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# Ruxolitinib *versus* best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial

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## ABSTRACT

RESPONSE is an open-label phase 3 study evaluating the Janus kinase 1/Janus kinase 2 inhibitor ruxolitinib *versus* best available therapy for efficacy/safety in hydroxyurea-resistant or intolerant patients with polycythemia vera. This preplanned analysis occurred when all patients completed the Week 80 visit or discontinued. Objectives included evaluating the durability of the primary response (Week 32 phlebotomy-independent hematocrit control plus ≥35% spleen volume reduction), its components, and that of complete hematologic remission; and long-term safety. Median exposure was 111 weeks; 91/110 (82.7%) patients randomized to ruxolitinib remained on treatment. No patients continued best available therapy (98/112 [87.5%] crossed over to ruxolitinib, most at/soon after Week 32). At Week 32, primary response was achieved by 22.7% *vs.* 0.9% of patients randomized to ruxolitinib and best available therapy, respectively (hematocrit control, 60.0% *vs.* 18.8%; spleen response, 40.0% *vs.* 0.9%). The probability of maintaining primary and hemat-ocrit responses for ≥80 weeks was 92% and 89%, respectively; 43/44 spleen responses were maintained until Week 80. Complete hematologic remission at Week 32 was achieved in 23.6% of ruxolitinib-randomized patients; the probability of maintaining complete hematologic remission for ≥80 weeks was 69%. Among ruxolitinib crossover patients, 79.2% were not phlebotomized, and 18.8% achieved a ≥35% reduction from baseline in spleen volume after 32 weeks of treatment. New or worsening hematologic laboratory abnormalities in ruxolitinib-treated patients were primarily grade 1/2 decreases in hemoglobin, lymphocytes, and platelets. The thromboembolic event rate per 100 patient-years was 1.8 with randomized ruxolitinib treatment *vs.* 8.2 with best available therapy. These data support ruxolitinib as an effective long-term treatment option for hydroxyurea-resistant or intolerant patients with polycythemia vera. This trial was registered at *clinicaltrials.gov identifier: 01243944.*

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## Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm primarily characterized by erythrocytosis, although increased white blood cell and platelet counts are also common.[1] Patients with PV have increased risks of morbidity and mortality relative to comparable subjects in the general population (eg, same sex/age),[2,3] often resulting from thromboembolic events or progression to myelofibrosis (MF) or acute myeloid leukemia (AML).[2]

Treatment for PV aims to reduce the risk of thromboembolic events, relieve symptom burden, and minimize the risk of disease transformation to MF or AML.[4,5] Some patients obtain clinical benefit from cytoreductive treatment, often hydroxyurea;[6-8] however, approximately 25% of patients become resistant to or intolerant of hydroxyurea.[9] Ruxolitinib is a Janus kinase (JAK)1/JAK2 inhibitor approved by the US Food and Drug Administration (FDA) for patients with PV who have an inadequate response to or are intolerant of hydroxyurea,[10] and by the European Medicines Agency (EMA) for adult patients with PV who are resistant to or intolerant of hydroxyurea.[11]

The ongoing RESPONSE trial is a global, multicenter, phase 3 study comparing ruxolitinib with best available therapy in patients with PV who were resistant to or intolerant of hydroxyurea, per modified European LeukemiaNet (ELN) criteria.[4,12] In the primary analysis, a significantly greater proportion of patients treated with ruxolitinib achieved hematocrit control without phlebotomy along with a ≥35% reduction in spleen volume from baseline at Week 32 (the primary study endpoint) compared with patients treated with best available therapy.[12] This was a second preplanned analysis of the RESPONSE trial assessing durability of efficacy and the long-term safety of ruxolitinib treatment after all patients completed the Week 80 visit or discontinued the study.

## Methods

### Study Design

RESPONSE is an international, randomized, open-label, phase 3 study. The study design and primary analysis results have been described previously.[12] Briefly, eligible patients were randomized 1:1 to receive ruxolitinib (10 mg twice daily) or best available therapy (single-agent therapy deemed most appropriate by treating physician). Treatment options for best available therapy included hydroxyurea, interferon or pegylated interferon, pipobroman, anagrelide, immunomodulators (e.g. lenalidomide, thalidomide), or observation without pharmacologic treatment (except aspirin). Dose adjustments were permitted for safety and efficacy in patients receiving ruxolitinib; modifications could be made to best available therapy regimens for lack of response or side effects requiring treatment discontinuation. Low-dose aspirin was administered to all patients unless contraindicated. Phlebotomies as monotherapy or in combination with study treatment were mandatory for patients with a confirmed hematocrit >45% that was ≥3 percentage points higher than baseline or a confirmed hematocrit >48%, whichever were lower. Patients randomized to best available therapy were permitted to cross over to ruxolitinib at Week 32 if the primary endpoint was not met or after Week 32 following signs of disease progression (i.e. phlebotomy eligibility or splenomegaly progression). The study was approved by the central ethics committee or institutional review board at each participating institution and was conducted in accordance with the Declaration of Helsinki; all patients provided written informed consent.

