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Ruxolitinib for the Treatment of Patients With Polycythemia Vera

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SUMMARY

Polycythemia vera (PV) is a hematopoietic proliferative disorder associated with Janus-associated kinase (JAK)/signal transducer and activator of transcription (STAT) pathway dysregulation resulting in erythrocytosis and, possibly, leukocytosis and thrombocytosis. Patients diagnosed with PV experience a broad range of symptoms associated with a reduced quality of life, often develop splenomegaly, and have an increased risk of death compared to age-matched subjects without PV. Current treatment options, notably hydroxyurea, help with disease management; however, insufficient efficacy or progressive resistance occurs in some patients, highlighting the need for new treatment options. Ruxolitinib is an oral JAK1/JAK2 inhibitor that has been evaluated in phase 2 and 3 clinical trials in patients with PV who are intolerant of or resistant to hydroxyurea. In this setting, ruxolitinib treatment has demonstrated normalization of blood cell counts, reduction in splenomegaly, and improvements in PV-related symptom burden.

Keywords

polycythemia vera; myeloproliferative neoplasm; ruxolitinib; Janus kinase 1; Janus kinase 2; splenomegaly; thrombocytosis; erythrocytosis

1 Introduction

Polycythemia vera (PV) is classified as a myeloproliferative neoplasm (MPN) by the World Health Organization [1] and is uniquely defined by erythrocytosis, with possible leukocytosis and/or thrombocytosis, resulting from clonal expansion of a hematopoietic

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progenitor [2]. Estimations of PV prevalence range from 45 to 57 cases per 100,000 residents in the United States [3]; the international annual incidence rate is approximately 2 cases per 100,000 people [4].

Polycythemia vera is associated with dysregulation of the Janus-associated kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, predominantly from the constitutively active *JAK2^{V617F}* mutation or, less commonly, *JAK2* exon 12 mutations [5–7]. In healthy individuals, erythropoiesis is promoted by erythropoietin (EPO)–driven activation of JAK2 and downstream STAT signaling [8]. However, constitutive activation of JAK2 is associated with exaggerated erythroid proliferation in the absence of EPO [6,8–10]. Moreover, JAK2 is an important signaling component in granulopoiesis and thrombopoiesis [11–13], and a significant proportion of patients with *JAK2^{V617F}* mutations frequently experience leukocytosis and/or thrombocytosis [14,15].

The consequences of JAK2 activation and exaggerated hematopoietic progenitor cell proliferation in patients with PV are manifold. Patients with PV may experience a broad-ranging symptom burden that includes fatigue, pruritus, and painful splenomegaly [16–22]. The combined symptom burden experienced by some patients with PV is associated with reductions in quality of life (QoL) [16–18]. Patients with PV are at risk for cardiovascular and thrombotic events [23–25], as well as major hemorrhages [23]. Furthermore, PV may progress to myelofibrosis (MF) or acute myeloid leukemia (AML) [23–25]. Cardiovascular/thrombotic events and hematologic transformation are leading contributors to the reduced survival rate observed in patients with PV compared with the general population [23–26].

Elevated serum inflammatory cytokine levels [27,28] and increased granulocyte activation [28], often observed in patients with PV, suggest an increase in systemic inflammation. Higher than normal levels of C-reactive protein (CRP) are significantly correlated with *JAK2^{V617F}* allele burden [29]. Furthermore, preclinical evidence indicates that JAK2 and JAK1 play a role in pro-inflammatory cytokine signaling [8,30,31]. Finally, circulating levels of cytokines/cytokine signaling factors are significantly correlated with symptoms in patients with MF [32] and may have a similar effect in patients with PV. Taken together, these findings suggest that inflammatory responses in PV may be driven by constitutively active JAK/STAT signaling.

Traditional treatments for patients with PV include aspirin to reduce the risk of clotting [33] and phlebotomy to reduce red cell mass [34]. In addition, patients with high prognostic risk scores may benefit from the addition of cytoreductive therapy, such as hydroxyurea (HU) or interferon- α (IFN- α) [7,34,35]. However, some patients do not receive adequate benefit from traditional therapies [17,36,37]; hence the need to investigate newer treatment options. Ruxolitinib is a potent JAK1/JAK2 inhibitor [38] that is approved by the Food and Drug Administration (FDA) for the treatment of patients with PV who have had an inadequate response to or are intolerant of HU [39]. Ruxolitinib is also approved by the FDA for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-PV MF, and post-essential thrombocythemia MF. This review provides an overview of phase 2 and 3 clinical trials of ruxolitinib in patients with PV.

