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REVIEW ARTICLE

Ten years of experience with ruxolitinib since approval for polycythemia vera: A review of clinical efficacy and safety

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Abstract

The oral Janus kinase (JAK) 1/JAK2 inhibitor ruxolitinib was approved by the US Food and Drug Administration in 2014 for treatment of patients with polycythemia vera (PV) who have an inadequate response to or intolerance of hydroxyurea (HU). PV is a chronic myeloproliferative neoplasm defined by primary absolute erythrocytosis, bone marrow hypercellularity, and JAK mutations such as *JAK2*V617F. Patients with PV experience burdensome symptoms and are at risk of thromboembolic events, in particular those with resistance to or intolerance of initial treatments such as HU. Other risks for patients with PV include progression of disease to more aggressive forms with worse prognoses, such as myelofibrosis or blast-phase myeloproliferative neoplasms. This review summarizes the efficacy and safety of ruxolitinib from key phase 2 and 3 trials (MAJIC-PV, RESPONSE, RESPONSE-2, RELIEF, and Ruxo-BEAT), large real-world studies, and a decade of postmarketing surveillance safety data. The authors focus on improved blood count control, rates of thromboembolic events, symptom improvement, and markers of disease modification such as reduction of *JAK2*V617F allele burden in patients treated with ruxolitinib. They also discuss the well-characterized safety profile of ruxolitinib regarding hematologic and other adverse events of interest. In the 10 years since its approval, ruxolitinib remains a safe and effective standard-of-care treatment for PV. As the treatment landscape for PV continues to evolve in the coming years, the efficacy and safety profiles of ruxolitinib suggest it will remain a preferred treatment as monotherapy and as a potential backbone of future combination regimens.

KEYWORDS
JAK inhibitor, *JAK2*V617F, MAJIC-PV, polycythemia vera, RELIEF, RESPONSE, REVEAL, ruxolitinib, Ruxo-BEAT

INTRODUCTION

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm defined by primary absolute erythrocytosis, bone marrow hypercellularity, and Janus kinase (JAK) mutations such as *JAK2*V617F or mutations in *JAK2* exon 12.[1] Patients with PV experience both short- and long-term health concerns. Burdensome PV-related symptoms include pruritus, fatigue, night sweats, and splenomegaly-related discomfort.[2,3] Longer-term health concerns include increased risk of thrombosis,[4,5] risk of disease transformation to myelofibrosis or acute myeloid leukemia,[6,7] and reduced survival.[8,9] Although age of PV onset is typically mid-60s, approximately 10%–20% of patients with PV are between 15 and 39 years of age at diagnosis.[10] These adolescent and younger adult patients may carry an increased risk of thrombotic events compared with older adults, such as splanchnic venous thrombosis, which can be exacerbated by longer disease duration due to younger age at diagnosis.[10–12] For all patients with PV, treatment goals include resolution of disease-related signs or symptoms, managing cardiovascular risk factors, and reducing the risk of thrombotic and hemorrhagic complications via sustained hematocrit <45% and reduced white blood cell (WBC) counts.[13–16]

Risk of thromboembolic events guides treatment decisions for cytoreductive therapy regimens. National Comprehensive Cancer Network Practice Guidelines in Oncology (NCCN Guidelines) recommend that patients with PV are stratified into low-risk or high-risk groups based on the conventional risk model, which considers age <60 or ≥60 years and prior history of thrombosis.[14] Newer models can also be considered, such as Mutation-Enhanced International Prognostic Scoring Systems-PV, which additionally integrates leukocyte count ≥15 × 10^9/L, age >67 years, and adverse *SRSF2* mutations.[17] For patients with asymptomatic low-risk PV, NCCN Guidelines recommend management of cardiovascular risk factors, aspirin, and phlebotomy as initial treatment options, and for symptomatic low-risk disease with development of certain indications (e.g., disease-related symptoms, progressive thrombocytosis, and/or leukocytosis) recommends cytoreductive regimens including hydroxyurea (HU), ropeginterferon α-2b-njft, and peginterferon α-2a (for certain patients [e.g., younger or pregnant patients]).[14] High-risk PV NCCN Guidelines recommendations include management of cardiovascular risk factors, aspirin, and phlebotomy plus cytoreductive regimens as initial treatment options (HU, ropeginterferon α-2b-njft, peginterferon α-2a, or in certain circumstances [e.g., targeting pruritus or headache symptoms], ruxolitinib).[14]

Hydroxyurea is historically the first cytoreductive treatment of choice,[18] but resistance to or intolerance of HU occurs in up to 25% of patients as defined by the European LeukemiaNet (ELN) criteria.[19–23] Briefly, these formal ELN criteria define unacceptable HU-related toxicities and set thresholds defining persistently high hematocrit, blood cell counts, and splenomegaly-related symptoms for patients who take ≥2 g/day of HU for 3 months. However, few patients in practice are administered as much as 2 g/day of HU, and when criteria are modified to include patients on their personal maximum-tolerated HU dose, closer to 40% are resistant or intolerant.[22–24] Dose adjustments for HU are important to optimize efficacy and tolerability[25]; however, those increasing the dose for lack of efficacy are unlikely to achieve adequate clinical benefit after lowering to a more tolerable dose and should instead be considered for second-line treatment with ruxolitinib.

The last 20 years have been productive and exciting for treatment of PV. First came the 2005 discovery of the *JAK2*V617F mutation, which drives JAK2 hyperactivity and is present in nearly all patients with PV.[26] Since *JAK2*V617F discovery, several US Food and Drug Administration (FDA) approvals have transformed the treatment landscape. Ruxolitinib received FDA approval in 2014 for treatment of PV in patients with inadequate response to or intolerance of HU, regardless of risk status.[27] Ruxolitinib is also recommended by the NCCN Guidelines as a treatment option for patients with low-risk or high-risk PV with inadequate response or loss of response to initial cytoreductive therapy.[14,28] This review covers ruxolitinib efficacy and safety data from clinical trials and real-world settings in the decade since ruxolitinib was approved for use in PV.

Clinical trial experience: blood count control, thromboembolic events, and disease progression

Blood count control is a key treatment goal because of the association between lower hematocrit and WBC counts with lower risk of thromboembolic events.[16,29] Several clinical trials compared efficacy of ruxolitinib with best available therapy (BAT) at the time of the study (Table 1), demonstrating superior control of hematocrit and blood counts with ruxolitinib (Table 2).[30–34,38]

The RESPONSE trials were open-label, randomized, controlled phase 3 studies that evaluated phlebotomy-dependent patients with HU-resistant or intolerant PV and included the opportunity for patients receiving BAT to cross over to ruxolitinib after the primary end point (Table 1). RESPONSE evaluated patients with splenomegaly, whereas RESPONSE-2 evaluated patients without splenomegaly. RESPONSE had a composite primary end point of hematocrit control and a ≥35% reduction in spleen volume at week 32; the primary end point of RESPONSE-2 was hematocrit control at week 28.