### Endpoints

The primary analysis occurred when all patients completed the Week 48 visit or discontinued; the current preplanned analysis occurred when all patients completed the Week 80 visit or discontinued. The primary endpoint was the proportion of patients achieving both (1) hematocrit control without phlebotomy (defined as no phlebotomy eligibility between Weeks 8 and 32 with ≤1 phlebotomy eligibility from randomization to Week 8; phlebotomy eligibility was defined as hematocrit >45% and ≥3 percentage points higher than baseline or >48%, whichever were lower) and (2) ≥35% reduction from baseline in spleen volume (as measured by magnetic resonance imaging [MRI]) at Week 32. Complete hematologic remission (CHR; defined as hematocrit control, platelet count ≤400×10$^9$/L, and white blood cell count ≤10×10$^9$/L) was a key secondary endpoint.

Because most patients randomized to best available therapy crossed over to receive ruxolitinib at or immediately after Week 32, long-term comparisons between study treatment arms were no longer appropriate. Therefore, this analysis evaluated the durability of efficacy in patients originally randomized to the ruxolitinib arm and in those who received ruxolitinib after crossover, including durability of the primary response, hematocrit control, spleen volume reduction, and CHR. Patient-reported outcomes were not collected after Week 32, with the exception of the end-of-study visit for patients who discontinued; therefore, these data are not summarized.

Adverse events are reported regardless of causality and not limited to those considered to be related to treatment; serious adverse events and deaths are also reported. Adverse event data from the 80-week analysis are reported for patients originally randomized to the ruxolitinib arm, patients who received ruxolitinib after crossover (i.e. all randomized to the best available therapy arm and received ≥1 dose of ruxolitinib after crossover), and patients who received best available therapy.

Please see the *Online Supplementary Section* for details concerning exploratory and statistical analyses included in this report.

## Results

### Patients

In total, 222 patients were randomized to ruxolitinib (n=110) or best available therapy (n=112); patient enrollment and demographics were previously reported.[12] Median age in the ruxolitinib and best available therapy arms (62.0 and 60.0 years, respectively), median time since PV diagnosis (8.2 and 9.3 years), median duration of previous hydroxyurea therapy (3.1 and 2.8 years), mean *JAK2*V617F allele burden (76.2% and 75.0%), and median spleen volume (1195 and 1322 cm$^3$) at baseline were similar between treatment arms. Additionally, 60.0% of patients treated with ruxolitinib and 71.4% of patients treated with best available therapy were men.

At the time of data cutoff for the 80-week analysis, 91 patients (82.7%) randomized to receive ruxolitinib were still being treated (Figure 1), and the median exposure was 111 weeks. No patients were actively receiving best available therapy (median exposure, 34 weeks); 98 patients (87.5%) had crossed over to ruxolitinib, 81 (82.7%) of whom continued to receive ruxolitinib at data cutoff (median exposure, 75.6 weeks). Mean (SD) ruxolitinib dose was 26.7 mg/d (10.8 mg/d) at Week 32 and 28.4 mg/d

