

REVIEW

Haematological Malignancy – Clinical

Janus kinase inhibitors after ruxolitinib failure in myelofibrosis: A systematic review and pooled analysis of phase 3 efficacy and integrated safety across clinical trials and real-world evidence

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Summary

Ruxolitinib remains first-line standard of care for symptomatic myelofibrosis, but resistance/intolerance develops in most patients. Three Janus kinase inhibitors (JAKis) have entered the post-ruxolitinib space via distinct pivotal trials. We systematically searched prospective trials evaluating JAKi in refractory adults with myelofibrosis. Efficacy was assessed across phase 3 trials, with safety integrating phase 2 and real-world data. Pooled $\geq 35\%$ spleen volume reduction at week 24 was 32.7% (95% confidence intervals 27.3–38.6) for fedratinib, 15.8% (11.7–21.0) for momelotinib and 21.6% (13.8–32.3) for pacritinib 200 mg bis in die; pooled $\geq 50\%$ Total Symptom Score reduction rates were 32.8% (27.4–38.7), 25.3% (20.2–31.3) and 32.4% (22.9–43.7) respectively. Across safety datasets ($n = 1004$ trial; $n = 790$ real-world), fedratinib showed the highest grade ≥ 3 anaemia (34.3%) and any-grade diarrhoea (56.6%), whereas momelotinib the lowest (8.0%). Pacritinib carried the greatest risk of grade ≥ 3 bleeding (11.2%). Discontinuation due to adverse events was comparable across agents (~16%–17%). Real-world evidence from five momelotinib cohorts ($n = 580$) identified nephrotoxicity (glomerular filtration rate decline 17%–29%) and peripheral neuropathy (4%–20%) as monitoring targets. Despite limitations from differing study designs, each post-ruxolitinib JAKi shows a distinct efficacy/safety fingerprint mapping onto a phenotype, guiding second-line choice by clinical factors and prior adverse events.

KEYWORDS

fedratinib, momelotinib, myelofibrosis, pacritinib, pooled analysis, ruxolitinib failure, systematic review

INTRODUCTION

Myelofibrosis (MF) is the most clinically heterogeneous of the Philadelphia-negative myeloproliferative neoplasms, encompassing primary MF and post-polycythaemia vera/post-essential thrombocythaemia MF. Disease biology converges on constitutive activation of the Janus kinase (JAK)/signal transducer and activator of transcription protein (STAT)

pathway and a sustained pro-inflammatory cytokine cascade, with a clinical phenotype dominated by progressive splenomegaly, systemic constitutional symptoms and bone marrow failure with cytopenias.¹ Median overall survival in higher-risk disease remains under 5 years, and allogeneic haematopoietic stem cell transplantation is the only potentially curative option, but is feasible in a minority of patients.^{2,3}

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Since its approval in 2011, ruxolitinib has become the standard of care for symptomatic, splenomegalic MF, based on the COMFORT-I and COMFORT-II trials.^{4,5} However, ruxolitinib does not significantly modify the underlying disease biology and is constrained by dose-limiting myelosuppression in cytopenic patients.^{6,7} Real-world series and clinical trial follow-up consistently show that at 3 years, around half of treated patients have discontinued ruxolitinib due to resistance, intolerance or loss of response, and by 5 years, discontinuation rates exceed 70%, defining a clinically meaningful population for whom evidence-based second-line options are required.^{8,9}

Three additional JAK inhibitors (JAKis) are now approved or in late-phase development for this setting: fedratinib (a JAK2-selective inhibitor with off-target FLT3 activity), momelotinib (a JAK1/JAK2/ACVR1 inhibitor with hepcidin-suppressing erythropoietic activity) and pacritinib (a JAK2/IRAK1/ACVR1 inhibitor with minimal JAK1 inhibition and preserved haematological tolerance).¹⁰

No randomized head-to-head trial has compared these three agents. Differences in eligibility (platelet and haemoglobin thresholds, prior JAKi requirements, definitions of ruxolitinib failure), comparator (placebo, best available therapy [BAT] including ruxolitinib continuation, danazol) and end-point instruments (MFSAF v2.0 vs. v4.0, spleen response with or without confirmatory imaging at 24 weeks) complicate indirect comparisons, forcing clinicians and guideline committees to integrate disparate datasets when recommending second-line therapy.¹¹

In this work, we summarized the available evidence as a systematic review with arm-level pooled proportions for efficacy outcomes drawn exclusively from phase 3 pivotal trials, and we integrate all available safety data (pivotal phase 3, supporting phase 2/3b and real-world cohorts) to characterize the toxicity fingerprint of each drug at clinically meaningful exposure.

STUDIES COLLECTION

Aim

The aim of this review was to systematically assess the evidence on the efficacy and safety of second-line JAKis (fedratinib, momelotinib and pacritinib) in patients with MF after ruxolitinib failure, to inform a phenotype-driven framework for treatment selection, in accordance with PRISMA 2020 guidance and the PRISMA harms extension. The study selection is documented in the PRISMA 2020 flow diagram (Figure S1).

Study's eligibility criteria

Efficacy synthesis

Inclusion criteria for the efficacy synthesis were prospective phase 3 (or pivotal phase 2 supporting registration) trials of fedratinib, momelotinib or pacritinib, reporting data of adult patients with primary, post-polycythaemia vera or

post-essential thrombocythaemia MF, with prior exposure to ruxolitinib (defined per trial protocol as failure or intolerance). Trials in JAKi-naïve patients exclusively were excluded from the efficacy synthesis.

Safety synthesis

For the safety synthesis, we additionally included the phase 2 dose-finding PAC203 trial, the phase 3b FREEDOM trial, the placebo-controlled phase 3 JAKARTA-1 trial, and the phase 2 dose-ranging fedratinib SAR302503 trial, the latter incorporated into the pooled fedratinib trial denominator. For momelotinib, the phase 3 SIMPLIFY-1 trial (JAKi-naïve) was included as a drug-level safety reference, with real-world safety corroborated by five independent cohorts (UK-Wide, MoReLife, MOMGEMFIN, the Italian-US cooperative study, and a post-FDA-approval Mayo Clinic series in JAKi-naïve patients). For fedratinib, a US community-based retrospective cohort was included as the first real-world fedratinib safety dataset after ruxolitinib failure. For pacritinib, a single-centre real-world cohort (Mayo Clinic, $n = 60$) of patients treated outside clinical trials was included as the first real-world pacritinib safety dataset. The phase 3 PERSIST-1 trial, evaluating pacritinib at 400 mg once daily (not approved following the 2016 FDA clinical hold), was excluded from the quantitative pool, but its safety data were discussed descriptively to contextualize the drug-level cardiac and bleeding signals observed at this non-registered dose.

