Case Study Series

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# Cases in the Management of Polycythemia Vera: Switching From Hydroxyurea to Ruxolitinib to Resolve Symptoms and Improve Quality of Life



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## Case 1 of a 3-Part Series

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## Patient Case

A 65-year-old man was diagnosed with polycythemia vera (PV) 3 years ago (Table 1). He initially presented with several symptoms, including pruritus, headaches, night sweats, fatigue, and numbness and tingling in his fingers and toes. He also reported issues with concentration and dizziness. First, he went to his primary care doctor. Examination and blood work revealed a very high red cell count (erythrocytosis), a slightly elevated white cell count (leukocytosis), and an elevated platelet count (thrombocytosis). The patient was immediately referred to a hematologist based on his abnormal blood cell counts. The hematologist recommended treatment with therapeutic phlebotomy owing to the likely diagnosis of PV.

Following the phlebotomy, the patient's symptoms decreased, and he felt slightly better. The patient underwent a bone marrow biopsy and had additional blood work done. Less than a week later, his hematologist scheduled an office visit to discuss the results of the bone marrow biopsy, which showed hypercellularity and the presence of the mutation *JAK2* V617F, thus confirming the diagnosis of PV.

Because the patient was older than 60 years, he was at high risk of developing thrombosis. (Age ≥60 years and history of thrombosis are 2 established prognostic factors; the presence of either one renders the PV patient at high risk for a thrombotic event). The hematologist explained to the patient that thrombosis was the main complication of PV, which carries an increased risk of morbidity and mortality. Some patients may die from a blood clot that develops in a critical area, such as the heart, lungs, or brain. Therefore, treatment with medications (cytoreductive agents) was warranted to control the blood cell count in order to decrease thrombotic risk.

The patient underwent an additional therapeutic phlebotomy to reduce the hematocrit level to below 45%. At the same time, he began treatment with hydroxyurea chemotherapy pills, in order to maintain hematocrit below 45% and eliminate the need for phlebotomy. (This goal for a hematocrit level of <45% is standard response criteria in PV when patients are treated with phlebotomy

On the Cover

Colored scanning electron micrograph of a blood clot. Erythrocytes (red) are seen enmeshed in filaments of fibrin protein (white). Magnification: × 7000 at 6 × 7 cm size.

Credit: Susumu Nishinaga / Photo Researchers, Inc.

**Table 1.** Key Points of the Case

| |
|---|
| **Initial Clinical Presentation** |
| A 65-year-old man was diagnosed with polycythemia 3 years ago |
| His symptoms included pruritus, headaches, night sweats, fatigue, numbness and tingling in his fingers and toes, issues with concentration, and dizziness |
| He had a very high red blood cell count, slightly elevated white cell count, and elevated platelets |
| **Initial Treatment** |
| Therapeutic phlebotomies |
| Hydroxyurea |
| Low-dose aspirin |
| **Early Response** |
| Red blood cell counts normalized |
| Minimal improvement in symptoms |
| **Late Response** |
| After approximately a year and a half, his symptoms began to increase. The symptoms included pruritus after hot showers, night sweats, tiredness, numbness and tingling in the fingers and toes, and erythema |
| The patient's blood cell count remained well-controlled |
| **Next Treatment** |
| Ruxolitinib |
| **Response** |
| After approximately a month, the patient felt much better |
| After 2 months of treatment, most symptoms had completely resolved |
| The blood cell counts were maintained |
| The patient returned to the clinic for follow-up visits every 3 to 4 months. His blood cell counts remained under control. His quality of life continued to improve |

or cytoreductive therapy, such as hydroxyurea.[1]) Since the patient was at high risk for thrombosis, it would not have been appropriate to manage him with phlebotomy alone. An alternative choice of therapy to hydroxyurea is ropeginterferon alfa-2b. The US Food and Drug Administration approved this medication as therapy for PV patients in November 2021.[2] Interferon preparations are typically prescribed to younger PV patients who need cytoreductive therapy, based on concerns that older patients may not tolerate it. The goals of therapy with cytoreductive agents are not only to maintain hematocrit below 45%, but also to normalize counts of white blood cells and platelets (if elevated), decrease enlarged splenomegaly (if present), and control PV-related systemic symptoms (ie, improve quality of life). Low-dose aspirin was also prescribed to try to further reduce the risk of thrombosis.

After starting hydroxyurea at 500 mg daily, the patient required weekly therapeutic phlebotomy twice and no more. During treatment with hydroxyurea, the patient's hematocrit level was maintained at below 45%, and his white cell and platelet counts decreased to normal levels. Follow-up of the patient, with blood count monitoring, was decreased to once a month for 3 months and once every 3 to 4 months thereafter. The patient's symptoms improved to some degree after normalization of the blood cell counts. However, this improvement did not have a satisfactory impact on his overall quality of life. At each office visit, he would still convey issues with itching, tiredness, and fatigue.