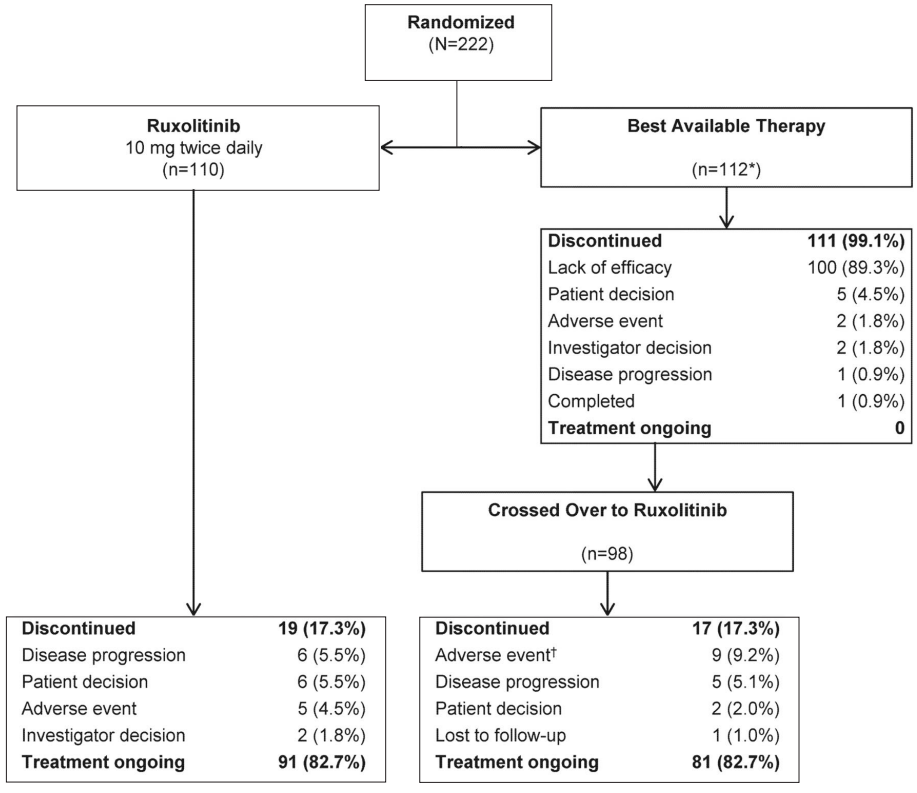


**Figure 1. Patient disposition.** *One patient withdrew consent and was not treated on study; initial best available therapy included hydroxyurea (n=66), interferon/pegylated interferon (n=13), anagrelide (n=8), immunomodulators (n=5), pipobroman (n=2), and observation (n=17). †2 patients who discontinued because of an adverse event died during follow-up.

(11.1 mg/d) at Week 80 (*Online Supplementary Figure S1*). The distribution of ruxolitinib dosing was similar at Week 32 and Week 80; the most common ruxolitinib dose was 20 mg/d at both time points (36.1% and 33.0%, respectively; *Online Supplementary Figure S2*). Among patients originally randomized to ruxolitinib, the most common reasons for discontinuation of study drug included disease progression (5.5%), patient decision (5.5%), and adverse events (4.5%) (Figure 1).

### Efficacy

The primary endpoint was previously reported to have been achieved by 23 patients (20.9%) originally randomized to ruxolitinib, and 1 patient (0.9%) receiving best available therapy at Week 32 ($P$<0.001).[12] During MRI data review for the current 80-week analysis, 2 additional patients randomized to ruxolitinib were identified as primary responders, bringing the total number of primary responders to 25 (22.7%). No additional responders were identified in the best available therapy arm. The probability of maintaining the primary response among patients originally randomized to ruxolitinib for ≥80 weeks from time of response was 92% (Figure 2).

The primary analysis previously reported that 60.0% of patients originally randomized to ruxolitinib achieved hematocrit control without phlebotomy by Week 32 compared with 19.6% of patients randomized to best available therapy;[12] however, analysis of data from the 80-week data cutoff revealed an additional patient in the best available therapy arm who had a phlebotomy at Week 8, bringing the proportion of patients with hematocrit control at Week 32 down to 18.8%. Among patients originally randomized to ruxolitinib, the probability of maintaining hematocrit control up to Week 80 from time of response was 89% (Figure 3). Of the 98 patients still receiving ruxolitinib at Week 32, 88 (89.8%) had no phlebotomy procedures between Weeks 32 and 80. Of the 109 patients randomized to best available therapy who did not discontinue before Week 8, 68 (62.4%) had ≥1 phlebotomy and 22 (20.2%) had ≥3 phlebotomies between Weeks 8 and 32.[12]

A higher proportion of patients originally randomized to ruxolitinib achieved ≥35% reduction in spleen volume at Week 32 compared with the best available therapy arm (40.0% *vs.* 0.9%); none of these patients lost their response at Week 80. Additionally, mean reductions in spleen volume increased over time in the ruxolitinib arm (*Online Supplementary Figure S3*).

The primary analysis previously reported that a CHR at Week 32 was achieved by 26 patients (23.6%) originally randomized to ruxolitinib compared with 10 patients (8.9%) randomized to best available therapy ($P$=0.003);[12] however, after correcting for the patient in the best available therapy arm who had a phlebotomy at Week 8, only 9 patients achieved CHR at Week 32 (8.0%; unadjusted, $P$=0.0016; with adjustment for baseline white blood cell and platelet status, $P$=0.0013 ). For patients originally randomized to ruxolitinib, the probability of maintaining their CHR for at least 80 weeks was 69%.