2 Treatment Overview

Advancing age [40] and prior vascular events [40,41] are independent predictors of thrombosis in patients with PV. Treatment recommendations for all patients with PV include antiplatelet therapy with low-dose aspirin (100 mg/day) and phlebotomy to maintain a hematocrit <45% [7,34,35]. Patients who are ≥60 years of age or with a history of thrombosis are high risk [7,35]; in addition to aspirin and phlebotomy, high-risk patients should receive cytoreduction with HU or recombinant IFN- α (rIFN- α). HU is the preferred option for high-risk patients in many countries where the off-label use of rIFN- α is not possible [7,35,42].

2.1 Unmet Needs in Patients With Polycythemia Vera

Many patients with PV receive clinical benefit from HU [7,35,36,42]; however, a subgroup of patients become intolerant of or resistant to HU [36] according to European LeukemiaNet (ELN) criteria [43]. Other treatment options are limited to IFN- α preparations, pipobroman, radioactive phosphorous (^{32}P), and busulfan [7,35,44]. Recombinant IFN- α has been shown to effectively reduce dependence on phlebotomy; however, the observed toxicity profile and treatment schedules via subcutaneous injection may reduce long-term tolerance and adherence in some patients [45,46]. Pipobroman, ^{32}P , and busulfan have leukemogenic properties [25,47,48] and are not commonly used in this setting. Some patients or physicians may also be reluctant to use HU because of similar concerns about the disputed potential for leukemic transformation [36,49,50].

Patients with PV often report a diminished QoL [16–18]; however, available evidence suggests that current treatment options offer limited improvement in QoL parameters. In a study of 538 patients with PV, treatment with HU, aspirin, IFN- α , or phlebotomy did not improve overall symptom burden per the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) [37]. Similarly, an analysis of 53 patients with PV reported that treatment with HU, IFN- α , busulfan, or ^{32}P was not associated with significantly improved scores for any of the MPN-SAF items [17].

2.2 Current and Emerging Treatment Options

2.2.1 Phlebotomy—Current treatment recommendations include a target hematocrit goal of <45% [7,35,51], which is supported by results from the phase 3 Cytoreductive Therapy in PV (CYTO-PV) clinical trial [34]. CYTO-PV data indicated a 4-fold lower death rate from cardiovascular or thrombotic events and a lower total cardiovascular event risk in patients who maintained hematocrit <45% versus those with hematocrit control between 45% and 50% [34]. However, phlebotomy procedures require patients to travel for a clinic visit, and phlebotomy intolerance as a result of patient anxiety, vasovagal reactions, or poor compliance is not uncommon [34,52,53], which may negatively affect long-term patient adherence. Furthermore, chronic phlebotomy regimens to control red blood cell production can induce iron deficiency [54,55], which may diminish clinical benefit.

2.2.2 Hydroxyurea—Current treatment options in high-risk patients include cytoreduction with HU to reduce the risk of thrombosis, manage hematocrit, and reduce spleen size

[7,35,36,42]. An analysis from the PV Study Group (PVSG) demonstrated reduced risk of thrombosis in patients treated with HU (n=51) compared with phlebotomy (n=134) [49], but HU was not associated with reduced risk of mortality. Data from the French Polycythemia Study Group indicated that treatment with HU (n=136) was associated with significantly longer overall survival and a reduced risk of leukemic transformation compared with pipobroman (n=149) [25]. Although interpretation of reported findings has been debated, HU treatment may be associated with the risk of skin cancer [56] and leukemic transformation [36,49,50], which may lead some physicians and patients to avoid HU as a treatment option. Some patients with PV experience toxic adverse reactions to HU, including leg ulcers or other mucocutaneous manifestations, gastrointestinal toxicity, and fever [36]. Furthermore, HU-related adverse reactions may be exacerbated in elderly patients [57]. Approximately 25% of patients with PV become intolerant of or resistant to HU [36]. A retrospective evaluation of the ELN criteria for HU intolerance and resistance reported that patients who were resistant to HU had increased risks of fibrotic/leukemic transformation and mortality compared with patients who responded to HU [36].

2.2.3 Interferon- α —As reviewed by Kiladjian et al. [45], several clinical trials report a role for IFN- α in patients with PV. Treatment with rIFN- α produces reductions in hematopoietic proliferation and the need for phlebotomy. However, patient benefit is sometimes limited by the treatment schedule and toxicity, especially at high doses, resulting in clinical trial discontinuation rates up to 42% [45]. Pegylated (PEG) alternatives have longer half-lives [58] and reduced renal excretion, which permit weekly rather than daily dosing [46]. Phase 2 clinical trials investigating PEG-IFN- α 2a demonstrated clinicohematologic response rates of 79% to 100%, with complete response observed in 54% to 95% of patients [59–62]. Furthermore, after median follow-up times of 21 and 31 months, complete molecular response (undetectable *JAK2*^{V617F}) was achieved by 14% and 24% of patients, respectively [59,60]. An ongoing phase 2 clinical trial of PEG-IFN- α 2b in patients with PV reported an 89% clinicohematologic response rate after 18 months on treatment, with 47% of patients achieving a complete response [63]. Toxicity-related discontinuation rates with PEG-IFN- α 2a and PEG-IFN- α 2b are lower than those reported for rIFN- α [45,59,60,62,63]. Two important prospective randomized clinical trials comparing the efficacy of PEG-IFN- α 2a and PEG-IFN- α 2b to treatment with HU in high-risk patients with PV should provide critical information needed to determine the role of PEG-IFN- α in this setting (ClinicalTrials.gov identifiers, NCT01259856 and NCT01949805) [64].