In both RESPONSE and RESPONSE-2, significantly more patients in the ruxolitinib arm than the BAT arm achieved the primary end point (RESPONSE [composite end point], 21% vs. 1%, $p < .001$; RESPONSE-2, 62% vs. 19%, $p < .0001$), and rates of complete hematologic response (CHR) were significantly higher with ruxolitinib than BAT[31,32] (Table 2). Consistent with better hematocrit control, phlebotomy requirement was lower with ruxolitinib. Fewer patients in the ruxolitinib arms required phlebotomies than in the BAT arms (RESPONSE: ruxolitinib, 20%; BAT, 62% [weeks 8–32]; RESPONSE-2: ruxolitinib, 19%; BAT, 60% [up to week 28]).[31,32] Elevated WBC counts are a risk factor for thrombosis,[13,29] and mean WBC counts were lower for patients treated with ruxolitinib versus BAT in both RESPONSE trials.[31,32] From week 8 through the primary analysis of

TABLE 1 Key ruxolitinib clinical studies in patients with PV.

Study name, study design	Phase (Trial ID)	Main inclusion criteria[a]
RESPONSE, RUX vs. BAT with available crossover to RUX at 32 weeks *N* = 222	3 NCT01243944	• Phlebotomy required for hematocrit control • Spleen volume ≥450 cm^3 • HU resistance/intolerance
RESPONSE-2, RUX vs. BAT with available crossover to RUX at 28 weeks *N* = 149	3b NCT02038036	• Phlebotomy required for hematocrit control • No palpable splenomegaly • HU resistance/intolerance
RELIEF, double-blind, double-dummy RUX vs. HU *N* = 110	3b NCT01632904	• HU treatment ≥12 weeks • Stable HU dose ≥4 weeks • MPN-SAF TSS cytokine symptom cluster score ≥8
MAJIC-PV, RUX vs. BAT, no crossover *N* = 190[b]	2 ISRCTN61925716	• High-risk PV • HU resistance/intolerance
Ruxo-BEAT, RUX vs. BAT with available crossover to RUX at 6 months *N* = 28[c]	2b NCT02577926	• Untreated PV (≤6 weeks' treatment) • High-risk PV • Frequent phlebotomy requirement or poor tolerance of phlebotomy • Symptomatic or progressive splenomegaly

Note: This table summarizes information for the key phase 2 and 3 clinical trials evaluating ruxolitinib in patients with PV that are discussed in this review.

Abbreviations: BAT, best available therapy; HU, hydroxyurea; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; PV, polycythemia vera; RUX, ruxolitinib.

[a]All trials were done in adults.

[b]A total of 180 were eligible for the modified intention-to-treat analysis.

[c]Interim analysis.

RESPONSE-2, mean WBC counts remained below 10×10^9/L for the ruxolitinib group versus above 10×10^9/L for the BAT group.[32] Correspondingly, exposure-adjusted rates of thromboembolic events were numerically lower in patients treated with ruxolitinib, although statistical analyses were not performed (Table 2). In both trials, >90% of patients were alive at 5 years of follow-up, but because most patients crossed over to ruxolitinib, clear conclusions regarding differences in overall survival between treatment arms cannot be drawn.

MAJIC-PV was an open-label, randomized, controlled phase 2 trial of ruxolitinib versus BAT in patients with high-risk PV who were resistant to or intolerant of HU.[34] MAJIC-PV enabled longer-term assessment of clinical outcomes than the RESPONSE trials by prohibiting treatment crossover. The primary end point was CHR per ELN criteria within 1 year of starting treatment; patients with high-risk PV received ruxolitinib or BAT for at least 1 year and were followed for up to 5 years.

In MAJIC-PV, more patients achieved CHR within 1 year with ruxolitinib versus BAT (ruxolitinib, 43%; BAT, 26%; $p = .02$), and CHRs were significantly more durable (hazard ratio [HR], 0.38 [95% confidence interval (CI), 0.24–0.61], $p < .001$). Additionally, hematocrit was lower in the ruxolitinib arm than the BAT arm; for most of the study, mean hematocrit values were maintained <37.5% in patients treated with ruxolitinib versus approximately 40% in patients treated with BAT. Patients treated with ruxolitinib had a much lower phlebotomy requirement (total phlebotomies: ruxolitinib, 83; BAT, 307; percentage of patients not requiring phlebotomies: ruxolitinib, 71%; BAT, 48%). Thrombosis-free survival (TFS) and event-free survival (EFS; a composite of major thrombosis, major hemorrhage, transformation, or death) were significantly improved with ruxolitinib treatment versus BAT (TFS: HR, 0.56 [95% CI, 0.32–1.0], $p = .05$; EFS: HR, 0.58 [95% CI, 0.35–0.94], $p = .03$). Three-year progression-free survival was numerically but not statistically higher (HR, 0.64 [95% CI, 0.36–1.15], $p = .13$), and 3-year overall survival did not differ between ruxolitinib versus BAT (HR, 0.73 [95% CI, 0.36–1.5], $p = .39$).

Patients are also at risk of PV transformation to myelofibrosis or blast phase, diseases with worse prognoses.[6,39–41] Fibrotic transformation is rare (RESPONSE: ruxolitinib, three events; BAT, one event; MAJIC-PV: ruxolitinib, five events; BAT, 10 events),[31,34] and leukemic transformation is rarer still (Table 2). However, disease transformation timelines are variable and depend in part on the complexity of the individual's genetic mutational landscape.[42–44] Correspondingly, there was no consensus among the RESPONSE trials and MAJIC-PV about whether PV transformation rates were different between patients treated with ruxolitinib versus BAT (Table 2).

Symptom improvements with ruxolitinib

Ruxolitinib improves PV-related symptoms, as measured by the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS). The percentage of patients who had ≥50% improvement in MPN-SAF TSS was much larger for ruxolitinib

TABLE 2 Key efficacy end points from clinical trials of ruxolitinib in patients with PV[a]