Blood cell counts improved over time in patients originally randomized to ruxolitinib (Figure 4). Among patients with elevated white blood cell counts (>$10\times10^9$/L) at baseline, improvements to ≤$10\times10^9$/L were achieved in 31.0% (27/87) of patients at Week 32, and 47.1% (41/87) at Week 80. Among patients with elevated baseline platelet counts (>$400\times10^9$/L), improvements to ≤$400\times10^9$/L were achieved

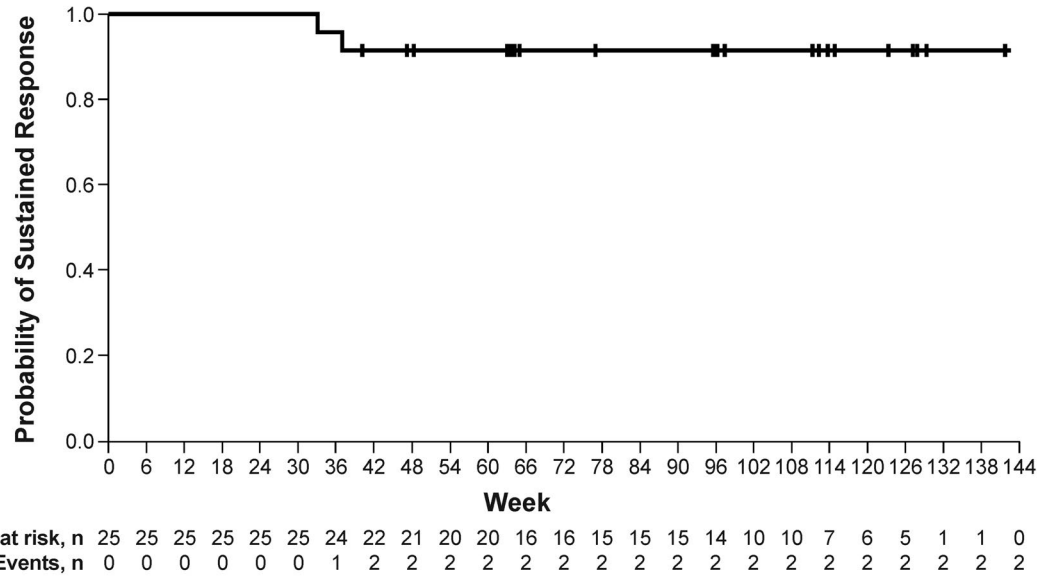


Figure 2. Durability of primary response with ruxolitinib treatment.

by 44.4% (24/54) of patients at Week 32 and 59.3% (32/54) at Week 80.

## Exploratory analyses

*Efficacy with ruxolitinib after crossover*

Phlebotomy requirement was similar between patients treated with ruxolitinib after crossover from best available therapy and patients originally randomized to the ruxolitinib arm. Among patients treated for up to 32 weeks, phlebotomy was not required by 73.6% (81/110) of patients originally randomized to the ruxolitinib arm, 79.2% (76/96) receiving ruxolitinib after crossover, and 25.0% (28/112) during treatment with best available therapy. Median (range) time to first phlebotomy was 131 (30–568) days for patients originally randomized to ruxolitinib, 144 (6–483) days for those receiving ruxolitinib after crossover, and 113 (31–337) days for those receiving treatment with best available therapy. The phlebotomy rate per 100 patient-years of exposure was lower among patients originally randomized to ruxolitinib (34.1) and receiving ruxolitinib after crossover (38.5) compared with patients receiving best available therapy (196.8).

Ruxolitinib after crossover was associated with reductions in spleen volume after 16 weeks of treatment (*Online Supplementary Figure S4*). After 32 weeks of treatment, a greater proportion of patients achieved a ≥35% reduction from baseline in spleen volume in patients originally randomized to ruxolitinib (40.0% [44/110]) and those receiving ruxolitinib after crossover (18.8% [18/96]) compared with patients receiving best available therapy (0.9% [1/112]; *Online Supplementary Table S1*). After 32 weeks of treatment, the mean percentage change from original baseline in spleen volume was –27.7% in patients originally randomized to ruxolitinib, –14.2% in those receiving ruxolitinib after crossover, and +4.5% in those receiving best available therapy.

The positive trend toward improved (i.e. reduced) blood cell counts observed in patients originally randomized to ruxolitinib was also observed in patients treated with ruxolitinib after crossover (Figure 4).

*JAK2V617F Allele Burden*

The mean (median) percentage change from baseline in *JAK2*V617F allele burden at Week 32 was –12.2% (–10.1%) and +1.2% (0.0%) in patients originally randomized to ruxolitinib and in those receiving best available therapy, respectively.[12] At Week 80, the mean (median) percentage change from baseline in *JAK2*V617F allele burden among patients originally randomized to ruxolitinib was –22.0% (–18.4%). Among patients who received ruxolitinib after crossover, the mean (median) percentage change from crossover baseline in *JAK2*V617F allele burden was –6.7% (–5.5%) 48 weeks after crossover.