2.2.4 Histone Deacetylase Inhibitors—Histone deacetylase (HDAC) expression is elevated in patients with PV [65]. Two HDAC inhibitors, vorinostat and givinostat, were evaluated in phase 2 clinical trials in patients with MPNs, including PV. Treatment with vorinostat or givinostat was associated with clinicohematologic response rates of 35% to 70% [66–68]. High toxicity-related discontinuation with vorinostat (44% after 24 weeks of treatment) may limit benefit in the PV setting [67]. Drug-related adverse events (AEs) led to discontinuation in 4% and 9% of patients in 2 givinostat studies [66,68]. Currently, no phase 3 clinical trials have been planned for vorinostat or givinostat in the PV setting.

2.2.5 Break Point Cluster-Abelson Inhibitors—Break point cluster-abelson (BCR-ABL) is a tyrosine kinase associated with regulation of hematopoiesis and chronic myeloid leukemia [69]. Imatinib is a tyrosine kinase inhibitor that was designed to target BCR-ABL, but also inhibits other tyrosine kinases, including JAK2 and c-KIT [70]. A phase 2 clinical trial in patients with PV demonstrated a clinicohematologic response rate of 55% after a median treatment duration of 8 months; no patients achieved complete remission [71]. In the safety analysis, 55% of patients discontinued treatment with imatinib because of nonhematologic toxicity. No phase 3 clinical trials of imatinib for patients with PV are currently indexed at ClinicalTrials.gov.

2.2.6 Janus-Associated Kinase Inhibitors—Janus-associated kinase inhibitors are being investigated in patients with PV because of inadequate responses to traditional therapies experienced by patients and the established role of JAK overactivation in the pathophysiology of PV. Phase 2 results are available for the JAK2 inhibitor lestaurtinib, which did not meet its primary endpoint of a 15% reduction in *JAK2*^{V617F} allele burden within 18 weeks of treatment. Phase 2 clinical trials with the JAK2 inhibitor LY2784544 (ClinicalTrials.gov identifier, NCT01594723) and the JAK1/JAK2 inhibitor momelotinib (ClinicalTrials.gov identifier, NCT01998828) are currently ongoing and awaiting results. Momelotinib is also under evaluation in a phase 3 clinical trial for patients with primary MF, post-PV MF, or post-essential thrombocythemia MF (ClinicalTrials.gov identifier, NCT02101268). Finally, development of the JAK2 inhibitor fedratinib was halted because of reports of Wernicke-like encephalopathy [72]. This review focuses on the clinical development of the JAK1/JAK2 inhibitor ruxolitinib as treatment for patients with PV.

3 Introduction to the Drug

Ruxolitinib ((R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate; JAKAFI® [United States]; JAKAVI® [Europe, Canada]) is a small-molecule tyrosine kinase inhibitor designed to inhibit hyperactive JAK/STAT signaling. Preclinical studies with ruxolitinib demonstrated potent inhibition of JAK1 and JAK2, rapid oral absorption [38], and a terminal half-life and activity profile sufficient for twice daily dosing [38,73]. Ruxolitinib is approved in the United States for the treatment of patients with intermediate or high-risk MF, including primary MF, post-PV MF, and post-essential thrombocythemia MF [39]. In Europe [74] and Canada [75], ruxolitinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary MF, post-PV MF, or post-essential thrombocythemia MF. Most recently, ruxolitinib was approved in the United States for the treatment of patients with PV who have had an inadequate response to or are intolerant of HU [39] and in Europe for adult patients with PV resistant to or intolerant of hydroxyurea [74].

3.1 Pharmacodynamics

The pharmacodynamics of ruxolitinib was investigated in a preclinical study, which reported high affinity for JAK1 and JAK2 [31]. Biochemical analysis of ruxolitinib revealed potent inhibition of JAK1 (mean [SD] 50% inhibitory concentration [IC₅₀], 3.3 nM [1.2]) and JAK2 (mean [SD] IC₅₀, 2.8 nM [1.2]) and modest affinity for the remaining JAKs, tyrosine

kinase 2 (TYK2; mean [SD] IC₅₀, 19.0 nM [3.2]) and JAK3 (mean [SD] IC₅₀, 428.0 nM [243.0]) [31]. The specificity of ruxolitinib for JAK1 and JAK2 was corroborated by an analysis of 26 additional kinases, none of which were significantly inhibited by ruxolitinib at concentrations 100-fold greater than the IC₅₀ of JAK1 or JAK2.