After approximately a year and a half, the patient's symptoms began to worsen. The patient developed pronounced pruritus after hot showers, night sweats, tiredness, numbness and tingling in the fingers and toes, and erythema. The patient's blood cell count remained well-controlled, however. The physician reassured the patient that the treatment was effective. However, the patient continuously expressed concern that his PV was not under control because he did not feel well. The doctor prescribed antihistamines, which slightly improved pruritus and erythema.

The doctor reviewed guidelines from the National Comprehensive Cancer Network (NCCN) for recommendations on how to assess the symptomatic benefits of cytoreductive therapy.[3] The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS; MPN10) is a questionnaire used in the management of patients with myeloproliferative neoplasms (MPNs), including PV.[4] The MPN10 lists 10 of the most common symptoms in MPNs. The patient judges the severity of each symptom with a score from 0 (not present) to 10 (worst ever). The highest symptom score is 100 points.

This patient had an MPN10 score of 22. This result led his doctor to consider a therapeutic strategy that would address the patient's important quality-of-life concerns, as well as control the blood cell counts and reduce the risk of thrombosis. A decision was made to change treatment to a therapy that would not only control the blood cell count but also address quality-of-life issues. In this setting, ruxolitinib was an appropriate choice, as it was approved in 2014 for second-line treatment of PV patients who are resistant, refractory, or intolerant to hydroxyurea.[5]

As evidenced by his continued symptoms, this patient was resistant to hydroxyurea. The patient was switched from hydroxyurea to ruxolitinib. In patients with PV, the typical starting dose of ruxolitinib is 10 mg twice daily.

Approximately two-thirds of patients may need a higher dose. In this patient's case, ruxolitinib was initiated not to improve the blood cell counts, but rather to control symptoms.

After receiving ruxolitinib for approximately 1 month, the patient reported feeling much better. After 2 months of treatment, most of his symptoms had completely resolved. During this time, his blood cell counts were maintained under control. The patient returned to the clinic for follow-up every 3 to 4 months. His blood cell counts remained under control, and his quality of life continued to be excellent.

## Overview of PV

PV is recognized by the World Health Organization as a chronic MPN (Table 2),[6] characterized by abnormal hematopoiesis (myeloid lineage), namely uncontrolled proliferation of red blood cells, white blood cells, and platelets; *JAK2* mutations (*JAK2* V617F in the vast majority of patients); and increased levels of proinflammatory cytokines.[7] In the United States, the prevalence was estimated to be 44 to 57 cases per 100,000 population,[8] and the median age is 62 years at diagnosis.[9] Patients with PV face a substantial symptom burden, which has a significant impact on quality of life.[10,11] Over time, PV can progress to myelofibrosis and/or transform to acute myeloid leukemia.[12,13]

### *Symptom Burden and Quality of Life*

Fatigue is one of the most frequently reported symptoms in PV, affecting up to 85% of patients,[10] and can be debilitating in some cases. Pruritus is present in approximately 65% of patients and can markedly affect quality of life. Pruritus can be triggered by stimuli such as water (aquagenic pruritus), physical activity, alcohol consumption, or changes in temperature. Mast cells and basophils play a role in this process. Other symptoms of PV include bone pain, night sweats,[14] visual disturbances, cognitive impairment, and migraines.[15] Approximately 30% to 40% of patients with PV have splenomegaly, which is often associated with advanced disease.[16]

The MPN10 questionnaire was developed to assess symptom burden in patients with MPNs, including PV. The questionnaire can be administered before initiation of treatment and during its course. Symptoms assessed by the MPN10 are fatigue, early satiety, abdominal discomfort, inactivity, problems with concentration, night sweats, pruritus, bone pain, fever, and unintentional weight loss.[17]

In addition, the natural history of the disease may include multiple complications, such as thrombosis and hemorrhage events. Less commonly, PV affects the abdominal venous circulation.[18] In one study, an estimated 4.2% of patients with PV experienced a major hemorrhage.[19] These events can affect quality of life and increase the risk for death.

### *Risk Stratification*

The most important traditional prognostic factors associated with an increased risk of thrombotic events are older age (≥60 years) and history of thrombosis.[19,20] These factors form the basis of risk stratification,[7] and were confirmed in the recent REVEAL study.[21] Low-risk PV patients are younger than 60 years old and have no history of thrombosis; high-risk patients are 60 years or older or have a history of thrombosis. The importance of mitigating thrombosis in PV was evidenced in a recent retrospective study.[22]

A novel prognostic system incorporating genetic information to predict survival has been proposed for PV. This system, referred to as the Mutation-Enhanced

**Table 2.** 2017 WHO Diagnostic Criteria for Polycythemia Vera[6]

| Diagnostic Criteria: Requires All 3 Major Criteria, or the First 2 Major Criteria Plus the Minor Criteria | |
|---|---|
| Major Criteria | Increased Hgb (>16.5 g/dL in men or >16.0 g/dL in women), or increased Hct (>49% in men or >48% in women), or other evidence of increased red cell volume (increased red cell mass) |
| | Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) |
| | *JAK2* V617F or *JAK2* exon 12 mutation |
| Minor Criteria | Serum erythropoietin level below the reference range for normal |

Hct, hematocrit; Hgb, hemoglobin; WHO, World Health Organization.