## Safety

The most common nonhematologic adverse events in the originally randomized ruxolitinib arm were headache, diarrhea, pruritus, and fatigue (Table 1); most events were grade 1 or 2. Relatively few new adverse events were observed after the primary analysis; the number of patients with any given adverse event from the 48-week to the 80-week analysis increased by no more than 4, and by 1 or 2 for most individual events. New or worsening hematologic laboratory abnormalities in the originally randomized ruxolitinib arm through Week 80 were primarily grade 1 or 2 decreases in hemoglobin, lymphocytes, and platelets (Table 2). Patients receiving treatment with ruxolitinib after crossover had a higher rate of decreased hemoglobin compared with those originally randomized to ruxolitinib; the rates of other hematologic adverse events (Table 2) and nonhematologic adverse events (Table 1) were generally consistent with those observed in patients originally randomized to ruxolitinib.

The rates of all grade and grade 3/4 thromboembolic events per 100 patient-years of exposure were 1.8 and 0.9, respectively, among patients originally randomized to rux-

olitinib *vs.* 4.1 and 2.7 in those receiving ruxolitinib after crossover, and 8.2 and 2.7 in those receiving best available therapy (Table 3). In the originally randomized ruxolitinib arm, thromboembolic events included portal vein thrombosis, cerebral infarction, ischemic stroke, and retinal vascular thrombosis; thromboembolic events in the best available therapy arm included deep vein thrombosis, myocardial infarction, pulmonary embolism, splenic infarction, thrombophlebitis, and thrombosis. Other adverse events of interest are shown in Table 4. Rates of herpes zoster infection were higher in patients receiving ruxolitinib (per 100 patient-years of exposure: originally randomized to ruxolitinib, 5.3; with ruxolitinib after crossover, 5.4; with best available therapy, none). Rates of nonmelanoma skin cancer per 100 patient-years of exposure were 4.4 in those originally randomized to ruxolitinib, 2.0 with ruxolitinib after crossover, and 2.7 with best available therapy. Among patients with a history of nonmelanoma skin cancer (originally randomized to ruxolitinib, n=12; with ruxolitinib after crossover, n=6; with best available therapy, n=7), rates of nonmelanoma skin cancer were similar between randomized treatments (24.2, 10.6, 22.3 per 100 patient-years of exposure, respectively). Among patients without a history of nonmelanoma skin cancer (originally randomized to ruxolitinib, n=98; with ruxolitinib after crossover, n=92; with best available ther-

**Table 1.** Nonhematologic adverse events in the 80-week and 48-week analyses adjusted for exposure.

| | 80-Week Analysis | | | | | | 48-Week Analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Ruxolitinib (n=110) | | Ruxolitinib Crossover (n=98) | | Best Available Therapy (n=111*) | | Ruxolitinib (n=110) | | Best Available Therapy (n=111*) | |
| Exposure, Patient-Years | 227.7 | | 147.6 | | 73.6 | | 170.0 | | 72.8 | |
| Rate per 100 Patient-Years of Exposure† | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 |
| Headache | 10.5 | 0.9 | 8.8 | 0 | 28.5 | 1.4 | 13.5 | 1.2 | 28.8 | 1.4 |
| Diarrhea | 9.7 | 0 | 5.4 | 0 | 12.2 | 1.4 | 12.4 | 0 | 12.4 | 1.4 |
| Pruritus | 9.7 | 0.4 | 8.8 | 0 | 32.6 | 5.4 | 11.2 | 0.6 | 34.3 | 5.5 |
| Fatigue | 8.3 | 0.4 | 6.8 | 0 | 23.1 | 4.1 | 11.2 | 0 | 23.4 | 4.1 |
| Muscle spasms | 7.9 | 0.4 | 3.4 | 0 | 9.5 | 0 | 8.8 | 0.6 | 6.9 | 0 |
| Dizziness | 7.5 | 0 | 7.5 | 0 | 14.9 | 0 | 8.8 | 0 | 15.1 | 0 |
| Increased weight | 7.5 | 0.4 | 6.8 | 0 | 1.4 | 0 | 7.6 | 0 | 1.4 | 0 |
| Dyspnea | 7.0 | 1.3 | 2.7 | 0 | 2.7 | 0 | 8.8 | 1.8 | 2.7 | 0 |
| Abdominal pain | 6.6 | 0.9 | 4.7 | 0 | 17.7 | 0 | 7.1 | 1.2 | 17.9 | 0 |
| Arthralgia | 6.1 | 0 | 4.7 | 0 | 10.9 | 1.4 | 7.6 | 0 | 11.0 | 1.4 |
| Back pain | 5.7 | 0.4 | 5.4 | 0.7 | 6.8 | 0 | 5.9 | 0.6 | 6.9 | 0 |
| Cough | 5.7 | 0 | 5.4 | 0 | 8.2 | 0 | 7.6 | 0 | 8.2 | 0 |
| Nasopharyngitis | 5.7 | 0 | 6.1 | 0 | 12.2 | 0 | 7.6 | 0 | 12.4 | 0 |
| Constipation | 5.3 | 0.4 | 6.8 | 0 | 4.1 | 0 | 7.1 | 0.6 | 4.1 | 0 |
| Herpes zoster | 5.3 | 0.9 | 5.4 | 0.7 | 0 | 0 | 6.5 | 1.2 | 0 | 0 |
| Pyrexia | 5.3 | 0 | 5.4 | 0.7 | 6.8 | 0 | 5.9 | 0 | 6.9 | 0 |