Event	Treatment arm	RESPONSE[30,31]	RESPONSE-2[32,33]	MAJIC-PV[35]
Main trial results[b]				
N[c]	RUX	110	74	93
	Control	BAT, 112	BAT, 75	BAT, 87
Hematocrit control, %[d]	RUX	60.0	62 $p < .0001$ vs. BAT	≥97[e]
	Control	19.6	19	93
CHR, %[f]	RUX	23.6	23.0	43
	Control	8.9	5.0	26
	p value	$p = .003$	$p = .0019$	$p = .02$
PHR, %[f]	RUX	NR	NR	54
	Control	NR	NR	67
≥35% Spleen reduction	RUX	38.2	N/A	NR
	Control	0.9	N/A	NR
≥50% reduction in MPN-SAF TSS from BL	RUX	49	45	61[g] $p = .001$ vs BAT
	Control	5	23	30[g]
*JAK2*V617F allele burden				
Mean allele burden at BL, % (mean change from BL to study end, %)	RUX	76.2 (−12.2)	NR	Median, 64 (>50% reduction, 56% of pts)[h] $p < .001$ vs BAT
	Control	75.0 (+1.2)	NR	Median, 58 (>50% reduction, 25% of pts)[h]
Thromboembolic events	RUX	All grades, 0.9 Grades 3/4, 0.9	All grades, 1.4	Overall, 24.3 Pts with <50% reduction in *JAK2*V617F allele burden, 32 Pts with ≥50% reduction in *JAK2*V617F allele burden, 18
	Control	All grades, 5.4 Grades 3/4, 1.8	All grades, 4.0	Overall, 36.8 Pts with <50% reduction in *JAK2*V617F allele burden, 42 Pts with ≥50% reduction in *JAK2*V617F allele burden, 21
Transformations	RUX	Week 81 MF, 2.7 AML, 0.9	NR	MF, 5.4 AML, 4.3
	Control	Week 34 MF, 0.9 AML, 0 Week 81 (after crossover) MF, 2.1 AML, 1.0	NR	MF, 11.5 AML, 0
5-year follow-up results[b]				
Durable Hct control	RUX	Median not reached	Week 80, 47 Week 260, 22	N/A
	Control	N/A	Week 80, 3	N/A
	RUX	(−38)	53 (Median, −15)	N/A

TABLE 2 (Continued)

Event	Treatment arm	RESPONSE[30,31]	RESPONSE-2[32,33]	MAJIC-PV[35]
*JAK2*V617F, mean allele burden at BL, % (mean change from BL to study end, %)	Control	See primary analysis above	74 (Median, +2.0)	N/A
	Crossover	(−23)	73% at crossover, (−14)	N/A
>50% reduction in MPN-SAF TSS from BL	RUX	NR	45	N/A
	Control	NR	16	N/A
5-year follow-up results per 100 PY[c]				
Thromboembolic events	RUX	All grades, 1.2 Grades 3/4, 0.7	All grades, 1.5	N/A
	Control	All grades, 8.2 Grades 3/4, 2.7	All grades, 3.7	N/A
	Crossover	All grades, 2.7 Grades 3/4, 1.5	All grades, 2.9	N/A
Transformations	RUX	MF, 2.1 AML, 0.2	MF, 0.6	N/A
	Control	MF, 1.4 AML, 0	MF, 1.9	N/A
	Crossover	MF, 1.8 AML, 0.6	MF, 0.5	N/A

Note: This table reports efficacy data from the ruxolitinib, BAT, and crossover arms of the preliminary and 5-year follow-up publications of key clinical studies of ruxolitinib in patients with PV.

Abbreviations: AML, acute myeloid leukemia; BAT, best available therapy; BL, baseline; CHR, complete hematologic response; Hct, hematocrit; HU, hydroxyurea; MF, myelofibrosis; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; N/A, not applicable; NR, not reported; PHR, partial hematologic response; Pts, patients; PY, patient-years; RUX, ruxolitinib; TE, thromboembolic event; TSS-C, MPN-SAF TSS cytokine symptom cluster.

[a]Data presented in the table are limited to studies that reported efficacy data for five or more of the categories listed above. Therefore, efficacy data that were reported in Ruxo-BEAT[35,36] (RUX, $n = 44$; BAT, $n = 34$) and RELIEF[37] (RUX, $n = 54$; HU, $n = 56$) are presented in this footnote. Ruxo-BEAT reported reductions in median Hct from BL to month 6 (RUX, 46% to 41% [$p < .001$]; BAT, 44% to 42% [$p = .045$] in the BAT arm); phlebotomy requirements were reduced between BL and month 6 (RUX, 93% to 14% required phlebotomy; BAT, 80% to 16%).[36] In an earlier interim analysis of Ruxo-BEAT ($N = 28$, RUX treatment arm only), median allele burden for patients treated with RUX was 44% at BL, with a mean change of −10% at 6 months.[35] RELIEF reported 43.4% of patients in the RUX group versus 29.6% of patients in the HU group achieved ≥50% reduction in TSS-C score ($p = .139$); mean allele burden at BL was 47.7% in the RUX group and 47.9% in the HU group; TEs (all grades) were reported in 3.7% and 3.6% of the RUX and HU groups, respectively; there were zero transformations to MF or AML.

[b]Treatment durations were: RESPONSE, 32 weeks (256 weeks for 5-year follow-up); RESPONSE-2, 28 weeks (260 weeks for 5-year follow-up); RELIEF, 16 weeks; MAJIC-PV, 1 year; Ruxo-BEAT, 6 months.

[c]Number of patients in the efficacy analysis population; the percentage data in individual rows may be based on fewer patients (see studies for details).

[d]For RESPONSE and MAJIC-PV trials, Hct control was defined as Hct <45% without phlebotomy.

[e]Combined complete responders and partial responders; does not capture patients who may have demonstrated Hct control but not fulfilled other complete response or partial response criteria.

[f]Defined by European LeukemiaNet consensus guidelines.[15]

[g]Achieved at any time point in study.

[h]At final time point.

(range between trials, 45%–61%) than BAT (range, 5%–30%) in RESPONSE, RESPONSE-2, and MAJIC-PV (Table 2). RESPONSE also recorded larger percentages of patients with ≥50% improvement in MPN-SAF TSS for specific symptom clusters (cytokine cluster, 64% vs. 11%; hyperviscosity cluster, 37% vs. 13%; splenomegaly cluster, 62% vs. 17% for ruxolitinib vs. BAT, respectively).[31] Furthermore, symptom improvements were relatively quick, with ruxolitinib surpassing BAT at first measurement in MAJIC-PV (month 2) and RESPONSE-2 (week 4).[32,34]

RELIEF was a double-blind, double-dummy, phase 3b trial that evaluated ruxolitinib versus HU in patients with PV symptoms despite well-controlled disease on HU.[37] Although only 43.4% of

patients treated with ruxolitinib versus 29.6% treated with HU ($p = .139$) achieved the overall primary end point (≥50% improvement from baseline in MPN-SAF TSS), pruritus was significantly improved in the ruxolitinib arm, with a ≥50% improvement achieved by 54.2% of patients compared with 32.0% in the HU arm ($p = .027$).[37]

Efficacy in patients without HU exposure

To build on the approved indication of ruxolitinib for patients resistant to or intolerant of HU, the phase 2b Ruxo-BEAT trial (NCT02577926) evaluated the safety and efficacy of ruxolitinib in the first-line setting.[35,36] The study set an aggressive primary end point of CHR, requiring complete resolution of symptoms as well as blood count and spleen size normalization.[45] This end point was met by one patient in each treatment arm (ruxolitinib, 2.3%; BAT, 2.9%) in an interim analysis of 78 patients with ≤6 weeks of previous treatment followed by ruxolitinib ($n = 44$) or BAT ($n = 34$) treatment for ≥6 months.[36] However, from baseline to month 6, median hematocrit was significantly reduced from 46% to 41% ($p < .001$) in the ruxolitinib arm versus from 44% to 42% ($p = .045$) in the BAT arm, and ruxolitinib significantly reduced spleen size (ruxolitinib, 15.4 to 13.4 cm [$p < .001$]; BAT, 14.5 to 14.3 cm [$p = .377$]).[35,36] Furthermore, Ruxo-BEAT demonstrated improvements in pruritus from baseline to month 6 with ruxolitinib (median MPN-SAF score for pruritus: ruxolitinib, 2.5 [IQR, 0–5] to 1 [IQR, 0–2], $p = .002$; BAT, 3 [IQR, 1–8] to 4 [IQR, 1–6], $p = .346$), despite the study's inclusion of patients without symptoms at baseline, which may mask symptom improvements.[35] These interim results indicate that ruxolitinib as initial cytoreductive treatment is associated with clinical benefit.