Adapted from Swerdlow SH et al. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2017.[6]

**Table 2.** European LeukemiaNet Recommendations for the Definition of Resistance/Intolerance to Hydroxyurea in Patients With Polycythemia Vera[29,35]

| Definition of Resistance/Intolerance to Hydroxyurea |
|---|
| Need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/d of hydroxyurea<br>OR |
| Uncontrolled myeloproliferation (ie, platelet count >400 × $10^9$/L and WBC count >10 × $10^9$/L) after 3 months of at least 2 g/d of hydroxyurea<br>OR |
| Failure to reduce massive (>10 cm from the costal margin) splenomegaly by >50% as measured by palpation or failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/d of hydroxyurea<br>OR |
| Absolute neutrophil count <1.0 × $10^9$/L or platelet count <100 × $10^9$/L or hemoglobin <10 g/dL at the lowest dose of hydroxyurea required to achieve a complete or partial clinicohematologic response[a]<br>OR |
| Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematologic toxicities, such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of hydroxyurea |

GI, gastrointestinal; WBC, white blood count. [a]Complete response is defined as hematocrit <45% without phlebotomy, platelet count ≤400 × $10^9$/L, WBC count ≤10 × $10^9$/L, and no disease-related symptoms. Partial response is defined as hematocrit <45% without phlebotomy or a response in 3 or more of the other criteria.

Adapted from Barosi G et al. *Br J Haematol.* 2010;148:961-963[29] and Barbui T et al. *J Clin Oncol.* 2011;29(6):761-770.[35]

International Prognostic System for PV (MIPSS-PV), is based on a 3-tiered model. Points are scored based on the following factors: 2 points for a leukocyte count of 15 × $10^9$/L or higher, 3 points for age older than 67 years, 1 point for abnormal karyotype, and 2 points for harboring the *SRSF2* spliceosome mutation.[23] After the points are totaled, patients are stratified into low-risk (0 or 1 points), intermediate-risk (2 or 3 points), or high-risk (≥4 points) groups. When the MIPSS-PV score was applied to a group of 336 patients with PV, the risk score correlated with overall survival: the median overall survival was 24 years in the low-risk group, 13.1 years in the intermediate-risk group, and 3.2 years in the high-risk group.[23]

## Rationale for Treatment Decisions

Treatment recommendations are based on the risk-adapted classification of patients in low-risk (age <60 years and no prior thrombosis) vs high-risk (age ≥60 years or a history of thrombosis) groups.[1] The goals of PV treatment are to strictly maintain the hematocrit below 45%, normalize counts of white blood cells and platelets, control splenomegaly, reduce symptoms, and improve quality of life, while prolonging survival by preventing thrombotic complications, progression to myelofibrosis, and leukemic transformation.

### *Treatments for PV*

Two main therapies are used in the up-front setting to prevent thrombosis in PV patients (depending on the risk level of thrombosis). Therapeutic phlebotomy plus low-dose aspirin are recommended for low-risk patients (<60 years old and no history of thrombosis), while cytoreduction is required (in addition to phlebotomy and low-dose aspirin) for high-risk patients (age ≥60 years or history of thrombosis).[1,24] The multicenter ECLAP study demonstrated that treatment with low-dose aspirin (70 mg/day to 100 mg/day) led to a significant reduction (60%) in the combined risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, and death from other cardiovascular causes. The use of low-dose aspirin did not increase the risk of major bleeding episodes (relative risk, 1.62; 95% CI, 0.27-9.71).[25]

The goal of maintaining the hematocrit below 45% is based on data from the CYTO-PV study. This study showed that strictly maintaining the hematocrit below 45% (by phlebotomy, hydroxyurea, or both) significantly reduced the risk of thrombosis as compared with maintaining it in the range of 45% to 50% in *JAK2*-mutated PV patients.[26] A total of 365 patients with PV were randomly assigned to groups with a target hematocrit of 45% to 50% in one arm vs lower than 45% in the other arm. Phlebotomy was initially performed every other day or twice a week until the target hematocrit level was reached. Patients at high risk for thrombosis (≥65 years or with a history of thrombosis) or who required cytoreductive therapy for progressive thrombocytosis or splenomegaly received treatment with hydroxyurea. The risk of death from cardiovascular causes or a major thrombotic event was 10% in patients with hematocrit in the range of 45% to 50% vs 3% in those with hematocrit below 45% (*P*=.007).