Outcomes

The pre-specified primary efficacy outcome was $\geq 35\%$ reduction in spleen volume from baseline (SVR35) at week 24, assessed by central, blinded MRI or CT. Secondary efficacy outcomes were $\geq 25\%$ spleen volume reduction (SVR25) at week 24, $\geq 50\%$ reduction in MFSAF Total Symptom Score (TSS50) at week 24, and transfusion independence (TI) at week 24 (the most stringent 12-week terminal definition where available). Pre-specified subgroup outcomes were SVR35 and TSS50 in patients with baseline platelet counts $< 50 \times 10^9/L$, and TI rates in baseline transfusion-dependent or haemoglobin $< 10 g/dL$ subgroups.

Pre-specified safety outcomes were grade ≥ 3 haematological toxicities, any-grade diarrhoea, grade ≥ 3 bleeding, grade ≥ 3 cardiac events, any-grade peripheral neuropathy, all reported cases of Wernicke or Wernicke-like encephalopathy, and treatment discontinuation due to adverse events. Safety denominators were the as-treated safety population reported by each trial.

Statistical analysis

For each efficacy outcome and each drug, we calculated arm-level pooled proportions as $\Sigma \text{ events} / \Sigma \text{ patients across}$

studies of the same drug, with 95% confidence intervals (CIs) derived by the Wilson score method. For the principal efficacy outcomes, pairwise comparisons between drugs were performed by Fisher's exact test. The same arm-level pooling and Wilson CI approach were applied to safety outcomes. Risk of bias in randomized trials was assessed independently by two reviewers across the five standard domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result). Real-world cohorts were not included in the efficacy synthesis because spleen and symptom responses in these series were assessed by non-equivalent methods (predominantly palpation rather than centrally-read volumetric imaging, and without systematic MFSAF administration) and at heterogeneous timepoints, rendering them non-commensurable with the trial-defined SVR35 and TSS50 end-points.

No formal network meta-analysis was performed, as the absence of a common comparator linking momelotinib, fedratinib and pacritinib precluded a connected network. Additionally, the pooled SVR35 estimate for momelotinib was recomputed after excluding SIMPLIFY-2, in which there was no ruxolitinib washout and a BAT arm comprising 89% of patients on continued ruxolitinib could dilute the momelotinib effect. The pooled SVR35 estimate for fedratinib was recomputed after excluding JAKARTA-2 to assess the influence of this single-arm phase 2 trial on the overall signal. For grade ≥ 3 thrombocytopenia in momelotinib trials, the SIMPLIFY-2 and MOMENTUM rates were analysed separately and then pooled, given the structurally different baseline platelet distributions between the two populations. For pacritinib, the registered 200 mg twice-daily regimen was the sole unit of analysis in all between-drug comparisons of efficacy and safety. The 400 mg once-daily regimen was used only for the within-trial dose comparison in PERSIST-2 (symptom response) and, descriptively, for the safety signals of the non-registered dose in PERSIST-1.

All analyses were performed in MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium; <https://www.medcalc.org>; 2020) and Prism 9 (version 9.5.1, 528, 24 January 2023).

RESULTS

Study selection and characteristics

The systematic search identified five phase 3/pivotal phase 2 trials meeting eligibility criteria for the efficacy synthesis: JAKARTA-2 ($n=97$), SIMPLIFY-2 ($n=156$, 104 momelotinib), MOMENTUM ($n=195$, 130 momelotinib), FREEDOM2 ($n=201$, 134 fedratinib) and PERSIST-2 ($n=311$, 106/104 across 200 mg BID/400 mg every day).^{12–16} For the integrated safety synthesis, the fedratinib trial pool comprised JAKARTA-2 ($n=97$), FREEDOM ($n=38$), FREEDOM2 ($n=134$), JAKARTA-1 ($n=96$, 400 mg arm)

and SAR302503 ($n=31$), totalling $n=396$. The momelotinib trial pool comprised SIMPLIFY-1 (JAKi-naïve, $n=214$), SIMPLIFY-2 ($n=104$) and MOMENTUM ($n=130$), totalling $n=448$. The pacritinib 200 mg BID pool comprised PERSIST-2 ($n=106$) and PAC203 ($n=54$), totalling $n=160$. Real-world safety cohorts: momelotinib (UK-Wide $n=85$, MoReLife $n=60$, MOMGEMFIN $n=154$, Italian-US $n=221$, Mayo post-FDA $n=60$; total $n=580$), fedratinib (US community, $n=150$), pacritinib (Mayo, $n=60$, predominantly 100 mg). PERSIST-1 (pacritinib 400 mg QD, $n=220$) was discussed descriptively only. The integrated safety dataset comprised 1794 patients (1004 trial; 790 real-world).^{17–30}

Trial characteristics are summarized in Table 1, while patients' basal characteristics are reported in Table S1.

Efficacy outcomes from phase 3 trials

Spleen volume reduction at week 24

Pooled across the three fedratinib phase 3 trials ($n=266$), SVR35 at week 24 was 32.7% (95% CI 27.3–38.6). For momelotinib (MOMENTUM + SIMPLIFY-2, $n=234$), pooled SVR35 was 15.8% (11.7–21.0). For pacritinib 200 mg BID (PERSIST-2, $n=74$), SVR35 was 21.6% (13.8–32.3) (Table 2; Figure 1). Fedratinib significantly exceeded momelotinib (relative risk [RR] 2.07, 95% CI 1.45–2.95; $p<0.0001$) and was numerically higher than pacritinib BID (RR 1.51, 0.97–2.36; $p=0.08$); momelotinib and pacritinib BID did not differ (RR 0.73, 0.44–1.22; $p=0.27$). Restricted to MOMENTUM alone, momelotinib SVR35 was 23.1% (16.7–31.0), comparable to pacritinib BID ($p=0.85$).

SVR25 at week 24

SVR25 (reported by FREEDOM, FREEDOM2, MOMENTUM): pooled fedratinib 51.5% (87/169; 43.9–59.0), momelotinib (MOMENTUM only) 50.5% (41.0–59.9; Figure S2), statistically indistinguishable ($p=0.91$), suggesting the SVR35 fedratinib advantage reflects deeper shrinkage rather than a higher responder fraction.

Symptom response (TSS50) at week 24

Pooled TSS50 rates were closest between fedratinib and pacritinib 200 mg BID (32.8% [86/262, 27.4–38.7] and 32.4% [22.9–43.7], respectively), with momelotinib somewhat lower (25.3% [20.2–31.3]) (Figure 2). The fedratinib pool includes JAKARTA-2, FREEDOM and FREEDOM2, with the JAKARTA-2 denominator set to the intention-to-treat (ITT) $n=100$, consistent with the 27% rate reported in the primary publication. Pacritinib at the non-registered 400 mg once-daily dose produced a lower response fraction (17.3% [10.4–27.4]); the direct within-trial comparison of the two pacritinib schedules confirmed superiority of the

TABLE 1 Characteristics of included trials and real-world cohorts.