Disease modification with ruxolitinib

Definitive criteria for disease modification are not yet established; however, potential indicators of disease modification include *JAK2*V617F allele burden (the fraction of total *JAK2* carrying the *JAK2*V617F variant) and inflammatory cytokines. Typical initial treatments such as phlebotomy, aspirin, and HU can improve blood counts and reduce risk of cardiovascular events, but there is no evidence that they modify underlying disease.[46–48] Targeted treatments such as ruxolitinib have the potential to directly modify disease and therefore contribute toward long-term remission or a disease cure.[49]

*JAK2*V617F allele burden correlates with disease severity, including elevated blood counts and risks of thrombosis and fibrotic transformation, and may also increase over time with clonal expansion of *JAK2*V617F-positive hematopoietic stem cells.[43] In MAJIC-PV, reduction in allele burden was larger for patients receiving ruxolitinib versus BAT at final observation (molecular response [>50% allele burden reduction]: ruxolitinib, 56% [median follow-up, 48 months]; BAT, 25% [median follow-up, 36 months], $p < .001$).[34] Median time to molecular response was 36 months in patients treated with ruxolitinib and was not reached with BAT; once achieved, molecular response was generally durable. For patients treated with ruxolitinib who achieved molecular response, progression-free survival, EFS, overall survival, and achievement of CHR within 1 year were significantly more likely than for those who did not. Thromboembolic events occurred in a numerically smaller proportion of patients with versus without molecular response (Table 2), although this difference did not reach statistical significance.

Reductions in *JAK2*V617F during ruxolitinib treatment have also been observed in other clinical trials. Patients treated with ruxolitinib in RESPONSE and RESPONSE-2 had reductions in *JAK2*V617F allele burden through long-term treatment, including those who crossed over to ruxolitinib from BAT (Figure 1; Table 2), whereas those treated with BAT in the primary analysis before crossover had increases.[30,33,50] Patients in the Ruxo-BEAT trial, who had no previous exposure to HU, experienced significant reductions in median *JAK2*V617F allele burden from 44% to 34% ($p < .001$).[35] Similar findings were reported in an analysis of a cohort of patients derived from various ruxolitinib clinical trials, with eight of 65 (12%) evaluable patients achieving *JAK2*V617F ≤2%.[51] Additionally, allele burden was reduced during combination therapy with interferon (IFN)-α2 in the COMBI trials.[52,53]

Increased cytokine levels and chronic inflammation may contribute to the PV disease state through genetic and epigenetic changes or directly through hyperactive JAK/STAT signaling and clonal expansion.[54] There is some evidence that ruxolitinib modifies cytokine levels: high plasma levels of inflammatory markers (e.g., sICAM, sIL-2Rα, sIL-6R, sTNFRII) are elevated in PV but decreased with ruxolitinib treatment over the course of a phase 2 study.[55]

Real-world data

Longitudinal data for patients treated with ruxolitinib in real-world settings reinforce the efficacy and safety of ruxolitinib observed in clinical trials.[56–61] Several recent observational studies reported numerically higher percentages of patients with sustained hematocrit <45% and lower WBC counts after ruxolitinib treatment compared with baseline (Table 3; see Table S1 for baseline characteristics across clinical and real-world studies). Of these observational studies, we focus on findings from REVEAL (NCT02252159), the largest prospective study of patients with PV to date.

An analysis of REVEAL included 147 patients with low- or high-risk PV who started on HU treatment and switched to ruxolitinib for at least 3 months.[57] Before the treatment switch (at index), signs of inadequate disease management were higher among the 147 patients who switched compared with 906 patients who remained on HU. For example, a higher percentage of patients who switched to ruxolitinib had elevated WBC count (ruxolitinib, 18.1%; HU, 7.8%). Other signs of inadequate disease management at baseline included larger phlebotomy burden (mean 1.3 vs. 0.7 phlebotomies in the 6 months before index for ruxolitinib and HU, respectively), higher mean MPN-