Ruxolitinib effectively blocks the downstream signaling effects of JAK1 and JAK2 activity. Preincubation of whole blood samples with ruxolitinib inhibited interleukin-6–driven STAT3 phosphorylation (mean [SD] IC₅₀, 282 nM [54]) and thrombopoietin-driven STAT3 phosphorylation (mean [SD] IC₅₀, 281 nM [62]) [31]. Ruxolitinib inhibits the activity of wild-type JAK2 and the constitutively active *JAK2*^{V617F} mutation, which is present in most patients with PV [5]. Application of ruxolitinib to *JAK2*^{V617F}-expressing cell lines inhibited phosphorylation of the JAK2 targets STAT3, STAT5, and extracellular signal-regulated kinase (ERK) and promoted apoptosis in a dose-dependent manner [31]. Furthermore, ruxolitinib inhibited hematopoietic progenitor cell proliferation from erythroid (erythroid burst-forming units [BFU-E]) and myeloid (myeloid colony-forming units [CFU-M]) origins in samples from healthy subjects (BFU-E IC₅₀, 407 nM; CFU-M IC₅₀, 551 nM) and patients with PV (BFU-E IC₅₀, 223 nM; CFU-M IC₅₀, 444 nM) [31]. Ruxolitinib mitigated several consequences of JAK2 activation and the PV disease state in a murine model of PV. Mice treated with ruxolitinib had reduced *JAK2*^{V617F} allele burden, lower STAT3 phosphorylation levels, smaller spleen size, and reduced mortality compared with controls [31].

3.2 Pharmacokinetics and Metabolism

The pharmacokinetics of ruxolitinib was investigated in healthy subjects in 2 phase 1 studies. In both studies, the maximum plasma concentration was observed within 2 hours of oral administration of a single 5- to 200-mg dose [38,73]. The terminal half-life was approximately 2 to 5 hours [38,73], and accumulation of ruxolitinib after twice daily dosing was negligible [73]. The systemic exposure (area under the curve from time 0 to infinity) was dose-proportional between 5 and 200 mg [38,73].

In healthy subjects, oral ruxolitinib is primarily eliminated by the cytochrome P450 (CYP) 3A4 enzyme [76], with the parent drug accounting for <1% of the excreted dose [38]. Most of the parent drug is metabolized 6 to 12 hours postdose, such that unmetabolized parent ruxolitinib is the predominant serum drug product 6 hours postdose (58% of drug or drug metabolites), and persists for 12 hours (25%) [38]. Excretion is mostly through urine (74% total mean recovery) and feces (22%); 70% of the initial dose is excreted within 24 hours of dosing in most patients.

Patients with hepatic or renal impairment [77], as well as patients receiving a CYP3A4 inhibitor [76], may require ruxolitinib dose reductions. Patients with mild-to-severe hepatic impairment experienced 28% to 87% increased total dose exposure compared with healthy subjects [77]. Similarly, greater severity of renal impairment is associated with increased ruxolitinib metabolite exposure [77].

4 Clinical Efficacy

4.1 Phase 2 Clinical Trial

An open-label, multicenter, phase 2 study evaluated ruxolitinib in patients with PV who were intolerant of or resistant to HU (Table 1) [28]. The study objectives included assessment of hematocrit and blood cell counts, splenomegaly resolution, and PV-related symptom improvement. Treatment with ruxolitinib was associated with a 97% response rate by Week 24 per modified 2009 ELN criteria, with a complete response achieved in 59% of patients (partial response: hematocrit <45% without phlebotomy after Week 4; complete response: hematocrit <45% without phlebotomy, platelet count $400 \times 10^9/L$, white blood cell count $10 \times 10^9/L$, normal spleen size by palpation, and no pruritus within the previous week). The response was durable, as evidenced by 85% of responding patients maintaining a hematocrit <45% without phlebotomy for 48 weeks. Furthermore, patients experienced a 22% mean reduction in *JAK2*^{V617F} allele burden by Week 144, with allele burden reduced by at least half in 24% of patients during the first 3 years of treatment. Finally, treatment with ruxolitinib was associated with reductions in PV-related symptom severity. By Week 4, a 50% reduction in the severity of pruritus and/or bone pain was experienced by >90% of patients, whereas a 50% reduction in night sweats severity was reported by >70% of patients. For most patients, the reduction in symptom burden was sustained through Week 144.