Besides maintaining the hematocrit below 45%, controlling white blood cell counts is another therapeutic goal in PV, given that leukocytosis is associated with inferior survival, risk of leukemic transformation, and thrombotic/hemorrhagic events.[27-29] The risk of major thrombosis was nearly four-fold higher in patients with a white blood cell count of 11 × $10^9$/L or higher vs less than 7 × $10^9$/L when a subanalysis of the CYTO-PV data was performed.[30] Hydroxyurea and interferons are

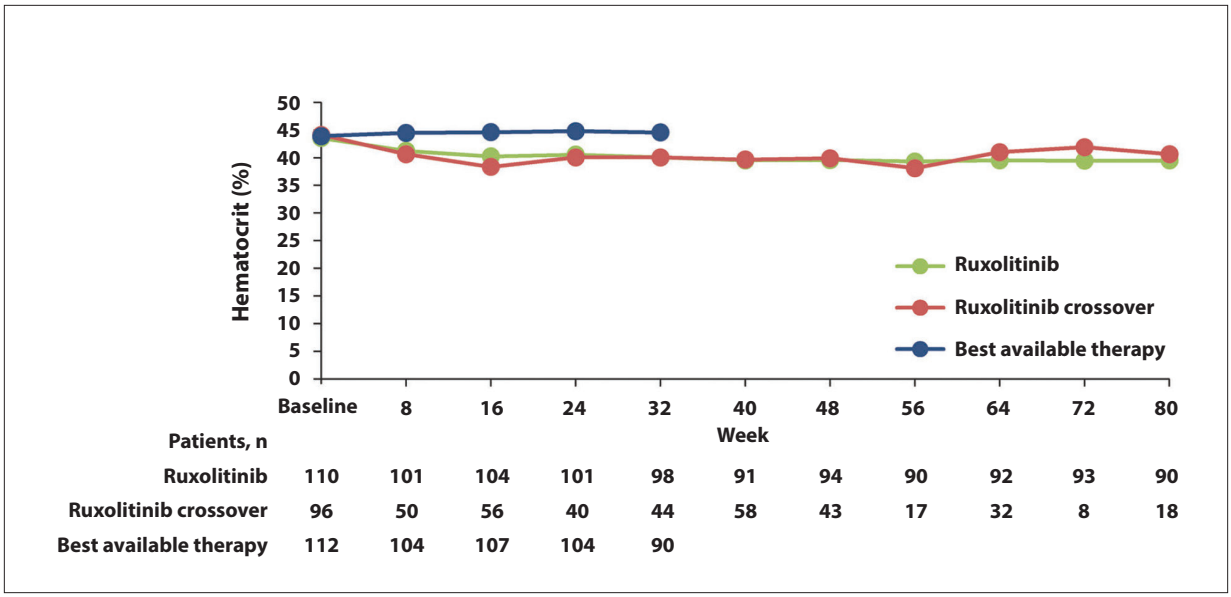


**Figure 1.** Mean hematocrit levels at the 80-week follow-up analysis of the RESPONSE trial. The figure includes all data points with >5 patients. For patients in the ruxolitinib crossover group, the baseline represents the date of crossover to ruxolitinib. Data for the ruxolitinib arm and the BAT arm are from the 80-week data cutoff. Data for the ruxolitinib crossover patients are from the 48-week data cutoff. Adapted from Verstovsek S et al. *Haematologica*. 2016;101(7):821-829.[36]

the recommended frontline options for cytoreductive therapy in PV. A nonrandomized study of 51 patients with PV demonstrated that the "as-needed" addition of hydroxyurea to therapeutic phlebotomy reduced thrombotic risk compared with a historical control group of patients treated with phlebotomy alone.[31] Some historical data have suggested that prolonged use of hydroxyurea may be associated with leukemic transformation.[32] Other novel studies have suggested that older age and the use of other alkylating agents (but not hydroxyurea alone) are independent risk factors for leukemic transformation.[9]

Despite the significant role that hydroxyurea has in the frontline management of PV, up to one-quarter of patients ultimately become resistant to (11%) or intolerant of (13%) treatment.[7] A set of criteria has been developed to define and identify patients with resistance or intolerance to hydroxyurea (Table 3).[29]

### *Ruxolitinib: Data From the RESPONSE Trials*

The Janus kinase (JAK) 1/2 inhibitor ruxolitinib received regulatory approval in 2014 and is recommended in guidelines from the NCCN[3] and European LeukemiaNet[1] as a second-line treatment in patients who become resistant to or are intolerant to hydroxyurea, or who respond poorly to hydroxyurea. Two international, randomized phase 3 studies compared treatment with ruxolitinib vs best available therapy (BAT) in patients with PV. The RESPONSE trial enrolled patients with PV who were resistant or intolerant to hydroxyurea, were dependent on phlebotomy, and had splenomegaly (spleen volume ≥450 $cm^3$).[33] RESPONSE-2 enrolled a similar population, but the patients did not have palpable splenomegaly.[34] Resistance or intolerance to hydroxyurea was defined according to the recommendations from European LeukemiaNet.[29,35]