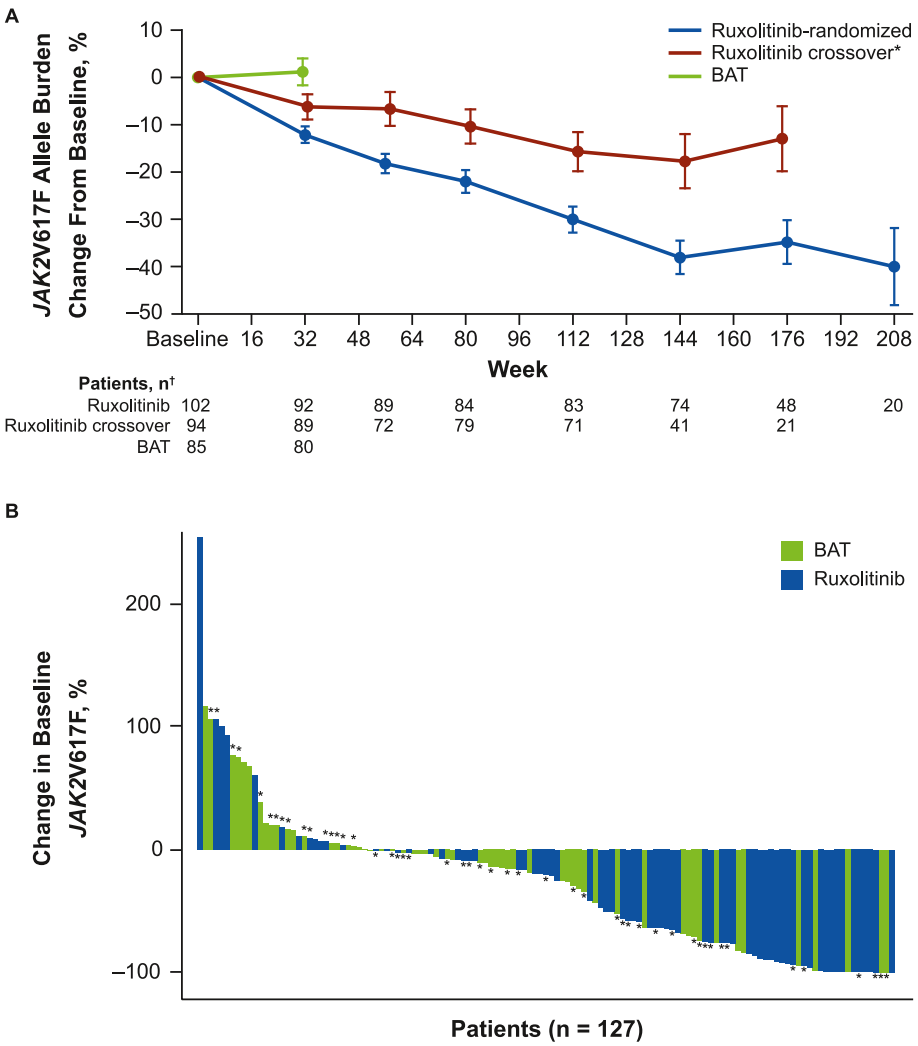

FIGURE 1 Changes in *JAK2*V617F allele burden. (A) Mean change in *JAK2*V617F allele burden from study baseline in RESPONSE. *For the ruxolitinib-crossover arm, baseline was defined as the final assessment before crossing over from BAT to ruxolitinib. †Data were excluded from figure if there were less than five data points within a treatment group at any visit. Figure reproduced from Vannucchi et al.[50] under a CC–BY Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). (B) Waterfall plot of change in *JAK2*V617F allele burden from study baseline to latest time point in MAJIC-PV. *Patients with additional driver mutations. Figure reproduced from Harrison et al.[34] under a CC–BY–NC–ND Creative Commons Attribution–NonCommercial–NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en). BAT, best available therapy.

SAF TSS scores (ruxolitinib, 27.5; HU, 17.3), and more patients with palpable spleen (ruxolitinib, 27.2%; HU, 9.3%). Among patients who switched to ruxolitinib, HU was most commonly discontinued for lack of efficacy (36.1%).

After 12 months of follow-up on ruxolitinib, 77 patients (83.8%) maintained hematocrit ≤45%, and 47 patients (49.5%) maintained WBC counts $\leq 10 \times 10^9$/L. Additionally, 110 patients (74.8%) no longer required phlebotomies after 12 months of treatment. The mean change in MPN-SAF TSS scores from baseline to 12 months of ruxolitinib treatment was −6.5 (SD, 14.4), and the percentage of patients with a palpable spleen dropped from 40.8% at index to 20.9% at 12 months. Thrombotic events occurred in 2.7% versus 4.2% of patients in the ruxolitinib group (median follow-up, 26 months) versus patients continuing on HU (median follow-up, 44 months). Overall, these data from real-world settings (Table 3) validated ruxolitinib efficacy characterized in clinical trial settings and further support that patients who show signs of inadequate disease management on HU treatment may benefit from a switch to ruxolitinib.

Anemia and thrombocytopenia in patients receiving ruxolitinib

Although PV is characterized by elevated blood counts, anemia and thrombocytopenia can occur in patients treated with ruxolitinib (Table 4). Often, anemia and thrombocytopenia are low-grade and managed with dose reductions, and platelet counts typically stabilize

TABLE 3 Real-world data from studies evaluating ruxolitinib in patients with PV.

	REVEAL[57]	Theocharides et al.[56]	Coltoff et al.[61]	Altomare et al.[60]	Pepe et al.[58]	Alvarez-Larrán et al.[59]
N[a]	147	350	126	249	83	105
Resistant or intolerant to HU, %	100	98.6	62.7	92.0	100[b]	100
Median tx duration, months	22.6	24.4	22.4	31.4	24.5	24
Evaluation time point, months	12	24	7.4	6	3	12
Hct <45%, %						
BL	66.2	48.4	Geometric mean % Hct, 41.8	18.9	39	51
FU	83.8	92.3	Geometric mean % Hct, 38.5	63.1	73	81
Mean WBC, $\times 10^9$/L						
BL	16.1	11.9	10.7	Median, 12.0	9.7	8.7
FU	13.0	9.0	8.7	NR	8.2	8.5
Phlebotomy eligible, %						
BL	NR	57.9	62.7	79.5	36	NR
FU	25.2	14.9	43.6	20.5	4	NR
Mean spleen length, cm						
BL	12.8	NR	4.9	NR	NR	NR
FU	7.0	NR	2.5	NR	NR	NR
Mean MPN-SAF TSS						
BL	27.5	24.3	NR	NR	NR	NR
FU	22.3	13.5	NR	NR	NR	NR
Thromboembolic events, %						
History before BL	27.2	19.7	VTE, 18 ATE, 22	NR	2.9 per 100 PY	VTE, 11 ATE, 17
FU	2.7	3.7	VTE, 0.8 ATE, 1.6	NR	3 per 100 PY	VTE: 1.9 (0.8 events per 100 PY) ATE, 1.0 (0.4 events per 100 PY)

Note: This table reports efficacy and safety data from key real-world studies of ruxolitinib in patients with PV.

Abbreviations: ATE, arterial thrombotic event; BL, baseline; FU, follow-up; Hct, hematocrit; HU, hydroxyurea; I, intolerant; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; NR, not reported; PY, person-year; R, resistant; tx, treatment; VTE, venous thrombotic event; WBC, white blood cell.

[a]Number of patients treated; the percentage data in individual rows may be based on fewer patients (see studies for details).

[b]Resistant or intolerant to previous cytoreductive therapy; 88% received prior HU.

with continued ruxolitinib treatment.[31,32,34] When safety interruptions or dose reductions are required, recommendations for restarting ruxolitinib and managing dose are summarized in the prescribing information (Table 5).

In both clinical trials and real-world studies, anemia was reported more frequently than thrombocytopenia and was more common in patients treated with ruxolitinib than BAT (Table 4). A large phase 4 European observational study reported that 28.9% of patients (n = 101/350) experienced any-grade anemia and 5.7% (n = 20/350) experienced anemia that required significant additional therapy,[56] which was similar to clinical trial data (any-grade anemia, 14%–43.6%; grade ≥3 anemia, 0%–7.5%; Table 4). Three studies reported rates of grade ≥3 anemia above 0: RESPONSE (ruxolitinib, 1.8%; BAT, 0%); phase 4 European observational study (ruxolitinib, 5.7%); and MAJIC-PV (ruxolitinib, 7.5%; BAT, 1.1%). By contrast, any-grade thrombocytopenia ranged from 3.0%–24.5% among patients treated

TABLE 4 Summary of clinical trial safety data from studies evaluating ruxolitinib in patients with PV.