Trial	Phase/design	N (active arm)	Drug	Comparator	Setting (RUX exposure)	Used for
JAKARTA-2 ^{12,13}	Phase 2 single-arm	97 (ITT)	Fedratinib 400 mg QD	None	Post-RUX	Efficacy and safety
FREEDOM2 ¹⁴	Phase 3 RCT	134 fed/67 BAT	Fedratinib 400 mg QD	BAT (78% RUX)	Post-RUX	Efficacy and safety
SIMPLIFY-2 ³⁰	Phase 3 RCT	104 mom/52 BAT	Momelotinib 200 mg QD	BAT (89% RUX)	Post-RUX, no washout	Efficacy and safety
MOMENTUM ¹⁵	Phase 3 RCT	130 mom/65 dan	Momelotinib 200 mg QD	Danazol	Post-JAKi, anaemic	Efficacy and safety
PERSIST-2 ¹⁶	Phase 3 RCT	106 BID/104 QD	Pacritinib 200 mg BID	BAT	Plt ≤100, ~45% post-RUX	Efficacy and safety
FREEDOM ¹⁷	Phase 3b single-arm	38	Fedratinib 400 mg QD	None	Post-RUX plus mitigation	Safety only
PAC203 ¹⁸	Phase 2 dose-finding	54 (200 BID arm)	Pacritinib 200 mg BID	Lower doses	Post-RUX	Safety only
JAKARTA-1 ¹⁹	Ph3 RCT placebo-control	96 (400 mg arm)	Fedratinib 400 mg QD	Placebo	JAKi-naïve	Safety only
SAR302503 ²⁰	Phase 2, dose-ranging RCT	31 (pooled active arms)	Fedratinib 300/400/500 mg QD	Placebo	Mixed JAKi exposure (included JAKi-naïve)	Safety only
SIMPLIFY-1 ²⁸	Phase 3, double-blind RCT	214 mom/215 rux	Momelotinib 200 mg QD	Ruxolitinib	JAKi-naïve	Safety only
PERSIST-1 ²⁷	Phase 3, open-label RCT	220 (400 mg QD arm)	Pacritinib 400 mg QD (non-registered dose)	BAT (excluded JAKi)	JAKi-naïve and JAKi-experienced	Descriptive context only; excluded from quantitative safety pool
UK-Wide ²²	RWE multicentre	85	Momelotinib	—	78% RUX-exposed	Safety RWE
MoReLife ²⁴	RWE multicentre	60	Momelotinib	—	55% RUX-exposed	Safety RWE
MOMGEMFIN ²¹	RWE multicentre	154	Momelotinib	—	77% RUX-exposed	Safety RWE
Mayo Clinic Momelotinib Series ²³	RWE uncentric	60	Momelotinib	—	JAKi-naïve	Safety RWE
Italian-US cohort ²⁶	RWE multicentre	221	Momelotinib	—	Post-RUX	Safety RWE
US community cohort ²⁵	RWE multicentre	150	Fedratinib	—	Post-RUX	Safety RWE
Mayo Clinic Pacritinib series ²⁹	RWE, single-centre, retrospective	60	Pacritinib (41/60 at 100 mg; 19/60 at 200 mg BID)	—	68% JAKi-experienced; 25% plt <50 × 10 ⁹ /L	Safety RWE

Note: As described in the text, for PERSIST-2 only, the 200 mg BID arm was retained for the primary efficacy analysis.

Abbreviations: Plt: platelets; BAT, best available therapy; BID, twice daily; DAN, danazol; JAKi, JAK inhibitor; QD, once daily; RCT, randomized clinical trial; RUX, ruxolitinib; RWE, real-world evidence.

TABLE 2 SVR35 at week 24 by drug and trial.

Drug	Trial	Events/N	Rate (%)	95% CI
Fedratinib	—	—	—	—
	JAKARTA-2	30/97	30.9	22.6–40.7
	FREEDOM2	48/134	35.8	28.2–44.2
	FREEDOM	9/35	25.7	14.2–42.1
Pooled fedratinib		87/266	32.7	27.3–38.6
Momelotinib	—	—	—	—
	MOMENTUM	30/130	23.1	16.7–31.0
	SIMPLIFY-2	7/104	6.7	3.3–13.2
Pooled momelotinib		37/234	15.8	11.7–21.0
Pacritinib 200 mg BID	PERSIST-2	16/74	21.6	13.8–32.3
Pacritinib 400 mg QD	PERSIST-2	11/75	14.7	8.4–24.4

Note: Pooled estimate = Σ events/ Σ N across trials of the same drug. Bolded values are the pooled data.

Abbreviation: CI, confidence interval; SVR35, $\geq 35\%$ spleen volume reduction from baseline by central MRI/CT.

twice-daily regimen (RR 1.87, 95% CI 1.03–3.39; $p = 0.038$), supporting the registered dose. Between-drug comparisons yielded $p = 0.075$ for fedratinib versus momelotinib and $p = 0.83$ for fedratinib versus pacritinib BID. Only the fedratinib-versus-pacritinib-400-mg-QD comparison reached significance ($p = 0.006$), reflecting the inferiority of the non-registered once-daily schedule rather than a class-level fedratinib advantage.

Transfusion independence at week 24

TI at week 24 (no transfusions and no haemoglobin $< 8\text{ g/dL}$ over 12 weeks) was pre-specified only for momelotinib: pooled 36.3% (30.4–42.7; MOMENTUM 30.8%, SIMPLIFY-2 43.3%). Fedratinib trials did not pre-specify a comparable strict TI end-point (FREEDOM2 and PERSIST-2 reported transfusion-burden reduction descriptively; pacritinib BID transfusion-burden reduction was 22% vs. 9% BAT). A pooled cross-drug TI estimate is therefore not computable (Table S2).

Subgroup of severe thrombocytopenia (platelets $< 50 \times 10^9/\text{L}$)

In the platelet $< 50 \times 10^9/\text{L}$ subgroup, pacritinib 200 mg BID achieved SVR35 in 29.0% (9/31, PERSIST-2, vs. 3% BAT, $p = 0.045$) and 31% in PAC203. Momelotinib (MOMENTUM post hoc) achieved 22.2% (4/18). Fedratinib data are unavailable (JAKARTA-2 excluded platelets < 50 ; FREEDOM2 required ≥ 50). Pacritinib remains the only agent with prospective phase 3 data in this subgroup.