4.2 RESPONSE Phase 3 Clinical Trial

RESPONSE is an ongoing randomized, open-label, multicenter, phase 3 trial that evaluated ruxolitinib versus standard therapy for efficacy and safety in patients with PV who had splenomegaly and were intolerant of or resistant to HU (ClinicalTrials.gov identifier, NCT01243944) [78]. The primary endpoint was a composite of hematocrit control and a 35% reduction in spleen volume at Week 32. Hematocrit control required 1 phlebotomy eligibility (hematocrit >45% and 3 percentage points above baseline or hematocrit >48%, whichever was lower) between randomization and Week 8 and no phlebotomy eligibility between Weeks 8 and 32. The primary endpoint significantly favored ruxolitinib, having been met by 21% of patients in the ruxolitinib arm versus 1% in the standard therapy arm ($P<0.001$; Table 2). Furthermore, the individual components of the primary endpoint were achieved by a greater proportion of patients in the ruxolitinib arm. Hematocrit control was achieved in 60% versus 20% of patients randomized to ruxolitinib versus standard therapy, respectively; a 35% reduction in spleen volume was achieved by 38% versus 1%. Responses were durable, with 94% of ruxolitinib-treated patients who achieved the primary endpoint maintaining hematocrit control and spleen volume reduction for 1 year.

A greater proportion of patients receiving ruxolitinib compared with standard therapy achieved complete hematologic remission (CHR) at Week 32 (ruxolitinib, 24%; standard therapy, 9%; $P=0.003$), which was a composite of hematocrit control and normalization of platelet and leukocyte cell counts [78]. Most patients (89%) in the ruxolitinib arm who achieved CHR maintained remission until Week 48 [79]. CHR may be an informative endpoint for patient survival. Hematocrit maintenance <45% has been associated with improved survival [34]. Furthermore, leukocytosis has been associated with an increased

risk of death in patients with PV [23]; however, further investigation will be required to determine if normalization of white blood cell counts improves patient survival.

Compared with standard therapy, ruxolitinib was associated with better management of PV-related symptoms in this patient population. A greater proportion of patients in the ruxolitinib arm achieved a 50% improvement in the MPN-SAF total symptom score (ruxolitinib, 49%; standard therapy, 5%) [78]. Furthermore, treatment with ruxolitinib was associated with improvements in individual symptom scores at Week 32, including sweating while awake, night sweats, itching, early satiety, dizziness, abdominal discomfort, skin redness, muscle ache, headache, tiredness, concentration problems, vision problems, and numbness/tingling in the hands/feet, whereas patients treated with standard therapy had little improvement or worsening of individual symptom scores.

4.3 RELIEF Phase 3b Clinical Trial

RELIEF (ClinicalTrials.gov identifier, NCT01632904) evaluated improvement of PV-related symptoms with ruxolitinib versus HU in patients reporting disease-related symptoms while receiving a stable dose of HU [80]. The primary endpoint was the proportion of patients with a 50% improvement in the MPN-SAF total cytokine symptom cluster score (itching, tiredness, muscle ache, night sweats, sweats while awake) at Week 16, and was achieved by 43.4% of patients in the ruxolitinib arm and 29.6% in the HU arm ($P=0.139$; odds ratio, 1.82; 95% CI, 0.82–4.04). Although statistical significance was not achieved for the primary endpoint in this population of patients with generally well-controlled PV receiving a stable dose of HU, there was evidence of symptomatic benefit. For example, at Week 16 a 50% improvement in itching was experienced by 40.0% in the ruxolitinib arm and 26.4% in the HU arm, and a 50% improvement in tiredness by 54.2% and 32.0%, respectively.

5 Safety and Tolerability

5.1 Phase 1 Clinical Trial

The safety and tolerability of ruxolitinib was initially evaluated in a randomized, placebo-controlled phase 1 dose-escalation trial in healthy subjects [73]. Results from this trial established 25 mg twice daily and 100 mg once-daily as the maximum tolerated doses of ruxolitinib.

5.2 Phase 2 Clinical Trial

The safety and tolerability profile of ruxolitinib was further evaluated in an open-label, multicenter, phase 2 trial of patients with PV who were intolerant of or resistant to HU [28]. AEs in patients receiving ruxolitinib ($n=34$) were primarily of grades 1 or 2, with anemia (grade 1/2, 67.6%; grade 3/4, 8.8%) and thrombocytopenia (grade 1/2, 35.3%; grade 3/4, 8.8%) identified as the most frequent. Anemia and thrombocytopenia were generally managed by dose interruptions and/or reductions and were not the cause for any discontinuations. The most common nonhematologic AE was diarrhea (grade 1/2, 23.5%; grade 3/4, 0). At the end of the 144-week study, 2 (5.9%) patients discontinued treatment because of AEs (grade 3 renal neoplasm and atrial flutter).

5.3 RESPONSE Phase 3 Clinical Trial

The safety and tolerability of ruxolitinib were evaluated in comparison with standard therapy in RESPONSE [78]. Overall, ruxolitinib was tolerated by most patients, with 85% of patients randomized to ruxolitinib remaining on treatment after a median follow-up of 81 weeks. Furthermore, none of the patients in the ruxolitinib arm discontinued treatment because of cytopenias, in agreement with similar findings from the phase 2 study [28,78].