	Treatment arm	RESPONSE[30,31]	RESPONSE-2[32,33]	RELIEF[37]	MAJIC-PV[34]
Main trial results[a]					
N	RUX	110	74	54	93
	Control	BAT, 111	BAT, 75	HU, 56	BAT, 87
Any-grade AE/grade ≥3 AE, %					
Anemia	RUX	43.6/1.8	14.0/0	37.0/0	NR/7.5
	Control	30.6/0	2.7/1.0	23.2/1.8	NR/1.1
Thrombocytopenia	RUX	24.5/5.5	3.0/0	9.3/0	NR
	Control	18.9/3.6	8.0/4.0	26.8/1.8	NR
Neutropenia	RUX	1.8/0.9	1.0/1.0	3.7/3.7	NR
	Control	8.1/0.9	1.0/1.0	12.5/1.9	NR
Event, %					
NMSC	RUX	3.6	0	1.9[b]	NR
	Control	1.8	1.3	0	NR
BCC	RUX	NR	0	0	3.2
	Control	NR	0	0	1.1
MCC	RUX	NR	0	0	0
	Control	NR	0	0	0
SCC	RUX	NR	0	1.9	6.5
	Control	NR	1.3	0	0
Herpes zoster	RUX	6.4	1.4	1.9	9.7
	Control	0	0	0	3.4
5-year follow-up, per 100 PY					
Any-grade AE/grade ≥3 AE					
Anemia	RUX	8.9/0.9	8.7/0	N/A	N/A
	Control	5.4/0	5.6/1.9	N/A	N/A
	Crossover	8.8/0.6	9.7/1.0	N/A	N/A
Thrombocytopenia	RUX	4.4/1.2	1.5/0.3	N/A	N/A
	Control	16.3/2.7	15.0/5.6	N/A	N/A
	Crossover	1.2/0.3	1.9/0.5	N/A	N/A
Neutropenia	RUX	NR (<5)	NR/0.3	N/A	N/A
	Control	NR (<5)	NR/1.9	N/A	N/A
	Crossover	NR (<5)	NR/0	N/A	N/A
Herpes zoster, any grade/grade ≥3	RUX	4.7/0.5	3.9/0.9	N/A	N/A
	Control	0/0	0/0	N/A	N/A
	Crossover	3.9/0.6	3.9/0	N/A	N/A
All infections,[c] any grade/grade ≥3	RUX	18.9/3.5	14.7/2.1	N/A	N/A
	Control	59.8/4.1	33.7/3.8	N/A	N/A
	Crossover	19.1/6.1	15.1/2.5	N/A	N/A

(Continues)

TABLE 4 (Continued)

	Treatment arm	RESPONSE[30,31]	RESPONSE-2[32,33]	RELIEF[37]	MAJIC-PV[34]
Event					
NMSC, *n*/PY (rate per 100 PY)	RUX	22/428.4 (5.1)	9/334.3 (2.7)	N/A	N/A
	Control	2/73.6 (2.7)	1/53.4 (1.9)	N/A	N/A
	Crossover	9/329.9 (2.7)	6/206.0 (2.9)	N/A	N/A
NMSC in patients with no history of NMSC, *n*/PY (rate per 100 PY)	RUX	14/385.3 (3.6)	NR	N/A	N/A
	Control	1/70.1 (1.4)	NR	N/A	N/A
	Crossover	6/307.5 (2.0)	NR	N/A	N/A
NMSC in patients with previous NMSC, *n*/PY (rate per 100 PY)	RUX	8/43.0 (18.6)	NR	N/A	N/A
	Control	1/3.5 (28.5)	NR	N/A	N/A
	Crossover	3/22.4 (13.4)	NR	N/A	N/A
SCC, *n*/PY (rate per 100 PY)	RUX	6/428.4 (1.4)	NR	N/A	N/A
	Control	0/73.6 (0)	NR	N/A	N/A
	Crossover	4/329.9 (1.2)	NR	N/A	N/A
Ad hoc analysis on MACE from clinical trials					
Incidence of MACE, *n*/PY (rate per 100 PY)	RUX	3/428.4 (0.70)	N/A	0/79.8 (0)	N/A
	Control (before or without crossover)	1/74.6 (1.34)	N/A	0/23.0 (0)	N/A
	Control (plus crossover)	4/404.6 (0.99)	N/A	2/91.6 (2.18)	N/A
	Control (after crossover)	3/329.9 (0.91)	N/A	2/68.5 (2.92)	N/A

Note: This table reports safety data from the ruxolitinib, BAT, and crossover arms of the preliminary and 5-year follow-up publications of key clinical studies of ruxolitinib in patients with PV. Data presented in the table are limited to studies that reported safety data for more than three of the categories listed above. Safety data from the clinical trial Ruxo-BEAT (two separate interim analyses: [$N = 28$; RUX arm only][35] or [RUX, $n = 44$; BAT $n = 34$][36]) and three of the real-world studies reported in Table 3 (Theocharides et al.[56] [$N = 350$], Pepe et al.[58] [$N = 83$], and Coltoff et al.[61] [$N = 126$], each reporting only a RUX treatment arm) are therefore reported in this footnote. Anemia and thrombocytopenia rates were only reported in Theocharides et al.[56] (28.9% of patients with any-grade anemia, 5.7% of patients with anemia "requiring significant additional therapy," and 4.0% of patients with any-grade thrombocytopenia). NMSC was reported in 3.1% and 2.4% of patients in Theocharides et al.[56] and Pepe et al.,[58] respectively. Herpes zoster was reported in 14.3%, 3.4%, 2.4%, and 1.6% of patients in Ruxo-BEAT,[35] Theocharides et al.,[56] Pepe et al.,[58] and Coltoff et al.,[61] respectively. In Ruxo-BEAT, infections and infestations (RUX, 18%; BAT, 35%; $p = .12$) and cardiac disorders (RUX, 5%; BAT, 0%; $p = .50$) were also reported.[36]

Abbreviations: AE, adverse event; BAT, best available therapy; BSC, basal cell carcinoma; HU, hydroxyurea; MACE, major adverse cardiovascular event; MCC, Merkel cell carcinoma; N/A, not applicable; NMSC, nonmelanoma skin cancer; NR, not reported; PY, patient-years; RUX, ruxolitinib; SCC, squamous cell carcinoma.

[a]Treatment durations were: RESPONSE, 32 weeks (256 weeks for 5-year follow-up); RESPONSE-2, 28 weeks (260 weeks for 5-year follow-up); RELIEF, 16 weeks; MAJIC-PV, 1 year.

[b]An additional case of SCC developed in a patient in the RUX arm after the 16-week blinded treatment phase.

[c]Inclusive of herpes zoster. For RESPONSE, infections other than herpes zoster included nasopharyngitis, bronchitis, upper respiratory tract infection, and cellulitis, all of which occurred at lower rates in the RUX arm than the BAT arm; for RESPONSE-2, infections other than herpes zoster included urinary tract infection, pneumonia, sepsis and septic shock, progressive multifocal leukoencephalopathy, hepatitis B reactivation, opportunistic infections, and other infections excluding tuberculosis.

with ruxolitinib in clinical trials or real-world studies and was more common in patients treated in control arms than with ruxolitinib in RESPONSE-2 and RELIEF (Table 4). Thrombocytopenia rates were high in RESPONSE (any-grade: ruxolitinib, 24.5%; BAT, 18.9%; grade ≥3: ruxolitinib, 5.5%; BAT, 3.6%) but lower in RESPONSE-2 (any-grade: ruxolitinib, 3.0%; BAT, 8.0%; grade ≥3: ruxolitinib, 0%; BAT, 4.0%) and RELIEF (any-grade: ruxolitinib, 9.3%; BAT, 26.8%; grade ≥3: ruxolitinib, 0%; BAT, 1.8%; Table 4).