The RESPONSE trial randomly assigned 110 patients to receive ruxolitinib and 112 patients to receive BAT (as selected by the investigator).[33] Ruxolitinib was initiated at a dose of 10 mg twice daily. Doses were increased to achieve and maintain a hematocrit level below 45% without phlebotomy, reduce spleen size (as assessed by magnetic resonance imaging [MRI]), and normalize white blood cell and platelet counts. BAT included hydroxyurea (at a dose that did not cause unacceptable side effects); interferon or pegylated interferon; pipobroman; anagrelide; immunomodulators, such as lenalidomide or thalidomide; or no medication. This treatment could be changed based on lack of response or treatment intolerance.[33]

The primary study endpoint was a composite of the proportion of patients who achieved both hematocrit control through week 32 and reduction of 35% or more in spleen volume from baseline at week 32. Hematocrit control was defined as the absence of phlebotomy from week 8 to 32 and no more than 1 phlebotomy between randomization and week 8. A phlebotomy was required when the hematocrit was above 45% (≥3 percentage points higher than the baseline) or above 48%, whichever was lower.[33] Spleen volume was measured by centrally reviewed MRI or computed tomography.

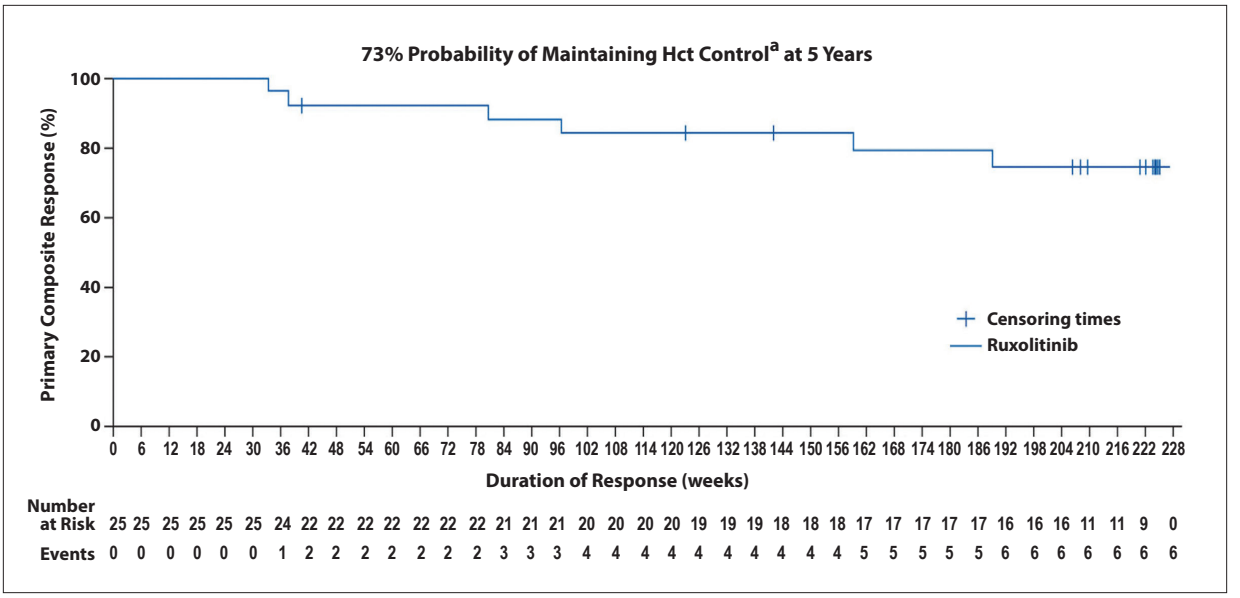


**Figure 2.** The median duration of primary response (patients who achieved both Hct control without phlebotomy and 35% or more reduction from baseline in spleen volume) was not reached in a 5-year analysis of the RESPONSE trial. Twenty-five patients responded. There were 6 events. Nineteen patients were censored. The crosses indicate patients who were censored. [a]Absence of phlebotomy eligibility. Hct, hematocrit. Adapted from Kiladjian JJ et al. *Lancet Haematol*. 2020;7(3):e226-e237.[37]

Secondary endpoints included the proportion of patients who had a primary response at week 32 that was maintained at week 48, and the proportion of patients who achieved complete hematologic remission (defined as hematocrit control, platelet count ≤400 × $10^9$/L, and white blood cell count ≤10 × $10^9$/L) at week 32. Other endpoints included the duration of response, symptom reduction, and safety. Crossover from the BAT arm to the ruxolitinib arm was allowed at week 32 if the primary endpoint had not been met and in the case of disease progression.