Time-to-response and duration of response

Time-to-response and response duration were reported too heterogeneously to support arm-level pooling. Onset of spleen and symptom responses with fedratinib and momelotinib was typically observed within the first 1–2 and 1–3 months of treatment, respectively, whereas pacritinib trials did not report time-to-response as a dedicated metric. For the duration of spleen response, the evidence was markedly asymmetric. FREEDOM2 reported a median duration of 86.3 weeks by imaging (118.3 weeks by palpation), while in the single-arm JAKARTA-2, the median was not reached. In MOMENTUM, week-24 spleen responses to momelotinib were durable through week 48, with no responder showing spleen regrowth from baseline, although a formal median duration was not estimable within the 24-week randomized period owing to the open-label crossover design. Neither PERSIST-2 nor PAC203 reported a median duration of spleen response, as both were truncated by the 2016 FDA clinical hold, precluding reliable estimates of durability.

Integrated safety analysis

The integrated safety dataset (1794 patients; 1004 trial, 790 real-world) is summarized in Table 3. Fedratinib showed the highest pooled grade ≥ 3 anaemia rate, 34.3% (136/396), consistent across JAKARTA-2 (38.1%), FREEDOM (39.5%), FREEDOM2 (27.6%), JAKARTA-1 (30.0%), with SAR302503 the highest (58%), reflecting supra-registration dosing (300–500 mg). The real-world cohort (haemoglobin $< 10\text{ g/dL}$ in 91%) confirms the predominance of anaemia. Pacritinib BID showed an intermediate rate (21.2%; PERSIST-2 21.7%, PAC203 20.4%), with no real-world erythropoietic benefit (anaemia response 1/47, 2%). Momelotinib had the lowest rate (8.0%, 36/448); real-world cohorts confirmed the anaemia-sparing profile (haemoglobin response 37%–84%, TI 21%–48%, treatment-emergent anaemia $\leq 4.8\%$).

For thrombocytopenia, fedratinib pooled grade ≥ 3 rate was 17.2% (68/396; SAR302503 16%). The momelotinib pooled estimate (12.9%) reflects heterogeneity and should not be read as a single rate (SIMPLIFY-1 7.0%, SIMPLIFY-2, MOMENTUM 28%); [Correction added on 25 September 2026, after first online publication: The preceding sentence was corrected.] real-world cohorts ranged 6.2% (MOMGEMFIN) to 28% (Mayo), with stable platelet counts over 3–6 months in MOMGEMFIN/MoReLife/Italian-US, confirming a baseline-driven (not drug-induced) signal—thrombocytopenia was nonetheless the leading cause of discontinuation in the cooperative cohort (6.3%). Pacritinib BID showed 32.5% (PERSIST-2 32.1%, PAC203 33.3%); the real-world cohort (predominantly 100 mg) reported 45% (27/60) grade ≥ 3 thrombocytopenia and 18% (11/60) grade ≥ 3 neutropenia, consistent with enrolment of a heavily thrombocytopenic population (25% with baseline platelets $< 50 \times 10^9/\text{L}$). After accounting for baseline distribution, none of the three

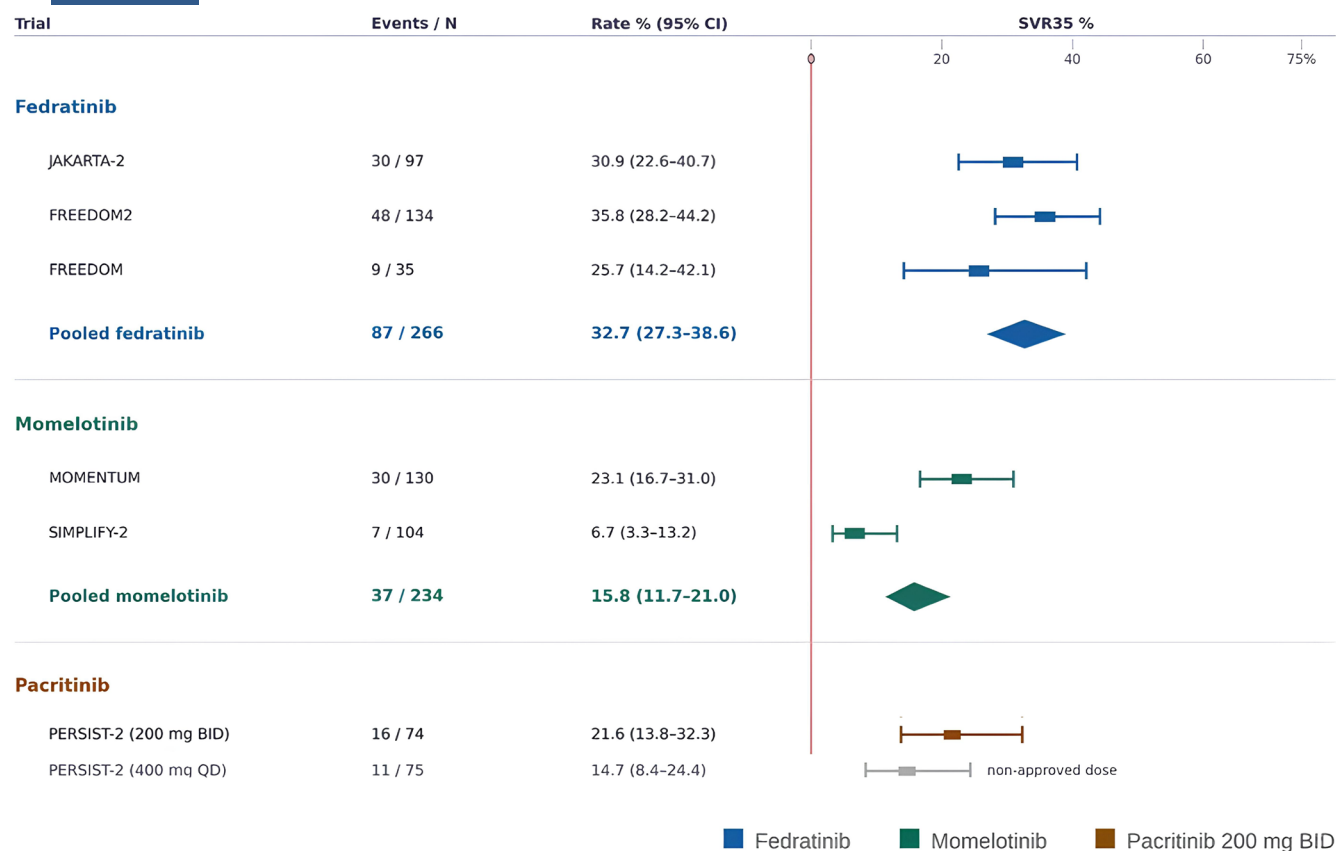


FIGURE 1 Pooled arm-level proportions of $\geq 35\%$ spleen volume reduction (SVR35) at week 24 per drug and trial, with 95% Wilson confidence intervals. Diamond = pooled estimate.

drugs show a catastrophic thrombocytopenia signal at registered exposure.

