, Budapest, Hungary; [6]GSK plc, Philadelphia, PA, USA; [7]Evidera, London, UK

Introduction

- Janus kinase (JAK) inhibitors are effective for improving symptoms and reducing spleen volume for most patients with myelofibrosis (MF)[1-3]
- However, safety profiles can differ, and some approved JAK inhibitors have been associated with hematologic toxicity such as anemia and thrombocytopenia[1,2]
- The JAK1/JAK2/activin A receptor type 1 inhibitor momelotinib has shown consistent benefit in terms of spleen response, symptom response, and transfusion-independent rates when evaluated in 3 phase 3 trials (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM)[4-6]
- Pacritinib is an oral kinase inhibitor targeting JAK2/fms related receptor tyrosine kinase 3/interleukin 1 receptor associated kinase 1 that is approved for patients with MF and severe thrombocytopenia (platelet counts <50×10^9/L)[3]
- Understanding differences in safety, tolerability, and anemia outcomes between momelotinib and pacritinib can help inform treatment choices in MF
- In this analysis, we report the results from an indirect treatment comparison (ITC) of safety outcomes between momelotinib and pacritinib in JAK inhibitor–experienced and JAK inhibitor–naive patients with MF

Objective

- To compare safety and anemia outcomes between momelotinib and pacritinib in patients with MF

Methods

- Matching-adjusted indirect comparison (MAIC)[7,8] was used to compare safety outcomes from phase 3 momelotinib trials and phase 2 or 3 pacritinib trials
- Safety outcomes occurring in ≥15% of the momelotinib arm of SIMPLIFY-1[4]/SIMPLIFY-2[5]/MOMENTUM[6] or the 200-mg pacritinib arm of PERSIST-2[9]/PAC203[10] were analyzed
  - Grade 3/4 anemia and thrombocytopenia were considered primary outcomes; other safety outcomes occurring in ≥15% of patients were considered secondary outcomes
- Hemoglobin (Hb) improvement at week 24, which included Hb improvement of ≥1 g/dL and ≥2 g/dL (in patients with baseline Hb <10 g/dL) and clinical improvement in Hb was also assessed; sensitivity analyses with and without inclusion of Hb levels in the 4-week post-transfusion period were performed, as it was unclear how this was handled in PERSIST-2 (as presented at SOHO 2022[11])
  - Hb levels ≤4 weeks from RBC transfusion were excluded; scenarios including post-transfusion Hb levels were also explored
  - Clinical improvement in Hb was defined using International Working Group criteria[12]: improvement of ≥2 g/dL at anytime through week 24 (for ≥8 weeks, rolling) and not taking into account Hb levels ≤4 weeks from RBC transfusion, or no RBC transfusion for ≥8 weeks (rolling)
- The analysis population included JAK inhibitor–experienced and JAK inhibitor–naive patients, as PERSIST-2 enrolled both populations and separate data were not reported
  - Pooled SIMPLIFY-1/SIMPLIFY-2/MOMENTUM data were compared vs pooled PERSIST-2/PAC203 data or vs PERSIST-2 data alone, as not all outcomes of interest were reported in PAC203
- Momelotinib patient data were reweighted to match momelotinib and pacritinib populations on baseline characteristics prioritized by expert clinical input
  - For safety outcomes, MAICs vs PERSIST-2 were carried out by matching populations on JAK inhibitor exposure, Dynamic International Prognostic Scoring System (DIPSS), Total Symptom Score, platelet counts, spleen length, transfusion independence, hemoglobin levels, Eastern Cooperative Oncology Group status, and age; MAICs vs PERSIST-2/PAC203 were additionally adjusted for sex and MF subtype
  - For anemia outcomes, MAICs vs PERSIST-2 were carried out in a subpopulation of patients with available Hb data
    - Transfusion independence response estimates were considered unreliable, as they resulted in an effective sample size (ESS) that was too small
- Odds ratios (ORs), risk ratios, and risk differences (RDs) between outcomes were estimated after population adjustment
- Sensitivity analyses with alternative models adjusting for factors that were considered as medium or lower importance per clinical guidelines, such as MF subtype and spleen length, were also performed

Results

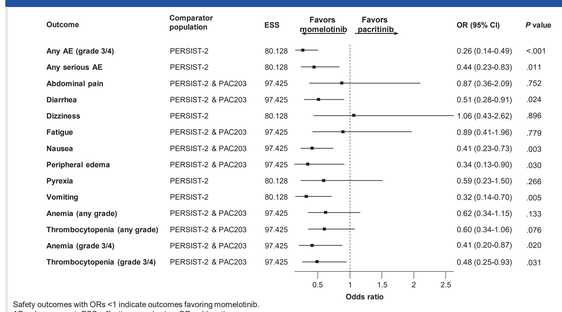
Table 1. Demographics and Baseline Characteristics Before and After Adjustment