Data cutoff for the primary analysis occurred when all patients reached week 48 or discontinued therapy. In the primary analysis, the composite primary endpoint of both hematocrit control and reduction in spleen volume of at least 35% was reported in 20.9% of the ruxolitinib arm vs 0.9% of the control arm ($P$<.001).[33] Prior response to hydroxyurea did not seem to affect response to ruxolitinib, as response rates were similar among patients who had unacceptable side effects from hydroxyurea (22.0%) and those with an inadequate response to hydroxyurea (19.6%). In the ruxolitinib arm, at least 1 component of the primary endpoint was met in 77.3% of patients.[33]

Ruxolitinib was also beneficial compared with BAT when each endpoint was assessed individually at week 32. For example, the rate of hematocrit control through week 32 was higher with ruxolitinib vs BAT (60.0% vs 19.6%), as was the percentage of patients who achieved a reduction in spleen volume of 35% or higher from baseline at week 32 (38.2% vs 0.9%). Complete hematologic response was reported in 23.6% of patients in the ruxolitinib arm vs 8.9% of patients in the control arm ($P$=.003).[33] The secondary endpoint of a primary response at week 32 that was maintained at week 48 was achieved by 19.1% of patients in the ruxolitinib arm vs 0.9% of those in the control arm ($P$<.001).[33]

Fewer therapeutic phlebotomy procedures were required between weeks 8 and 32 in the ruxolitinib arm compared with the BAT arm. At least 1 phlebotomy was needed by 19.8% of patients in the ruxolitinib arm vs 62.4% of patients in the BAT arm. Three or more phlebotomies were reported in 2.8% vs 20.2% of patients, respectively.[33]

The 14-item MPN-SAF TSS was used to assess the efficacy of ruxolitinib on symptoms. At week 32, a reduction in the MPN-SAF TSS of 50% or higher was reported in 49% of patients in the ruxolitinib arm vs 5% of patients in the control arm. This improvement was observed across all symptoms. Ruxolitinib-treated patients experienced a decrease in nearly all of the symptoms that were assessed. Among patients who received BAT, several symptom scores increased. Separate assessments of pruritus and global health status quality of life were consistent, with marked improvements among ruxolitinib-treated patients compared with little or no improvement observed with BAT.[33]

**Analysis of the RESPONSE Trial Data at 80 Weeks.** A second preplanned analysis of the RESPONSE trial

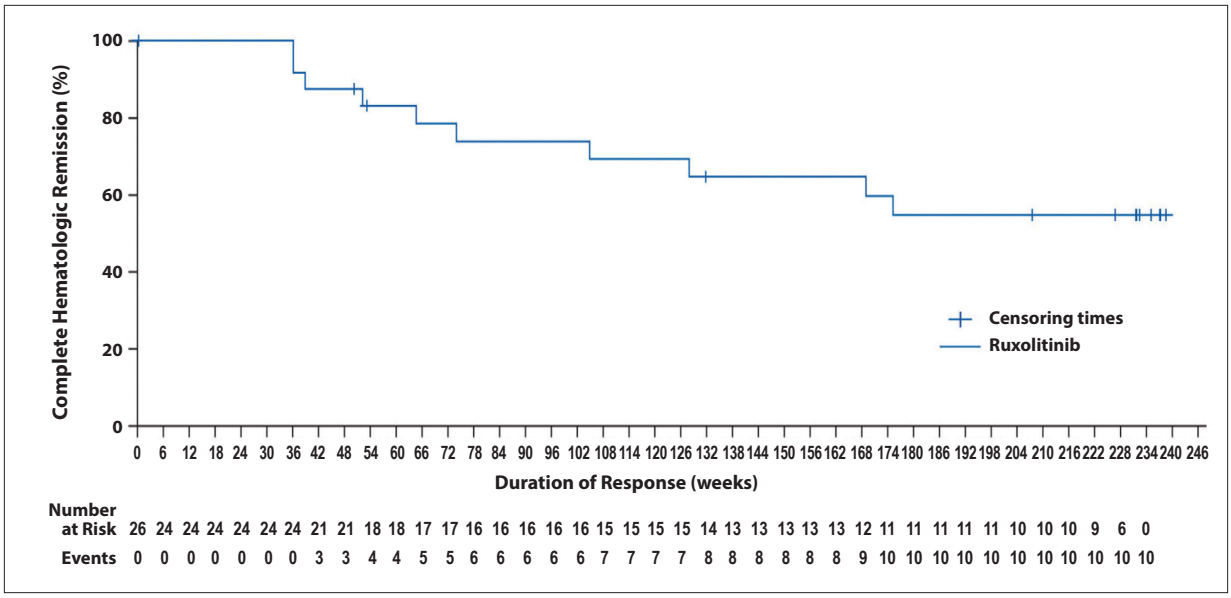


**Figure 3.** Complete hematologic remission in a 5-year analysis of the RESPONSE trial. Twenty-six patients responded. There were 10 events. Sixteen patients were censored. The crosses indicate patients who were censored. Adapted from Kiladjian JJ et al. *Lancet Haematol.* 2020;7(3):e226-e237.[37]

data focused on the durability of efficacy and long-term safety of ruxolitinib after all patients had completed the week 80 follow-up visit or discontinued the study.[36] During a review of the MRI data of the 80-week analysis, 2 additional ruxolitinib-treated patients were identified as primary responders, increasing the rate of primary responders to 22.7%. The probability of maintaining the primary response for at least 80 weeks from the time of response was 92% with ruxolitinib.