At Week 32, rates (per 100 patient-years) of all AEs (ruxolitinib, 64.7; standard therapy, 145.6) and grades 3 or 4 AEs (ruxolitinib, 28.8; standard therapy, 44.0) were lower in ruxolitinib-treated patients compared with standard therapy [78]. Lymphopenia (16.4%), thrombocytopenia (5.5%), dyspnea (2.7%), anemia (1.8%), and asthenia (1.8%) were the most frequent grade 3 or 4 AEs reported by patients receiving ruxolitinib (Table 3).

Other AEs of interest included herpes zoster infection, which was observed in 6.4% of patients in the ruxolitinib arm (all grade 1 or 2) and 0 patients in the standard therapy arm [78]. Grade 3 or 4 infections (any type) were observed in 3.6% of patients in the ruxolitinib arm and 2.7% of patients in the standard therapy arm. In RESPONSE, newly diagnosed nonmelanoma skin cancer (NMSC) occurred in 4 (3.6%) patients in the ruxolitinib arm and 2 (1.8%) patients in the standard therapy arm, all of whom (except 1 standard therapy patient) had a history of skin cancer or precancer [78]. A greater proportion of patients in the ruxolitinib arm had a history of skin cancer or precancer (ruxolitinib, 10.9%; standard therapy, 6.3%) [79], which may have affected the observed NMSC incidence rates.

5.4 RELIEF Phase 3b Clinical Trial

The most common nonhematologic AEs observed during randomized treatment in the ruxolitinib arm in RELIEF were fatigue (20.4%; HU arm, 10.7%), headache (16.7%; HU, 5.4%), and dizziness (13.0%; HU, 8.9%) [80]. In the HU arm, the most common AEs were diarrhea (19.6%; ruxolitinib arm, 9.3%) and constipation (12.5%; ruxolitinib, 7.4%). No patients experienced grade 3 or 4 (laboratory values) anemia or thrombocytopenia in the ruxolitinib arm. Two patients in the ruxolitinib arm experienced grade 3 or 4 neutropenia.

6 Regulatory Affairs

Ruxolitinib (JAKAFI®) was approved by the US Food and Drug Administration (FDA) in 2011 and represents the first drug approval available for the treatment of patients with intermediate or high-risk MF, including primary MF, post-PV MF, and post-essential thrombocythemia MF [39]. Ruxolitinib (JAKAVI®) was approved by the European Medicines Agency (EMA) [74] and Health Canada [75] in 2012 where it is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary MF, post-PV MF, and post-ET MF.

In December 2014, ruxolitinib was approved by the FDA for the treatment of patients with PV who have had an inadequate response to or are intolerant of HU [39]. In March of 2015 ruxolitinib was approved by the EMA for the treatment of adult patients with PV resistant to or intolerant of hydroxyurea [74]. RESPONSE (ClinicalTrials.gov identifier, NCT01243944) is a randomized, open-label, multicenter, phase 3 trial evaluating ruxolitinib

versus standard therapy in patients with PV who are intolerant of or resistant to HU. RESPONSE 2 (ClinicalTrials.gov identifier, NCT02038036) is a randomized, double-blind, phase 3b trial evaluating ruxolitinib versus standard therapy for efficacy and safety in patients with PV who are intolerant of or resistant to HU (results not available at the time of this publication). Unlike patients participating in RESPONSE, patients participating in RESPONSE 2 are not required to have palpable splenomegaly. RELIEF (ClinicalTrials.gov identifier, NCT01632904) was a phase 3b, randomized trial that evaluated ruxolitinib versus HU for the relief of symptoms in patients experiencing PV-related symptoms while receiving a stable dose of HU.

7 Conclusions

Polycythemia vera is a chronic malignancy that creates a worsening, life-long symptom burden that negatively affects patient QoL [16–18], and is associated with an increased risk of mortality [25,26]. Treatment for high-risk patients has traditionally been limited to off-label use of HU [7,35] with the potential for intolerance or resistance [36], and other potentially toxic cytoreductive therapies [7,35,44]. Clinicians can evaluate emerging treatment options for patients with PV as agents with newer mechanisms of action become available.

The JAK1/JAK2 inhibitor ruxolitinib is the first targeted treatment option for PV that has achieved regulatory approval. Phase 1 clinical trial results indicate that ruxolitinib is rapidly absorbed and has a high level of oral bioavailability [38,73]. Although currently available data do not have sufficient follow-up times to directly evaluate clinical benefits for mortality and thrombotic risk, surrogate endpoints used in the phase 2 and 3 clinical trials are promising. Treatment with ruxolitinib is associated with phlebotomy independence, hematocrit control, and normalization of leukocyte and platelet counts [78]. These benefits are important because elevated hematocrit [34] and leukocytosis [23] are associated with increased risk of death in patients with PV. Phase 2 and 3 results also support a role for ruxolitinib in managing PV-related symptom burden. In particular, ruxolitinib was more effective at reducing symptom severity in patients who were intolerant of or resistant to HU than standard therapy, which included HU, IFN- α -based treatment, pipobroman, anagrelide, and immunomodulators [78]. Finally, the toxicity profile associated with ruxolitinib was manageable [28,78]. These data support ruxolitinib as a valid therapeutic option for the subset of patients with PV who are resistant to or intolerant of HU.