Any-grade diarrhoea was substantially more common with fedratinib (56.6%, 224/396) and pacritinib 200 mg BID (41.9%, 67/160) than with momelotinib (21.2%, 95/448), but the fedratinib rate is driven predominantly by trials that did not mandate gastrointestinal (GI) prophylaxis: JAKARTA-2 (61.9%), JAKARTA-1 (66%) and SAR302503 (81%, at exploratory doses of 300–500 mg once daily). In the two trials that mandated proactive anti-emetic/anti-diarrhoeal prophylaxis and early intervention algorithms (FREEDOM and FREEDOM2), diarrhoea rates fell to 31.6% and 47.8%, respectively, and grade ≥ 3 diarrhoea remained $\leq 5\%$ across the fedratinib programme (13% in SAR302503). Notably, the US community real-world cohort reported diarrhoea in only 15.3% (23/150), a substantial gap likely reflecting routine premedication use in clinical practice (anti-emetic 42%, anti-diarrhoeal 38%, thiamine 53%). In real-world studies, momelotinib-related diarrhoea ranged from 4.1% to 16.7% across cohorts. For pacritinib, PAC203 showed a lower rate (29.6%) than PERSIST-2 (48.1%); these two trials differ both in dose exposure and in the enrolled population, PERSIST-2 including patients with more severe thrombocytopenia and a heavier baseline symptom burden, so the between-trial gap should not be attributed to dose alone. The real-world Mayo pacritinib cohort reported GI symptoms in

55% (33/60); at the non-registered 400 mg once-daily dose (PERSIST-1), diarrhoea also reached 55%.

Grade ≥ 3 cardiac events could not be pooled for momelotinib, as they were not consistently reported across the included trials. For fedratinib, FREEDOM reported a rate of 10.5% (4/38), including one grade 5 congestive heart failure. For pacritinib 200 mg BID, the pooled rate was 5.6% (9/160; PERSIST-2 6.6%, PAC203 3.7%). Historical context is relevant. At the non-registered 400 mg once-daily dose in PERSIST-1, severe cardiac events reached 8% (the signal that prompted the 2016 FDA clinical hold), whereas the 200 mg BID rate is comparable to BAT and represents the currently registered exposure. In the real-world Mayo pacritinib cohort, peripheral oedema (30%) and dyspnoea (25%) were the dominant cardiovascular findings, and no bleeding events were reported.

Peripheral neuropathy is a signal specific to momelotinib, absent in the fedratinib and pacritinib programmes. The pooled trial rate was 8.5% (38/448), almost entirely grade 1–2 (SIMPLIFY-1 10.3%, SIMPLIFY-2 11.0%, MOMENTUM 3.8%). Across real-world cohorts, rates were more variable: MOMGEMFIN reported 4.8% (mostly grade 1–2), the Italian–US cooperative cohort reported grade ≥ 3 events in 2.3% plus four additional low-grade cases, and the post-FDA-approval Mayo series reported 20% (grade 1 in 67%, grade 2 in 25%, grade 3 in 8%). Reversibility was heterogeneous in the Mayo series (complete recovery 33%, partial

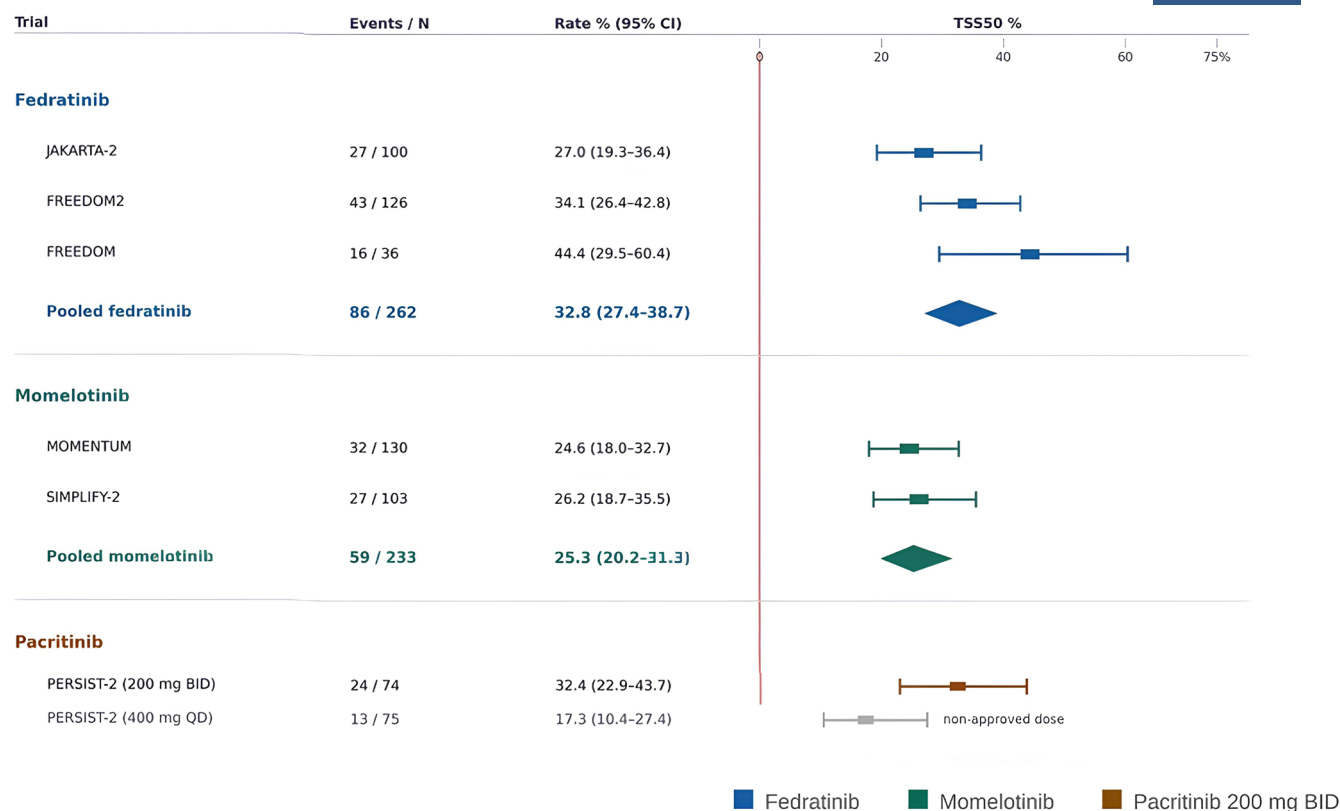


FIGURE 2 Pooled arm-level proportions of $\geq 50\%$ reduction in MFSAF Total Symptom Score (TSS50) at week 24 per drug and trial, with 95% Wilson confidence intervals. MFSAF V2.0 was used in all trials except FREEDOM/FREEDOM2 (V4.0). Diamond = pooled estimate.