Reduction in spleen volume of 35% or higher at week 32 was reported in 40% of the original ruxolitinib arm vs 0.9% of patients in the control arm.[36] None of the patients in the ruxolitinib arm lost their response at week 80. Additionally, patients in the ruxolitinib arm exhibited increases in the mean reduction of spleen volume over time. Among patients randomly assigned to ruxolitinib, the probability of maintaining a complete hematologic response for at least 80 weeks was 69%.[36] Red blood cell counts improved in ruxolitinib-treated patients over time (Figure 1). Among patients with elevated white blood cell counts (>10 × $10^9$/L) at baseline, 31.0% showed improvement and had a white blood cell count of 10 × $10^9$/L or less at week 32, and 47.1% achieved this white blood cell count at week 80. Among patients with elevated platelet counts (>400 × $10^9$/L) at baseline, an improvement to 400 × $10^9$/L or less was recorded in 44.4% of patients at week 32 and 59.3% of patients at week 80.[36]

**Five-Year Follow-Up.** The investigators conducted a 5-year analysis of patients in the RESPONSE trial.[37] The improvements in primary composite response, complete hematologic remission, and overall clinicohematologic response initially observed were maintained with long-term ruxolitinib therapy. At the time of data cutoff, 24% of the primary responders had progressed (defined as phlebotomy eligibility, progression of splenomegaly, or both). A total of 74% (95% CI, 51-88) of patients maintained a primary response at 224 weeks (starting from week 32). The median duration of primary response was not reached at the time of study completion (Figure 2).

At 5 years, the duration of complete hematologic remission starting from week 32 was 55% (95% CI, 32-73; Figure 3).[37] Among 26 patients with a complete hematologic remission at week 32, 38% had progressed by week 256. Among 66 patients who achieved hematocrit control at week 32, 24% had progressed by week 256. In the ruxolitinib arm, 83% of 94 patients had no phlebotomy requirement, and 6% of 94 patients needed 3 or more phlebotomies after week 80 until week 256. Overall, fewer phlebotomies were required in patients who were initially assigned to the ruxolitinib arm and had crossed over to ruxolitinib compared with those treated with BAT only. Among the 70 patients who had an overall clinicohematologic response at week 32, 30% had progressed by week 256. Thus, there was a 67% (95% CI, 54-77) probability of maintaining a clinicohematologic response at 224 weeks (starting from week 32; Figure 4). The median duration of a clinicohematologic response was not reached.[37]

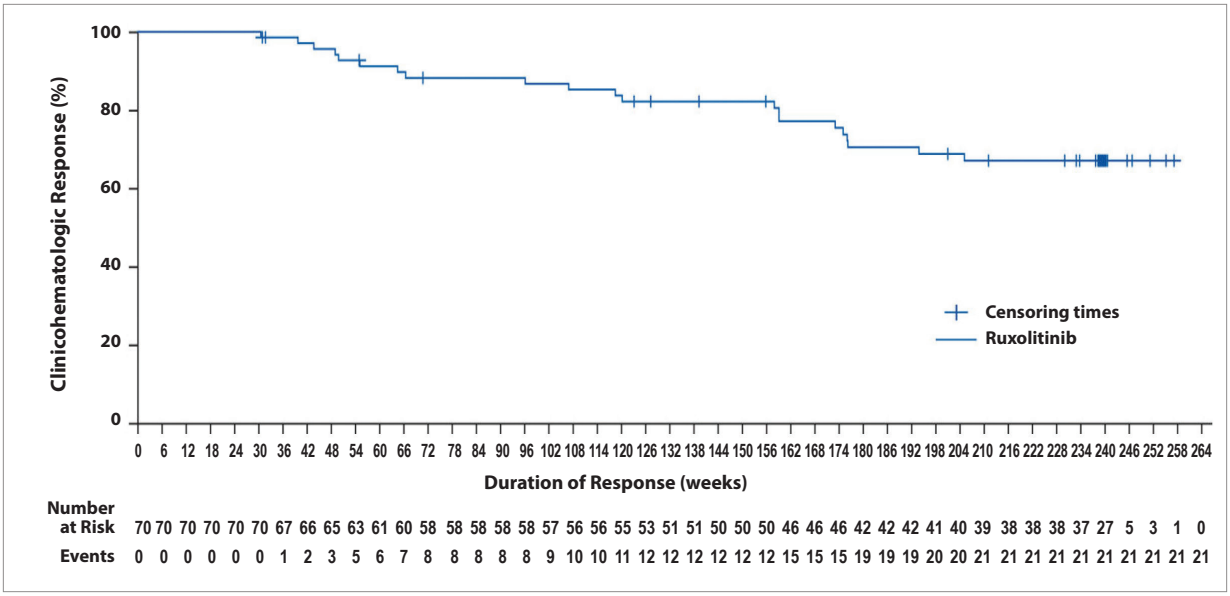


**Figure 4.** Overall clinicohematologic response in a 5-year analysis of the RESPONSE trial. Seventy patients responded. There were 21 events. Forty-nine patients were censored. The crosses indicate patients who were censored. Adapted from Kiladjian JJ et al. *Lancet Haematol*. 2020;7(3):e226-e237.[37]