8 Expert Commentary

Phase 2 and 3 clinical trial data support ruxolitinib as a safe and effective treatment option for patients with PV who are intolerant of or resistant to HU [28,78]. These data are important given the notable proportion of patients who experience HU intolerance/resistance [36]. In addition, the unmet needs associated with other currently available cytoreductive agents suggest that ruxolitinib may be a rational treatment option for many patients. Some patients derive benefit from standard rIFN- α -based therapies [81,82], but the inconvenient administration and dosing schedule [46], and the high-dose toxicity rates observed in clinical trials [83] suggest that, for a subgroup of patients, PV will be poorly managed because of

drug intolerance and nonadherence. PEG-IFN- α alternatives are currently in development that demonstrate reduced renal excretion with a serum half-life that is approximately 10 times longer than unpegylated rIFN- α [46], allowing for weekly rather than daily dosing. PEG-IFN- α 2a and PEG-IFN- α 2b demonstrate promising efficacy and safety results in phase 2 clinical trials [59,60,84]; however, results from ongoing phase 3 clinical trials are needed to determine an evidence-based place for these treatment options in PV. Other second-line cytoreductive options — including busulfan, ^{32}P , and pipobroman — are generally avoided because of clinically observed leukemogenic potential, especially when used after HU treatment [25,47,48]. HDAC inhibitors are also in development in this setting, with promising phase 2 safety results, albeit with higher AE-related discontinuation rates than would be desired, and await phase 3 validation [66,67].

Unlike alternative cytoreductive options, which function by indiscriminate cytoreduction, ruxolitinib is a potent JAK1/JAK2 inhibitor that targets overactivation of the JAK/STAT pathway, an important constituent in the etiology of PV [6,9,10,85]. In vitro data suggest that ruxolitinib preferentially inhibits progenitor colony formation in cells with the *JAK2^{V617F}* mutation compared with wild-type cells and also promotes apoptosis of *JAK2^{V617F}*-expressing cells [31]. Although ruxolitinib-driven cytoreduction may lead to dose-limiting anemia in some patients with MF [86], in the PV setting, which is defined by erythrocytosis, such reductions in red blood cell counts may be beneficial and make ruxolitinib a rational treatment option for proliferative phase PV. No hematologic AEs were cause for discontinuation in the phase 2 or 3 clinical trials of ruxolitinib in patients with PV [28,78]. However, ruxolitinib may be associated with increased infection risks [78], and preclinical data suggest that ruxolitinib may affect T-cell differentiation and proliferation [88]. It is important for patients who are treated with ruxolitinib to be monitored for signs and symptoms of infection and treated promptly [39]. Finally, ruxolitinib may offer an added benefit as an anti-inflammatory agent. Patients with PV who have increased serum levels of CRP (a marker for systemic inflammation) are at increased risk of thrombosis, a key driver of mortality in this setting [29]. Ruxolitinib is a potent inhibitor of JAK1 and JAK2, both of which play a role in signaling proinflammatory cytokines [30,31]. The preliminary evidence in support of ruxolitinib as an anti-inflammatory agent is exciting but will need to be confirmed in future clinical trials.

Revised treatment guidelines will be necessary to educate healthcare professionals about the appropriate use of ruxolitinib in the PV setting. Based on clinical evidence, patients who are intolerant of or resistant to HU should be considered for ruxolitinib. As the development of other JAK inhibitors and clinical studies of PEG-IFN- α progress, a revised expert consensus statement regarding the specific clinical/pathologic characteristics of patients who could benefit from different treatment options may be warranted.

9 Five-Year View

An important step towards improving outcomes for high-risk patients with PV is to methodically compare new treatment options with traditional therapies in prospective randomized trials. Such was the case for ruxolitinib in its recent approval by the FDA and the EMA for patients with PV who have had an inadequate response to or are intolerant of

HU. Further study of the safety profile associated with long-term ruxolitinib treatment of patients with PV will be important in the coming years, with particular interest in NMSC, herpes and other infections, and fibrotic/leukemic disease transformation. In addition to ruxolitinib, there is potential for several new agents to be approved over the next 5 years. Several other JAK inhibitors are being investigated in patients with PV; however, at present it remains unclear how they might compare with ruxolitinib. In addition, PEG-IFN- α treatments may receive approval for the treatment of patients with PV in coming years, pending phase 3 clinical trial results. It will be important to incorporate ruxolitinib and other approved treatment options into new evidence-based treatment guidelines.