25%, none 42%), independent of dose reduction. The overall range (4.8%–20%) and the incomplete reversibility warrant active neurological monitoring.

Wernicke-like encephalopathy is fedratinib-specific: four cases across the programme (one JAKARTA-2, two FREEDOM2 and one post-cut-off SAR302503), pooled 1.0% (4/396; 0.4–2.6), programme-level $\sim 7/600$. The real-world cohort reported no cases (0/150), with thiamine prescribed in 53%.

Nephrotoxicity emerged almost entirely from real-world data, not pre-specified in pivotal momelotinib trials. Renal impairment ranged 1.4% (MOMGEMFIN, any grade) and 2.7% (Italian-US, grade 3/renal failure) to 17% (MoReLife, grade 1–2, resolving in 4/10, persisting in 5/10) and 29% (Mayo, glomerular filtration rates decline $>20\%$, 23% crossing to abnormal creatinine, 2 patients reaching severe chronic kidney disease). Independent predictors (Mayo): pre-existing renal impairment, older age, leucocytosis; decline largely reversible on discontinuation.

Taken together, integrating phase 2/real-world data confirms trial-derived signals at population scale (fedratinib GI/anaemia burden; pacritinib thrombocytopenia/bleeding, persisting at 45% in real-world; momelotinib anaemia benefit), while surfacing momelotinib nephrotoxicity and variable neuropathy reversibility under-captured by pivotal trials. Discontinuation due to AEs was similar across trial pools (fedratinib 15.4%, momelotinib 15.4%, pacritinib BID 16.2%). Real-world discontinuation was broadly consistent

with trial-level rates for fedratinib (2.7%) and momelotinib (4%–20%). The published pacritinib real-world experience is limited to a single 60-patient Mayo Clinic cohort characterized by severe baseline cytopenia (25% with platelets $<50 \times 10^9/L$), predominant treatment at the reduced 100 mg dose (41/60), frequent dose reductions, a high proportion of JAKi-experienced and heavily pretreated patients (68%), and consequently short treatment duration. The 88% discontinuation reported in this cohort therefore reflects an interaction between advanced disease phenotype and low-exposure dosing rather than a signal of drug-specific tolerability, and is not directly comparable with the 16.2% trial rate observed at the registered 200 mg BID exposure.

The overall pooled adverse events from clinical trials are reported in Figure 3.

DISCUSSION

This systematic review and arm-level pooled analysis provides clinically actionable findings on fedratinib, momelotinib and pacritinib in post-ruxolitinib MF. On the splenic-response end-point defining the JAK-inhibitor class since COMFORT, fedratinib produces the highest pooled SVR35 (32.7%), exceeding momelotinib (15.8%) and pacritinib BID (21.6%). This is tempered by the momelotinib estimate being heavily diluted by SIMPLIFY-2 (no ruxolitinib washout, BAT arm almost entirely continued ruxolitinib). Restricted to

TABLE 3 Pooled safety rates by drug across all included trials and real-world experiences.

Adverse event	Fedratinib		Mometotinib		Pacritinib 200 mg BID	
	Trials (<i>n</i> = 396)	Real-world (<i>n</i> = 150)	Trials (<i>n</i> = 448)	Real-world (<i>n</i> = 580)	Trials (<i>n</i> = 160)	Real-world (<i>n</i> = 60)
Anaemia, grade ≥ 3	34.3% (136/396) 29.8–39.2	NR	8.0% (36/448) 5.9–10.9	$\leq 4.8\%^a$	21.2% (34/160) 15.6–28.2	NR
Thrombocytopenia, grade ≥ 3	17.2% (68/396) 13.8–21.2	NR	12.9 (58/448) 10.0–16.4	6.2%–28% (by cohort)	32.5% (52/160) 25.7–40.1	45% (27/60)
Diarrhoea, any grade	56.6% (224/396) 51.6–61.4	15.3% (23/150) 10.4–22.0	21.2% (95/448) 17.7–25.2	4.1%–16.7% (by cohort)	41.9% (67/160) 34.5–49.6	55% (GI, 33/60)
Cardiac event, grade ≥ 3	10.5% (4/38, FREEDOM)	NR	NR	NR	5.6% (9/160) 3.0–10.3	NR
Bleeding, grade ≥ 3	3.0% (8/268) 1.5–5.8	NR	NR	NR	11.2% (18/160) 7.2–17.1	NR
Peripheral neuropathy, any grade	NR	NR	8.5% (38/448) 6.2–11.4	4.8%–20% (by cohort)	NR	NR
Nephrotoxicity (eGFR $\downarrow$ $>20\%$ creatinine $\uparrow$)	NR	NR	NR	1.4%–29% (by cohort)	NR	NR
Wernicke encephalopathy	1.0%^b (4/396) 0.4–2.6	0/150	NR	NR	NR	—
Discontinuation due to AE	15.4% (61/396) 12.2–19.3	2.7% (4/150) 1.0–6.7	15.4% (69/448) 12.4–19.0	4%–20% (by cohort)	16.2% (26/160) 11.3–22.7	88% ^c (53/60)

Note: Bolded values are the pooled data.

Abbreviation: NR, not reached.

^aFor real-world momelotinib, anaemia response is an efficacy end-point rather than a toxicity, so treatment-emergent anaemia was rarely reported.

^bThe fedratinib trial pool incorporates the phase 2 SAR302503 study (*n* = 31). The Wernicke count (4/396) comprises JAKARTA-2 (1), FREEDOM2 (2) and the SAR302503 post-cut-off case (1). The programme-level estimate across all fedratinib studies is approximately 7/600.

^cPacritinib real-world cohort: 68% JAKi-experienced, only 19/60 treated at 200 mg twice daily and 41/60 at 100 mg; 25% had baseline platelets $<50 \times 10^9/L$.

[Correction added on 25 September 2026, after first online publication: Footnote a was removed and the subsequent footnotes were relabelled].

[Correction added on 25 September 2026, after first online publication: The values under Mometotinib and Thrombocytopenia, grade ≥ 3 were corrected].

MOMENTUM, momelotinib SVR35 was 23.1%, indistinguishable from pacritinib BID. The fedratinib advantage may also reflect favourable selection (FREEDOM2 required platelets $\geq 50 \times 10^9/L$; JAKARTA-2 enrolled a less pre-treated population; FREEDOM included intermediate-1 risk patients). At the less stringent SVR25, fedratinib and momelotinib are indistinguishable (51.5% vs. 50.5%), suggesting fedratinib achieves deeper shrinkage in a fitter population rather than more responders overall.³¹ Each drug occupies a distinct anaemia–thrombocytopenia trade-off. Mometotinib is the only agent with prospective TI benefit (pooled 36.3%) and the lowest grade ≥ 3 anaemia (8.0%, including JAKi-naïve SIMPLIFY-1), attributable to ACVR1/hepcidin targeting.^{32–34} Discontinuation rates due to adverse events (AEs) were similar across drugs in the expanded pool (fedratinib 15.4%, momelotinib 15.4%, pacritinib BID 16.2%), confirming comparable practical tolerability with supportive care.