	Momelotinib before adjustment (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM; N=448)	MAIC vs pooled PERSIST-2/PAC203		MAIC vs PERSIST-2	
		Momelotinib after adjustment (ESS=97.43)	Pacritinib (PERSIST-2/ PAC203; N=128)	Momelotinib after adjustment (ESS=80.13)	Pacritinib (PERSIST-2; N=106[a])
Age, median, years[b]	68	68	NA (assumed to be 68)	67	67
Male, %	60.5	63.0	63.0	49.3	64.9
Prior JAK inhibitor treatment, %	52.2	63.2	63.2	44.6	44.6
MF subtype, %					
Primary MF	60.3	72.4	72.4	58.5	74.3
Post–polycythemia vera	20.5	18.8	18.8	27.5	18.9
Post–essential thrombocytopenia	19.2	8.8	8.8	14.0	6.8
DIPSS/IPSS risk category, %[c]					
Intermediate-1	16.7	20.0	20.0	18.9	18.9
Intermediate-2	54.7	51.5	51.5	51.4	51.4
High	28.4	28.5	28.5	29.7	29.7
Not available	0.2	0.0	0.0	0.0	0.0
TSS, %					
≥5	90.1	100	100	100	NA
≥13	69.1	76.9	100	100	100
ECOG PS, %					
0-1	87.7	86.9	86.9	87.8	87.8
2-3	12.3	13.1	12.2	12.2	10.8
Not available	0.0	0.0	0.9	0.0	1.4
RBC transfusion status, %[d]					
Dependent	38.9	38.5	25.6	35.6	18.9
Independent	43.5	45.7	45.7	50.0	50.0
Requiring	17.6	15.8	27.8	14.4	29.7
Not available	0.0	0.0	0.9	0.0	1.4
Hemoglobin <10 g/dL, %	62.2	65.0	65.0	59.5	59.5
Platelet count <50×10^9/L, %	6.1	42.7	42.7	41.9	41.9
Spleen length, cm[e]	12	14.5	NA (assumed to be 14.5)	15	15

DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS effective sample size; IPSS, International Prognostic Scoring System; ITT, intent to treat; JAK, Janus kinase; MAIC, matching-adjusted indirect comparison; MF, myelofibrosis; NA, not available; RBC, red blood cell; TSS, Total Symptom Score.
[a] Baseline characteristics were available for the subset of 74 patients from the ITT population; population matching was performed assuming that baseline characteristics in both sets (n=106 and n=74) were similar. [b] The median age in PERSIST-2 and PAC203 was 67 and 68.5 years, respectively; thus, the median age in the pooled pacritinib cohort was assumed to be 68 (scenarios using 67, 67.5, and 68.5 years provided similar results). [c] High- and intermediate-risk myelofibrosis in SIMPLIFY-1 was reclassified according to the DIPSS definition to facilitate comparability across studies. [d] Definitions of baseline transfusion independence and transfusion dependence were harmonized with the definitions used in PERSIST-2 and PAC203. [e] The median palpable spleen length in PERSIST-2 and PAC203 was 15 and 14 cm, respectively; thus, the median palpable spleen length in the pooled pacritinib cohort was be assumed to be 14.5 cm (scenarios using 14 and 15 cm provided similar results).

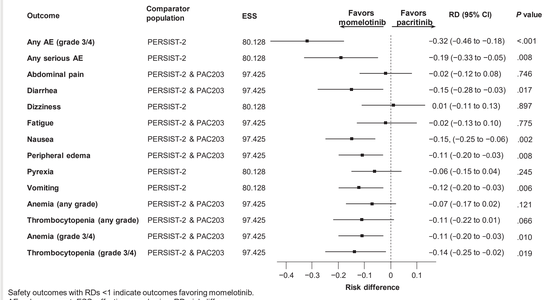
- After adjustment, patient populations were mostly well balanced with an acceptable ESS (**Table 1**)
  - ESS for safety outcomes was 97.43 for comparisons vs pooled PERSIST-2/PAC203
  - ESS for safety outcomes was 80.13 for comparisons vs PERSIST-2
- For anemia outcomes in a subpopulation of patients with available Hb data, the ESS was 47.64 for comparisons vs PERSIST-2
- Momelotinib had numerically favorable results for most safety outcomes, with statistically significantly lower odds and risk for all grades of diarrhea, nausea, peripheral edema, and vomiting as well as grade 3/4 and serious adverse events (AEs) (**Figure 1 and 2**)
  - ORs and RDs for anemia and thrombocytopenia (grade 3/4 or any grade) favored momelotinib vs pacritinib, significantly so for grade 3/4 events
  - No identified safety outcomes were significantly less likely with pacritinib

Figure 1. ORs for Safety Outcomes



Safety outcomes with ORs <1 indicate outcomes favoring momelotinib.
AE, adverse event; ESS, effective sample size, OR, odds ratio.