Now that ruxolitinib has received FDA and EMA approval in the PV disease setting and has the potential to become standard of care, it will be important to address several questions related to long-term clinical benefit and treatment sequencing. Reducing the risk of thrombosis is a primary treatment goal in PV, and long-term treatment data will be necessary to determine the effect of new treatments on thrombotic risk. Furthermore, associations between new treatments and durable management of *JAK2*^{V617F} allele burden, decreases in clonal dominance, reversal of disease-associated fibrosis, and reduced risk of hematological transformation will be important concepts to evaluate.

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10 Key Issues

1. PV is a chronic myeloproliferative disorder that is associated with erythrocytosis, leukocytosis, and thrombocytosis.
2. PV is nearly always associated with JAK/STAT pathway-activating mutations.
3. Mortality is increased in patients with PV, primarily because of increased incidence of thrombotic events and disease transformation to MF or AML.
4. Patients with PV experience a broad-ranging symptom burden that negatively affects their QoL.
5. High-risk patients with PV who become intolerant of or resistant to HU have limited treatment options.
6. Ruxolitinib is an oral JAK1/JAK2 inhibitor with rapid absorption and good bioavailability. Collectively, phase 2 and 3 safety and efficacy results support ruxolitinib as the first FDA-approved treatment option for patients with PV for whom HU has failed.
7. In the PV setting, ruxolitinib controls hematocrit, reduces the need for phlebotomy, normalizes blood cell counts, reduces splenomegaly, and improves PV-related symptom severity.
8. Ruxolitinib has a favorable tolerability profile; most AEs were grade 1 or 2 and managed by dose interruptions and/or reductions.

Table 1Phase 2 Trial Efficacy Results^a

Endpoint	Ruxolitinib (N=34)
Response rate, Week 24, ^b n (%)	33 (97)
Complete response	20 (59)
Partial response	13 (38)
Hematocrit controlled (<45%) until Week 144, ^c n (%)	20 (61)
Median white blood cell count	
Baseline	13.2 × 10 ⁹ /L
Week 144	6.9 × 10 ⁹ /L
Median platelet count	
Baseline	526.5 × 10 ⁹ /L
Week 144	281.0 × 10 ⁹ /L
Nonpalpable spleen, Week 144, ^d n (%)	15 (63)
Mean <i>JAK2</i> ^{V617F} allele burden reduction, Week 144, %	22

^a As reported by Verstovsek et al 2014 [28].

^b Per 2009 European LeukemiaNet criteria.

^c Out of 33 responding patients.

^d Out of 24 evaluable patients with palpable spleen at baseline.

Table 2RESPONSE Phase 3 Trial Efficacy Results^a

Endpoint, %	Ruxolitinib (n=110)	Standard therapy (n=112)	P Value
Primary composite endpoint, Week 32 ^b	21	1	<0.001
Components of primary endpoint, Week 32			
Hematocrit control	60	20	–
35% reduction in spleen volume	38	1	–
Durable response, Week 48 ^c	91	–	–
Complete hematologic remission, Week 32 ^d	24	9	0.003

^aAs reported by Vannucchi et al 2015 [78] unless otherwise noted.

^bHematocrit control without phlebotomy eligibility (hematocrit >45% and 3 percentage points higher than baseline or >48%, whichever was lower) AND a 35% reduction from baseline in spleen volume.

^cAs reported by Verstovsek et al 2014 [79]. Calculated as the proportion of patients who had a primary response at Week 32 that was maintained until Week 48.

^dHematocrit control without phlebotomy eligibility AND platelet count $400 \times 10^9/L$ AND white blood cell count $10 \times 10^9/L$.

Table 3RESPONSE Phase 3 Trial Summary of Adverse Events^a

Adverse Event, ^b %	Ruxolitinib (n=110)		Standard Therapy (n=111)	
	All grades	Grade 3–4	All grades	Grade 3–4
Hematologic ^c				
Anemia	43.6	1.8	30.6	0
Lymphopenia	43.6	16.4	50.5	18.0
Thrombocytopenia	24.5	5.5	18.9	3.6
Leukopenia	9.1	0.9	12.6	1.8
Neutropenia	1.8	0.9	8.1	0.9
Nonhematologic ^d				
Headache	16.4	0.9	18.9	0.9
Diarrhea	14.5	0	7.2	0.9
Fatigue	14.5	0	15.3	2.7
Pruritus	13.6	0.9	22.5	3.6
Dizziness	11.8	0	9.9	0
Muscle spasms	11.8	0.9	4.5	0
Dyspnea	10.0	2.7	1.8	0
Abdominal pain	9.1	0.9	11.7	0
Asthenia	7.3	1.8	10.8	0

^a As reported by Vannucchi et al 2015 [78].

^b Graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

^c New or worsening abnormalities, based on laboratory values.

^d Occurred in 10% of patients in either treatment arm.