The absence of a randomized head-to-head comparison is the dominant feature of this evidence base. A formal network

meta-analysis is precluded by the absence of any common comparator. BAT-with-rux (SIMPLIFY-2, PERSIST-2), BAT-without-ruxolitinib (FREEDOM2), danazol (MOMENTUM) and no comparator (JAKARTA-2/FREEDOM/PAC203) do not share a coherent reference.

The limitations are substantial. Arm-level pooling does not adjust for between-trial differences in baseline patient mix, which heavily influence both efficacy and safety estimates. Definitional heterogeneity is pervasive: TI is defined differently across trials, and only MOMENTUM was designed around this end-point; the MFSAF instrument changed version (v2.0 vs. v4.0) between eras, and spleen-volume confirmation criteria differ.^{35,36} Single-arm trials (JAKARTA-2, FREEDOM, PAC203) provide weaker causal inference and are restricted to safety, contributing to real-exposure denominators. Real-world cohorts ascertained AEs non-systematically and had shorter follow-up periods. Their rates are descriptive and not directly comparable with pooled trial estimates, and they under-capture toxicity, but surface signals that pivotal

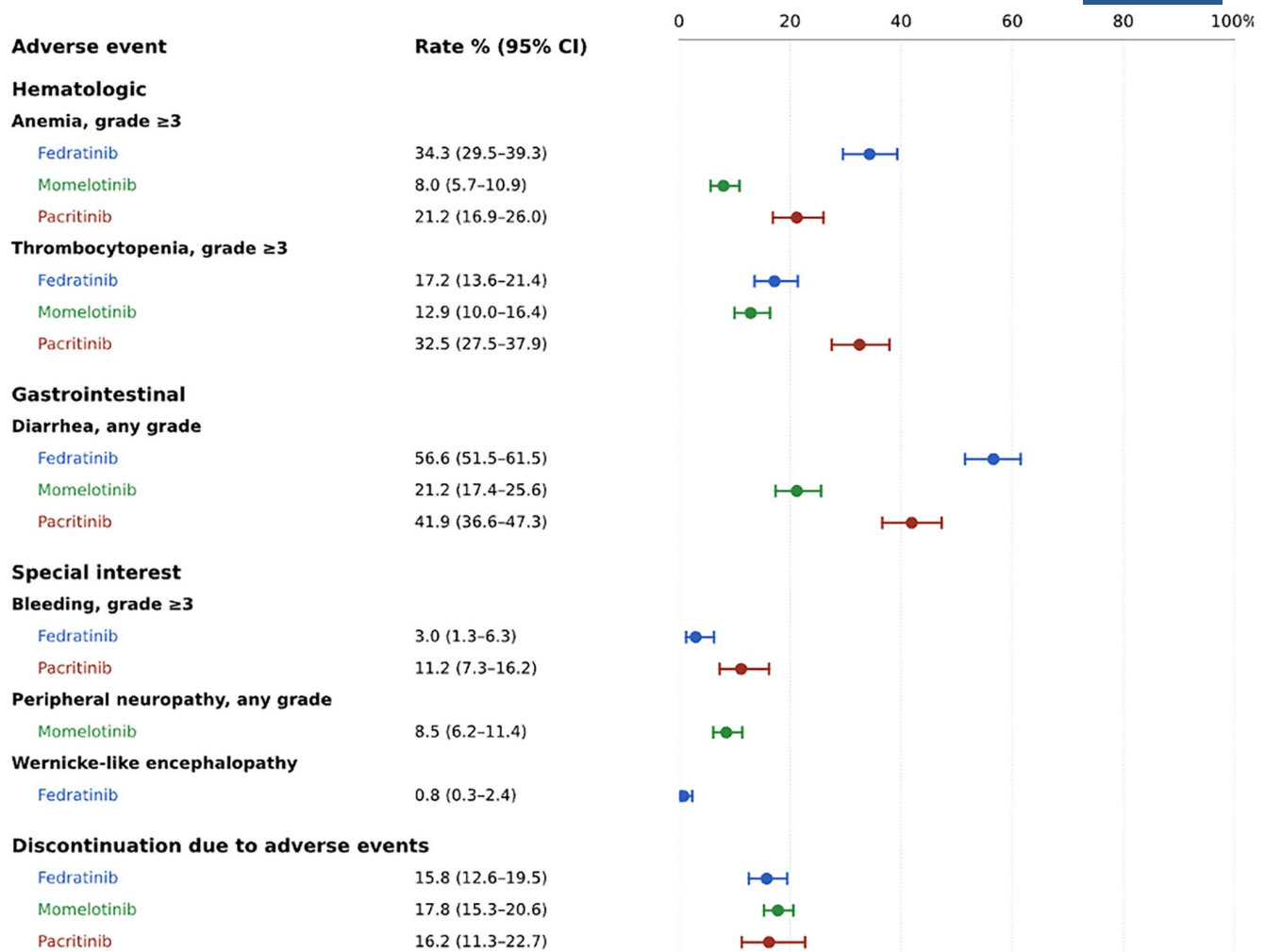


FIGURE 3 Pooled adverse event rates from clinical trials per drug, with 95% Wilson confidence intervals. [Correction added on 25 September 2026, after first online publication: Figure 3 and its caption were corrected].

trials were not designed to detect. PERSIST-2 was truncated by the 2016 FDA clinical hold, and JAKARTA-2 was terminated early for the same reason, causing unreconciled follow-up imbalances. Time-to-response and response duration could not be compared across agents because these parameters were reported with differing definitions, were affected by censoring due to early trial termination, and were confounded by cross-over designs. Harmonized durability data represent a priority for future prospective registries. We did not assess overall survival or leukaemic progression due to variable follow-up, cross-over designs and short randomized periods. These findings are consistent with a recent meta-analysis confirming SVR is associated with improved overall survival across approved JAKis, supporting the clinical relevance of between-drug differences in spleen response.³⁷