**1 patient was randomized to best available therapy but did not receive study treatment. †All grades adverse events occurring at a rate of ≥5 per 100 patient-years of exposure in the ruxolitinib arm in the 80 week analysis.*

**Table 2.** New or worsening decrease in hematologic laboratory values in the 80-week analysis adjusted for exposure.

| | 80-Week Analysis | | | | | | 48-Week Analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Ruxolitinib (n=110) | | Ruxolitinib Crossover (n=98) | | Best Available Therapy (n=111*) | | Ruxolitinib (n=110) | | Best Available Therapy (n=111*) | |
| Exposure, Patient-Years | 227.7 | | 147.6 | | 73.6 | | 170.0 | | 72.8 | |
| Rate per 100 Patient-Years of Exposure | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 |
| Hemoglobin | 27.2 | 0.9 | 40.0 | 2.7 | 47.6 | 0 | 34.7 | 1.2 | 48.1 | 0 |
| Lymphocytes | 27.2 | 9.7 | 29.8 | 6.8 | 78.8 | 27.2 | 32.9 | 11.8 | 78.3 | 27.5 |
| Platelets | 14.9 | 2.6 | 16.9 | 0.7 | 29.9 | 5.4 | 19.4 | 3.5 | 30.2 | 5.5 |
| Leukocytes | 6.6 | 0.9 | 6.8 | 0.7 | 19.0 | 2.7 | 8.2 | 1.2 | 19.2 | 2.7 |
| Neutrophils | 2.2 | 0.4 | 1.4 | 0.7 | 12.2 | 1.4 | 2.9 | 1.2 | 12.4 | 1.4 |

**1 patient was randomized to best available therapy but did not receive study treatment.*

apy, n=104), rates of nonmelanoma skin cancer were 2.0, 1.4, and 1.4 per 100 patient-years of exposure, respectively. Rates of transformation to MF and AML in patients originally randomized to ruxolitinib were 1.3 and 0.4 per 100 patient-years of exposure, respectively. One patient in the best available therapy arm had transformation to MF before crossover to ruxolitinib (rate of transformation, 1.4 per 100 patient-years of exposure); no patients in the best available therapy arm had transformation to AML before crossover. Among patients treated with ruxolitinib after crossover, 3 patients had transformation to MF (rate of transformation, 2.0 per 100 patient-years of exposure), 1 of whom developed AML (rate of transformation, 0.7 per 100 patient-years of exposure).

Serious adverse events occurred at a rate of 12.7 per 100 patient-years of exposure in patients originally randomized to ruxolitinib, and 19.0 with ruxolitinib after crossover at the 80-week analysis; the only serious adverse events reported by ≥2 patients in those originally randomized to ruxolitinib were basal cell carcinoma (1.3 per 100 patient-years of exposure), chest pain (0.9), and pneumonia (0.9). At the 48-week analysis, 2 patients in the best available therapy arm had died after crossing over to ruxolitinib; 1 due to central nervous system hemorrhage, and 1 due to multiorgan failure and hypovolemic shock. In the patient who died from central nervous system hemorrhage (a 66-year-old white woman), platelet counts were $1174\times10^9$/L during screening and $351\times10^9$/L at the Week 64 visit (137 days after crossover and 18 days before death), there was no history of hemorrhage, and the patient was receiving treatment with aspirin 81 mg once daily. The patient had grade 3 hypertension at randomization and intermittently throughout study treatment, which the investigator considered as a possible cause for the central nervous system hemorrhage. The patient who died from multiorgan failure and hypovolemic shock (a 50-year-old Asian woman) discontinued ruxolitinib on Day 645 because of grade 3 anemia. Fourteen days later,