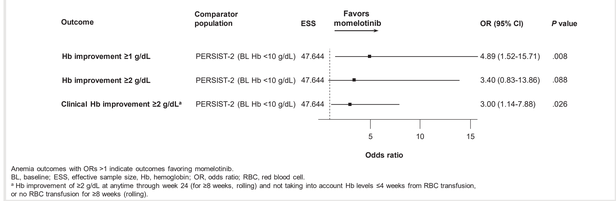
Figure 2. RDs for Safety Outcomes



Safety outcomes with RDs <1 indicate outcomes favoring momelotinib.
AE, adverse event; ESS, effective sample size, RD, risk difference.

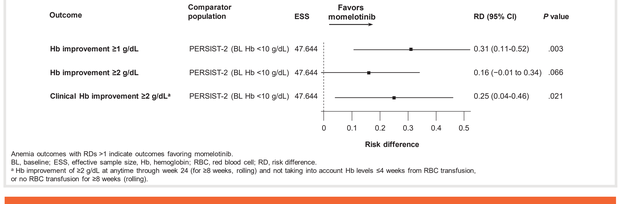
- Momelotinib was also associated with greater odds/possibility of Hb improvement of ≥1 g/dL or ≥2 g/dL (**Figure 3 and 4**)
  - Outcomes were similar regardless of whether post-transfusion Hb levels were excluded (**Figure 3 and 4**; significant for Hb improvement of ≥1 g/dL) or included (OR, 30.6 and 8.1 and RD, 0.69 and 0.36 for Hb improvement ≥1 g/dL and ≥2 g/dL, respectively; both significant)
- Sensitivity analysis adjusting for different matching characteristics showed consistency in results for point estimates
  - For all safety outcomes, MAIC results were similar across the different scenarios for DIPSS and median spleen length, suggesting the uncertainties around the conversion of International Prognostic Scoring System to DIPSS in SIMPLIFY-1, and the exact median spleen length in PAC203/PERSIST-2 did not affect MAIC conclusions

Figure 3. ORs for Anemia Outcomes



Anemia outcomes with ORs >1 indicate outcomes favoring momelotinib.
BL, baseline; ESS, effective sample size, Hb, hemoglobin; OR, odds ratio; RBC, red blood cell.
[a] Hb improvement of ≥2 g/dL at anytime through week 24 (for ≥8 weeks, rolling) and not taking into account Hb levels ≤4 weeks from RBC transfusion, or no RBC transfusion for ≥8 weeks (rolling).

Figure 4: RDs for Anemia Outcomes



Anemia outcomes with RDs >1 indicate outcomes favoring momelotinib.
BL, baseline; ESS, effective sample size, Hb, hemoglobin; RBC, red blood cell; RD, risk difference.
[a] Hb improvement of ≥2 g/dL at anytime through week 24 (for ≥8 weeks, rolling) and not taking into account Hb levels ≤4 weeks from RBC transfusion, or no RBC transfusion for ≥8 weeks (rolling).

Limitations

- Evaluable outcomes were limited by published aggregate data, so not all were feasible to compare
- Despite adjusting for prognostic factors/effect modifiers, MAIC analyses may be subject to unmeasured/residual confounding
- Comparisons between momelotinib and pacritinib were subject to limitations due to differences in inclusion criteria, the lack of reported baseline characteristics that may act as prognostic factors or treatment effect modifiers, and potential differences in outcome definitions in Hb improvement due to insufficient clarity in the comparator trial publications
- Anemia outcomes were based on a subpopulation of patients with available Hb data

Conclusions

- These results suggest that momelotinib provides a more favorable safety profile and improved anemia outcomes vs pacritinib
  - Patients treated with momelotinib had fewer grade 3/4 and serious AEs as well as fewer gastrointestinal AEs and hematologic AEs, including grade 3/4 anemia and thrombocytopenia, compared with patients treated with pacritinib
  - Momelotinib-treated patients also showed a significantly higher odds of Hb improvement of ≥1 g/dL vs pacritinib
- These results suggest that momelotinib is a safe and tolerable treatment and may provide improved anemia outcomes for patients with MF

Poster MPN-092

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Corresponding author email address: Lmasarova@mdanderson.org

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