TABLE 5 Dosing recommendations from Jakafi prescribing information.

Parameter	Dose recommendation
Recommended ruxolitinib starting dose	
Initial starting dose, which may be titrated based on safety and efficacy	10 mg bid
Dose reductions	
Hb ≥12 g/dL and PLT ≥100 × 10^9/L	No change required
Hb 10 to <12 g/dL and PLT 75 to <100 × 10^9/L	Dose reductions should be considered with the goal of avoiding dose interruptions for anemia and thrombocytopenia
Hb 8 to <10 g/dL or PLT 50 to <75 × 10^9/L	Reduce dose by 5 mg bid For patients on 5 mg bid, decrease dose to 5 mg once daily
Hb <8 g/dL or PLT <50 × 10^9/L or ANC <1.0 × 10^9/L	Interrupt dosing
Maximum restarting[a] dose after interruption, using the most severe parameter to determine maximum restarting dose	
Hb <8 g/dL or PLT <50 × 10^9/L or ANC <1 × 10^9/L	Continue hold
Hb 8 to <10 g/dL or PLT 50 to <75 × 10^9/L or ANC 1 to <1.5 × 10^9/L	5 mg bid[b] or no more than 5 mg bid less than the dose that resulted in dose interruption[c]
Hb 10 to <12 g/dL or PLT 75 to <100 × 10^9/L or ANC 1.5 to <2 × 10^9/L	10 mg bid[b] or no more than 5 mg bid less than the dose that resulted in dose interruption[c]
Hb ≥12 g/dL or PLT ≥100 × 10^9/L or ANC ≥2 × 10^9/L	15 mg bid[b] or no more than 5 mg bid less than the dose that resulted in dose interruption[c]

Note: This table presents dosing recommendations for starting or restarting ruxolitinib in patients with PV, as reported in the Jakafi prescribing information.

Abbreviations: ANC, absolute neutrophil count; bid, twice daily; Hb, hemoglobin; PLT, platelet.

[a]Dosing may be restarted after recovery of the hematologic parameter(s) to acceptable levels.

[b]Continue treatment for at least 2 weeks; if stable, may increase dose by 5 mg bid.

[c]The exception is dose interruption following phlebotomy-associated anemia, in which case the maximal restarting dose would not be limited to 5 mg less than the dose that resulted in dose interruption.

OTHER SAFETY CONSIDERATIONS

Major adverse cardiovascular events

In a post hoc analysis, RESPONSE and RELIEF were evaluated using the FDA definition for major adverse cardiovascular events (MACE; acute myocardial infarction, stroke, or cardiovascular mortality).[62] Exposure-adjusted incidence rates of MACE were similar between the ruxolitinib and control arms (Table 4)[63] despite extensive ruxolitinib exposure versus limited duration of control treatment exposure. Myocardial infarction was the most common specific MACE and occurred in no more than 1.2% of patients in any clinical trial or real-world study.[30,33,34,58]

Infections

Opportunistic infections may occur in patients treated with ruxolitinib because of disrupted cytokine signaling and resulting effects on immune system function, including altered lymphocyte functioning.[64,65] Herpes zoster (HZ) is a common infection in immunocompromised individuals.[66] In a systematic review and meta-analysis of ruxolitinib-associated infections, the combined odds ratio of HZ infection in the ruxolitinib versus BAT arms of the RESPONSE, RESPONSE-2, and RELIEF trials was 7.39 (95% CI, 1.33–41.07).[64] Although the numbers of HZ infections were relatively small in each of the trials that reported those data, the rates were higher in the ruxolitinib arm than the BAT arm (Table 4). In the 5-year follow-ups of RESPONSE and RESPONSE-2, exposure-adjusted grade 3 HZ infection occurred at a rate of 0.5–0.9 per 100 person-years versus 0 in the BAT group; for any-grade HZ infections, the exposure-adjusted rate was 3.9–4.7 per 100 person-years in ruxolitinib versus 0 for BAT.[30,33] Additionally, a retrospective, single-center real-world study reported HZ infections in nine of 53 patients with PV (17.0%) and 16 of 75 patients (21.3%) with myelofibrosis treated with ruxolitinib; the combined HZ incidence rate was 6.9 per 100 person-years compared with a range of 3.0–9.5 per 100 person-years for adults with hematologic malignancies or who had undergone hematopoietic stem cell transplant.[66,67] A nonlive subunit vaccine to prevent HZ may be considered for patients receiving ruxolitinib.[14]

Overall and grade ≥3 infection rates of any kind were lower with ruxolitinib than BAT treatment in the RESPONSE trials (Table 4). By contrast, in MAJIC-PV, the grade ≥3 infection rate was higher with ruxolitinib (17.2%) than BAT (9.2%), although no infections were atypical and none led to death.[34] For common infections of any grade, respiratory (ruxolitinib, 35.5% vs. BAT, 32.2%), cutaneous (ruxolitinib,

23.7% vs. BAT, 18.4%), genitourinary (ruxolitinib, 12.9% vs. BAT, 11.5%), and gastrointestinal (ruxolitinib, 10.8% vs. BAT, 10.3%) infections were numerically more frequent with ruxolitinib treatment than BAT, although no statistical analyses were reported.[34]

Nonmelanoma skin cancer and other malignancies

Nonmelanoma skin cancer (NMSC) has been observed with ruxolitinib treatment in long-term follow-up analyses from clinical trials (Table 4). In the 5-year follow-ups of both RESPONSE and RESPONSE-2, the overall exposure-adjusted rate of NMSC was higher in the ruxolitinib arm than the BAT arm. RESPONSE, but not RESPONSE-2, reported exposure-adjusted NMSC rates among patients with a history of NMSC versus without. Notably, incidence of NMSC was much higher in those who previously had NMSC than those who had not, regardless of treatment.[30] Furthermore, risk was not higher with ruxolitinib versus BAT in those with a history of NMSC, suggesting that ruxolitinib is an appropriate treatment option even with NMSC history (ruxolitinib, 18.6 per 100 patient-years; BAT, 28.5 per 100 patient-years).[30] Although a causal relationship between ruxolitinib use and NMSC incidence has not been established, periodic skin examinations are advised.