The central question in second-line selection is which disease biology dominates at ruxolitinib failure, since the three agents target distinct pathophysiological axes. Three phenotypes can help guide selection. The anaemic phenotype (Hb <10 g/dL, transfusion dependence) may favour momelotinib, the only agent with a randomized trial powered for TI and

a mechanism directly targeting MF-associated anaemia. Fedratinib's highest pooled grade ≥ 3 anaemia rate (34.3%) warrants caution, while pacritinib's transfusion data remain descriptive. The thrombocytopenic phenotype (platelets <50 $\times 10^9$ /L), for which fedratinib trials were not designed, may favour pacritinib on the basis of prospective phase 3 efficacy at this threshold and a pharmacological profile (minimal JAK1 inhibition, preserved platelet output) suited to this population. The numerically higher ≥ 3 bleeding rate observed with pacritinib compared with fedratinib is not a direct drug-versus-drug signal, as the pacritinib trials enrolled substantially more thrombocytopenic patients at baseline. Bleeding in this setting could be predominantly a manifestation of disease-driven cytopenia rather than of drug-specific coagulopathy.^{38,39} The proliferative phenotype (preserved counts, dominant splenomegaly, intact performance status) may favour fedratinib, which achieves the deepest splenic responses (pooled SVR35: 32.7%). Momelotinib, although evaluated in SIMPLIFY-1 as a first-line option, where it met non-inferiority in SVR35 versus ruxolitinib and demonstrated superior transfusion-related outcomes, showed

Phenotype-Driven Selection of JAK Inhibitors Post-Ruxolitinib in Myelofibrosis

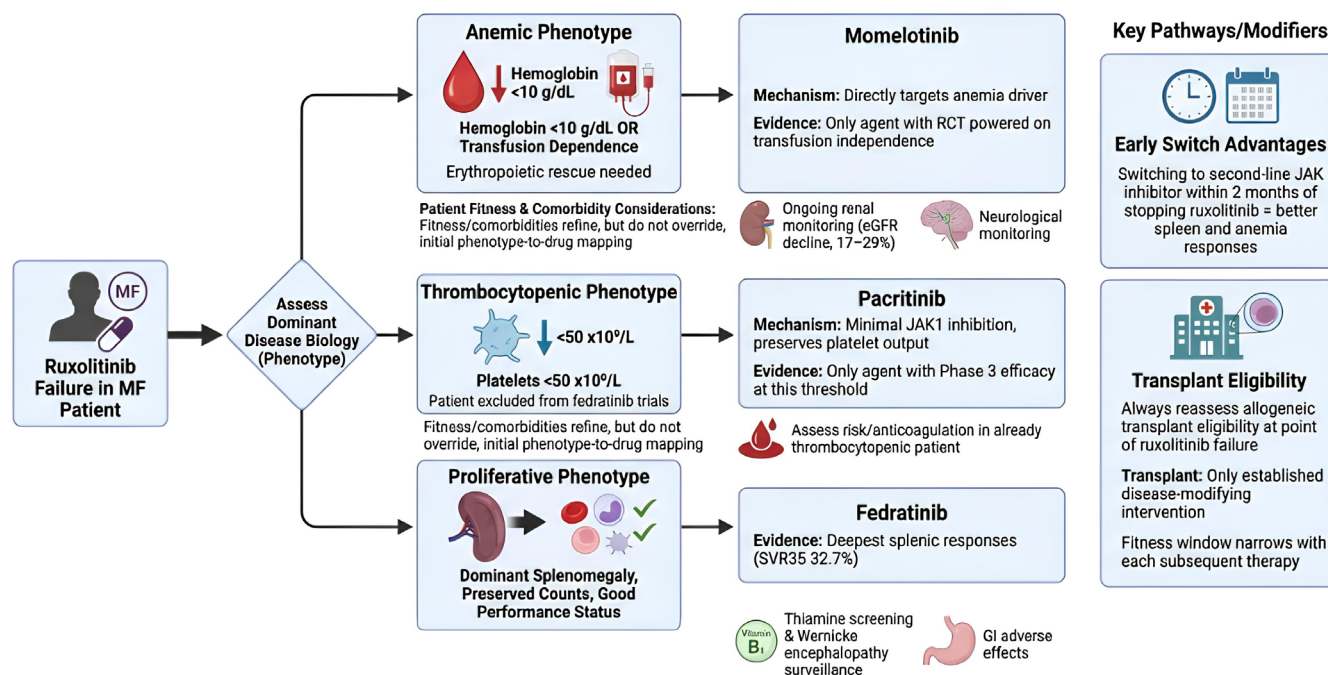


FIGURE 4 The phenotype-driven selection of JAK inhibitor after ruxolitinib failure, based on biological, clinical and fitness criteria, as described in the text. GI, gastrointestinal; JAK, Janus kinase; MF, myelofibrosis; RCT, randomized clinical trial; SVR35, spleen volume response $\geq 35\%$.

superiority against danazol in MOMENTUM across the primary TSS50 end-point and both key secondary endpoints (TI and SVR35). A post hoc pooled SIMPLIFY-1/MOMENTUM analysis subsequently identified the combined attainment of TI and SVR as a prognostically meaningful composite end-point.^{28,40,41}

Patient fitness represents the second decision layer. Momelotinib requires active renal and neurological monitoring (glomerular filtration rates decline >20% in 17%–29% across real-world cohorts; neuropathy variably reversible). Fedratinib requires attention to thiamine status and Wernicke surveillance, plus GI toxicity management. Pacritinib requires careful evaluation of bleeding history and anticoagulation in the already thrombocytopenic patient. These considerations refine the choice within a phenotype without overriding the phenotype-directed choice.

Beyond the scope of the present pooled analysis, two considerations drawn from the external literature further inform second-line management. First, a shorter transition interval from ruxolitinib to second-line therapy appears to favour better outcomes, with patients switching within 2 months achieving higher spleen and anaemia response rates than those with longer gaps.^{42,43} Second, allogeneic transplant eligibility should be formally reassessed at ruxolitinib failure rather than deferred.^{44,45} Notably, the rate of allogeneic transplantation after failure or intolerance of second-line agents could not be derived from our synthesis, as transplantation was not a pre-specified end-point in

the pivotal trials and was not systematically reported; the available estimates derive from heterogeneous retrospective cohorts not superimposable on the post-ruxolitinib second-line population, and this remains an open question for future registry-based study.

A proposed visual summary is reported in Figure 4.

CONCLUSION

Post-ruxolitinib JAKi selection is best guided by the dominant clinical phenotype rather than a single ranked drug list. Looking ahead, biomarker-driven patient selection, combination strategies incorporating anti-fibrotic or erythropoiesis-supporting agents, and prospective registries with harmonized end-points are the three priorities most likely to refine current practice.

AUTHOR CONTRIBUTIONS

Matteo Pacilli: Investigation. **Patrick Harrington:** Writing – review and editing; investigation. **Hillary Catellani:** Investigation. **Novella Pugliese:** Investigation. **Arianna Sbriglione:** Investigation. **Andrea Duminuco:** Conceptualization; investigation; writing – original draft; writing – review and editing; formal analysis; methodology. **Elena Torre:** Investigation. **Annalisa Santisi:** Investigation. **Giuseppe A. Palumbo:** Conceptualization; investigation; writing – review and editing; writing – original draft; supervision.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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