**Safety Outcomes.** Safety outcomes were reported at the primary analysis through week 32.[33] Both ruxolitinib and BAT were associated with a low rate of grade 3 or 4 nonhematologic adverse events. The overall rate of infections was 41.8% in the ruxolitinib arm vs 36.9% in the control arm. Grade 3 or 4 infections occurred in 3.6% vs 2.7% of patients, respectively. The rates of adverse events were also adjusted for cumulative exposure through the primary data cutoff (170.0 patient-years of exposure in the ruxolitinib group and 72.8 patient-years in the BAT group). In this analysis, the rate of grade 3 or 4 adverse events per 100 patient-years was 28.8 for patients in the ruxolitinib arm vs 44.0 in the BAT arm.[33]

At the 5-year follow-up, the rates of nonhematologic adverse events were generally lower with ruxolitinib compared with BAT.[37] The most common nonhematologic adverse events reported with ruxolitinib (in both the randomized arm and the crossover population) per 100 patient-years of exposure were pruritus (7.0 vs 6.1, respectively), diarrhea (7.0 vs 3.6), increased weight (6.1 vs 4.2), headache (5.8 vs 5.2), arthralgia (5.6 vs 3.3), fatigue (5.1 vs 3.9), and muscle spasms (5.1 vs 3.3).

Infection rates were lower in the ruxolitinib arm (18.9 per 100 patient-years of exposure in the randomized population and 19.1 per 100 patient-years in the crossover population) compared with the BAT arm (59.8 per 100 patient-years). An exception to this lower rate was herpes zoster infection, which was reported in 6.4% of patients in the ruxolitinib arm vs no patients in the control arm.[37]

The rates of secondary malignancies were 7.0 per 100 patient-years of exposure among patients originally assigned to treatment with ruxolitinib, 4.1 per 100 patient-years among those treated with BAT, and 4.5 per 100 patient-years in the crossover population. Rates of nonmelanoma skin cancer were 5.1, 2.7, and 2.7 per 100 patient-years of exposure, respectively.[37]

**RESPONSE-2 Trial.** RESPONSE-2 was a randomized, open-label phase 3b study that compared ruxolitinib vs BAT in patients with PV who did not have palpable splenomegaly.[38] The primary endpoint was the proportion of patients who achieved hematocrit control at week 28. The analyses included all patients in the intention-to-treat population.

The trial randomly assigned 74 patients to the ruxolitinib arm and 75 patients to the BAT arm. Hematocrit control was reported in 62% of patients in the ruxolitinib arm vs 19% of patients in the BAT arm (odds ratio, 7.28; 95% CI, 3.43-15.45; $P<.0001$). The most frequent hematologic adverse events of any grade were anemia, reported in 14% of the ruxolitinib arm vs 3% of the BAT arm, and thrombocytopenia, reported in 3% vs 8%, respectively.

A follow-up analysis of the RESPONSE-2 trial evaluated the durability of the efficacy and safety of ruxolitinib after patients visited their clinician at week 80 or discontinued the study.[38] At the time of the analysis, 93% of patients randomly assigned to ruxolitinib were still receiving this treatment. Among patients originally assigned to

the BAT arm, 77% had crossed over to ruxolitinib after week 28. By week 80, no patients remained in the control arm. Among patients in the ruxolitinib arm who achieved a hematocrit response at week 28, the probability that this response would be maintained up to week 80 was 78%. At week 80, durable complete hematologic remission was reported in 24% of patients in the ruxolitinib arm vs 3% in the control arm. The safety profile of ruxolitinib was similar to that reported in previous studies.[38]

Results from a 5-year follow-up analysis of the RESPONSE-2 study were recently published.[39] The median follow-up was 67 months. Between weeks 28 and 80, 58 of 75 patients (77%) in the BAT group crossed over to the ruxolitinib arm. Per the study's protocol, no patients continued BAT after week 80. Ninety-seven patients received ruxolitinib until week 260, including 59 of 74 patients (80%) in the ruxolitinib arm and 38 of 58 patients (66%) in the crossover groups. At week 260, durable hematocrit control was reported in 22% of the ruxolitinib group, with the estimated median duration not reached (95% CI, 144 to not reached). The median duration of hematocrit control was not reported for patients in the BAT arm owing to the small number of responders by week 80. During the 5-year follow-up, the median hematocrit level among patients in the ruxolitinib arm remained below 45%. By week 260, 60 phlebotomies were required by 74 patients in the ruxolitinib arm. In the BAT arm, 106 phlebotomies were required by 75 patients by week 80. The 5-year overall survival was 96% (95% CI, 87-99) in the ruxolitinib arm vs 91% (95% CI, 80-96) in the BAT arm.

## Disclosure

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