There was not a consistent trend in secondary malignancies between RESPONSE (secondary malignancies: ruxolitinib, 7.0 per 100 patient-years; BAT, 4.1 per 100 patient-years) and RESPONSE-2 (malignant tumor: ruxolitinib, 4.5 per 100 patient-years; BAT, 7.5 per 100 patient-years).[30,33]

Other nonhematologic adverse events

Among randomized clinical trials that compared ruxolitinib to active controls, dizziness (all grade 1–2) was the only frequent (in >10% of patients) any-grade nonhematologic adverse event (AE) that occurred at higher rates in patients treated with ruxolitinib in ≥2 trials.[31,37] Grade ≥3 nonhematologic AEs were generally infrequent with ruxolitinib versus BAT and lacked reproducibility between trials.[33,34,37]

Adverse events overall were less common with ruxolitinib treatment than with BAT in the original analyses of the RESPONSE trials, which reported exposure-adjusted AE rates because most patients crossed over to ruxolitinib treatment for the extension phases (RESPONSE primary analysis, 64.7 vs. 145.6 events per 100 patient-years; RESPONSE-2 primary analysis, 99.3 vs. 140.7 events per 100 patient-years).[31,32] After 5 years of follow-up, increased weight was the only grade ≥3 exposure-adjusted nonhematologic AE reported more frequently with ruxolitinib than BAT treatment by both RESPONSE trials (RESPONSE, 0.7% vs. 0%; RESPONSE-2, 0.6% vs. 0%).[30,33] Recent single-center studies support this finding, with approximately half of patients with MPNs gaining ≥5% their baseline body weight after initiating ruxolitinib.[68,69] Physicians should consult individually with patients starting on ruxolitinib regarding weight changes, also taking into account that in PV, a body mass index (BMI) under 25 kg/m^2 (i.e., normal or underweight) may paradoxically be associated with lower overall survival compared with BMI ≥25 kg/m^2.[70]

Real-world studies also had few consistent nonhematologic AEs other than infections or NMSC, although dizziness was reported in three studies. In a retrospective multicenter study evaluating 126 patients in the United States, 9.5% of patients experienced dizziness, but only one patient discontinued ruxolitinib due to dizziness.[61] Grade 2 dizziness was manageable with dose reductions for two patients among 83 patients at centers in Italy between 1988 and 2020.[58] A large European real-world study reported dizziness in 9.1% of patients.[56] The same study also reported increased weight (6%) and fatigue (4.6%) as the two most common nonhematologic AEs considered related to ruxolitinib.[56]

Postmarketing surveillance experience

Overall, 15,592 patients received ruxolitinib treatment in Novartis- and Incyte-sponsored clinical trials and managed access programs cumulatively since its development international birth date (February 29, 2008). As of February 22, 2024, cumulative estimated ruxolitinib postmarketing exposure was 388,271 patient-years, encompassing 10 years of use in ruxolitinib-approved indications (PV, MF, graft-versus-host disease). In total, 154,270 AEs were reported from postmarketing safety studies and registries, spontaneous reports, and literature cases (majority nonserious: 63%; n = 97,052). Importantly, postmarketing surveillance data are collected under less rigorous conditions than in clinical trials, have varied reporting rates over time, and require assumption of causality for regulatory reporting. Despite these limitations, postmarketing safety data for ruxolitinib are generally consistent with data from randomized controlled trials.

Most frequent AEs

The most frequent AEs in the ruxolitinib postmarketing data overall were related to low hemoglobin (anemia, 2.7%; hemoglobin decreased, 2.2%), related to low platelet count (thrombocytopenia, 1.7%; platelet count decreased, 2.2%), and fatigue (2.5%).

MACE

No confirmation of disproportionality for MACE was found in a January 2024 analysis using the ruxolitinib global safety, FDA Adverse Event Reporting System (AERS), and World Health Organization (WHO) VigiBase databases. Together with the low incidence of MACE from RESPONSE and RELIEF (Table 4), there is no evidence that ruxolitinib-treated patients with PV carry increased risk of MACE.

Infections

Rates of serious infections in postmarketing data remained similar to clinically observed rates, with no emergence of new types or patterns of serious infections.

NMSC and other malignancies

In the ruxolitinib global safety database, NMSC incidence was 0.46 cases per 100 patient-years. No new findings were identified compared with clinical trial results. The clinical trial and postmarketing data are consistent with recommendations in the United States prescribing information and European summary of product characteristics[27,71]; no conclusive evidence supports a causal relationship between ruxolitinib use and NMSCs.

No confirmation of disproportionality for lymphoma or other malignancies with ruxolitinib was found in a January 2024 analysis using the ruxolitinib global safety, FDA AERS, and WHO VigiBase databases, consistent with real-world evidence demonstrating no difference in lymphoma incidence between patients with or without JAK inhibitor exposure.[72]

Other JAK inhibitor-based AEs of interest

In ruxolitinib postmarketing data, there have been only three confirmed cases of progressive multifocal leukoencephalopathy and zero cases of Wernicke encephalopathy. These sporadic data are similar to the pre-ruxolitinib era, suggesting no association between ruxolitinib and these encephalopathies that are associated with some other JAK inhibitors.[73,74]

Future directions: ruxolitinib in combination treatments for PV

A focus of future PV treatment is combination regimens, for which ruxolitinib may be an effective backbone.[75] The COMBI-I and COMBI-II trials investigated combination treatment with ruxolitinib and IFN-α2 because ruxolitinib effectively reduces inflammation in PV, and inflammation inhibits IFN-α2 molecular remissions.[31,76] In COMBI-I, most patients were intolerant to IFN-α2 at baseline, but ruxolitinib addition enabled IFN-α2 administration at a lower, more tolerable effective dose.[52,53,77–79] Ruxolitinib plus IFN-α2 combination therapy demonstrated high CHR rates and a tolerable safety profile in both COMBI-I and COMBI-II.[52,80] Similarly, ropeginterferon α-2b-njft was approved by the FDA for use in PV in 2021 and exhibits a compatible risk-benefit profile for ruxolitinib.[81,82] Additionally, the hepcidin mimetic rusfertide may help abate iron deficiency that results from dysregulated iron homeostasis in some patients with poorly controlled hematocrit and repeated phlebotomies. Currently, a phase 3 trial is ongoing to evaluate rusfertide in combination with placebo or patients' current cytoreductive therapy including ruxolitinib.[83,84]

In conclusion, because of the chronic nature of PV, both immediate symptom relief and long-term risk of thromboembolic events are key factors guiding treatment decisions for physicians and patients. HU has historically been the primary choice for patients with PV and is still recommended as initial cytoreductive treatment; however, with substantial resistance and intolerance to HU, it is important for physicians to quickly recognize when HU may not adequately control PV. Ruxolitinib was approved 10 years ago and remains standard of care for patients who receive inadequate benefit from initial cytoreductive therapy. Ruxolitinib has longstanding and demonstrable efficacy and safety that position it to remain a preferred monotherapy option as well as potential backbone for future combination regimens.

AUTHOR CONTRIBUTIONS

Lucia Masarova: Conceptualization, writing–original draft, writing–review and editing, and visualization. **John Mascarenhas**: Writing–review and editing, writing–original draft, visualization, and conceptualization. **Raajit Rampal**: Conceptualization, writing–original draft, writing–review and editing, and visualization. **Wilson Hu**: Conceptualization, investigation, visualization, writing–review and editing, and writing–original draft. **Robert A. Livingston**: Conceptualization, visualization, writing–review and editing, and writing–original draft. **Naveen Pemmaraju**: Conceptualization, writing–original draft, visualization, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

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