**Table 3.** Thromboembolic events in the 80-week analysis adjusted for exposure.

| | Ruxolitinib (n=110) | | Ruxolitinib Crossover (n=98) | | Best Available Therapy (n=111*) | |
|---|---|---|---|---|---|---|
| Exposure, Patient-Years | 227.7 | | 147.6 | | 73.6 | |
| Events, Rate per 100 Patient-Years of Exposure | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 |
| All thromboembolic events | 1.8 | 0.9 | 4.1 | 2.7 | 8.2 | 2.7 |
| Portal vein thrombosis | 0.4 | 0.4 | 0 | 0 | 0 | 0 |
| Cerebral infarction | 0.4 | 0.4 | 0 | 0 | 0 | 0 |
| Ischemic stroke | 0.4 | 0 | 1.4 | 1.4 | 0 | 0 |
| Retinal vascular thrombosis | 0.4 | 0 | 0 | 0 | 0 | 0 |
| Myocardial infarction | 0 | 0 | 1.4 | 0.7 | 1.4 | 1.4 |
| Bone infarction | 0 | 0 | 0.7 | 0 | 0 | 0 |
| Coronary artery occlusion | 0 | 0 | 0.7 | 0 | 0 | 0 |
| Disseminated intravascular coagulation | 0 | 0 | 0.7 | 0.7 | 0 | 0 |
| Thrombosis | 0 | 0 | 0.7 | 0 | 1.4 | 0 |
| Deep vein thrombosis | 0 | 0 | 0 | 0 | 2.7 | 1.4 |
| Pulmonary embolism | 0 | 0 | 0 | 0 | 1.4 | 1.4 |
| Splenic infarction | 0 | 0 | 0 | 0 | 1.4 | 0 |
| Thrombophlebitis | 0 | 0 | 0 | 0 | 1.4 | 0 |

**1 patient was randomized to best available therapy but did not receive study treatment.*

**Table 4.** Adverse events of interest in the 80-week analysis adjusted for exposure.

| | Ruxolitinib (n=110) | Ruxolitinib Crossover (n=98) | Best Available Therapy (n=111*) |
|---|---|---|---|
| Exposure, Patient-Years | 227.7 | 147.6 | 73.6 |
| Events, n (Rate per 100 Patient-Years of Exposure) | | | |
| All infections | 67 (29.4) | 41 (27.8) | 43 (58.4) |
| Grade 3 or 4 | 9 (4.0) | 8 (5.4) | 3 (4.1) |
| Herpes zoster infection | 12 (5.3) | 8 (5.4) | 0 |
| Grade 3 or 4 | 2 (0.9) | 1 (0.7) | 0 |
| Nonmelanoma skin cancer | 10 (4.4) | 3 (2.0) | 2 (2.7) |
| Disease progression† | | | |
| Myelofibrosis | 3 (1.3) | 3 (2.0) | 1 (1.4) |
| Acute myeloid leukemia | 1 (0.4) | 1 (0.7) | 0 |

**1 patient was randomized to best available therapy but did not receive study treatment. †There was 1 additional report of myelofibrosis in the ruxolitinib arm, but this was not confirmed on bone marrow biopsy.*

the patient developed grade 4 disseminated intravascular coagulation, grade 3 acidosis, grade 1 pyrexia, and respiratory distress; was moved into the intensive care unit; and received a blood transfusion for anemia. The next day (16 days after the last dose of ruxolitinib), the patient died because of shock related to multiorgan failure, with the following ongoing events: anemia, cardiac failure, disseminated intravascular coagulation, dyspnea, peripheral edema, nephrotic syndrome, and pulmonary hypertension. The investigator managing this patient's care suspected an association between ruxolitinib treatment and the pulmonary hypertension event, but not other events (i.e. disseminated intravascular coagulation, hypovolemic shock, multiorgan failure, or nephrotic syndrome). These deaths were not considered treatment related. No new deaths were reported at the 80-week analysis data cutoff.

## Discussion

Long-term follow-up of the phase 3 RESPONSE trial demonstrates the durability of ruxolitinib efficacy in patients with PV who were resistant to or intolerant of hydroxyurea. For patients who achieved the composite primary response, Kaplan-Meier estimates predicted that most would maintain that response (92%) or the hematocrit control component (89%) up to Week 80. Furthermore, no patients who achieved spleen response at Week 32 (i.e. the primary analysis time point) lost the response at Week 80. Among all patients originally randomized to ruxolitinib treatment, mean hematocrit levels were approximately 40% at Week 32, where they remained through Week 80. Between Weeks 32 and 80, mean white blood cell counts decreased from $12.0\times10^9$/L to $10.7\times10^9$/L. During this time frame, mean reduction in spleen volume from baseline improved from –27.7% to –38.6%. Patients who were treated with ruxolitinib after crossover from best available therapy achieved similar benefits in hematocrit control, reduction in spleen volume, and normalization of blood cell counts as patients originally randomized to ruxolitinib. Furthermore, although patient-reported symptom severity was not assessed after Week 32, fatigue and pruritus were recorded as adverse events throughout the study. These events continued to occur at lower rates in patients who were randomized to or crossed over to ruxolitinib compared with those receiving best available therapy.

Control of blood cell counts is an important treatment goal for patients with PV. A large-scale randomized controlled trial testing the intensity of cytoreductive therapy in PV (CYTO-PV) demonstrated that high hematocrit levels (45%–50% *vs.* <45%) and high white blood cell counts ($\geq11\times10^9$/L *vs.* $<7.0\times10^9$/L) are associated with increased risk of cardiovascular/thromboembolic events.[6,13] However, maintaining a therapeutic hematocrit level with phlebotomy and/or hydroxyurea may be challenging for some patients. In the CYTO-PV study, approximately 25% of patients had hematocrit levels that were outside the target range 6 months after randomization.[14] Treatment with ruxolitinib in RESPONSE was associated with durable improvements in hematocrit levels, as well as reductions in white blood cell counts. Furthermore, although the study was not designed to evaluate thromboembolic event rates, the originally randomized ruxolitinib arm of RESPONSE was associated with a lower rate of thromboembolic events compared with the best available therapy arm. At Week 32, before crossover to ruxolitinib, there were 6 thromboembolic events in the best available therapy arm compared with 1 event in the ruxolitinib arm.[12] Although treatment with ruxolitinib after crossover was associated with rapid normalization of blood cell counts, thromboembolic event rates remained higher than in patients originally randomized to ruxolitinib. These data emphasize the importance of imple-

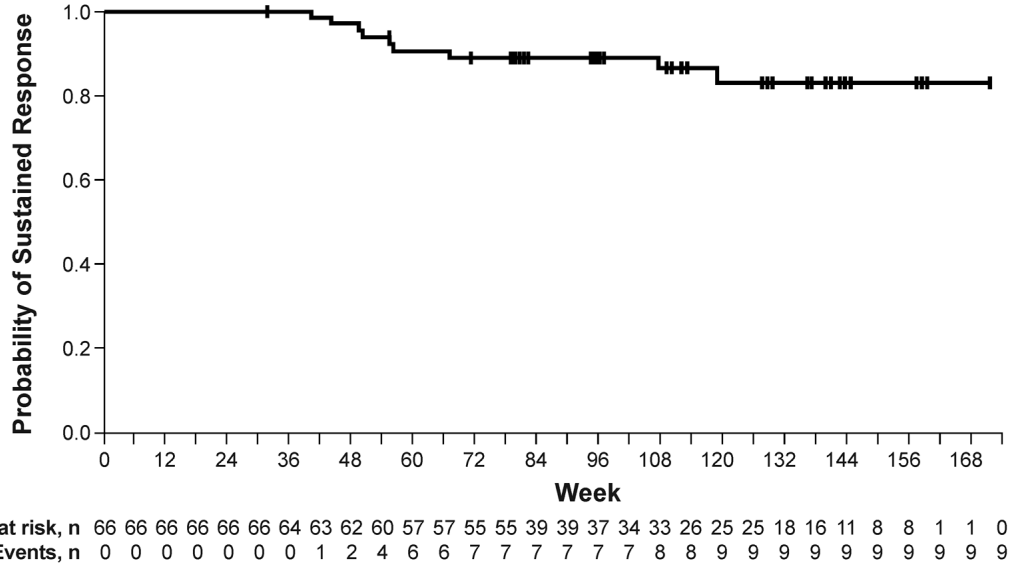


**Figure 3. Duration of hematocrit control with ruxolitinib treatment.** *Duration of the absence of phlebotomy eligibility is defined as the time from first occurrence of absence of phlebotomy eligibility until the date of the first documented progression.

menting early treatment changes to control blood counts, especially hematocrit, in patients with hydroxyurea-resistant or intolerant PV to minimize the risk of thromboembolic events.

Ruxolitinib continued to be tolerated by most patients during long-term treatment following the primary analysis, with 83% of patients still receiving treatment at a median exposure of 111 weeks. In agreement with the primary analysis,[12] most adverse events were grade 1 or 2, with relatively few new adverse events observed in the 80-week analysis. The rate of herpes zoster continued to be higher in the originally randomized ruxolitinib arm, as reported in the primary analysis.[12] Most herpes zoster infections were grade 1 or 2 and were resolved without sequelae. Nonmelanoma skin cancers were observed in the originally randomized ruxolitinib arm, mainly in

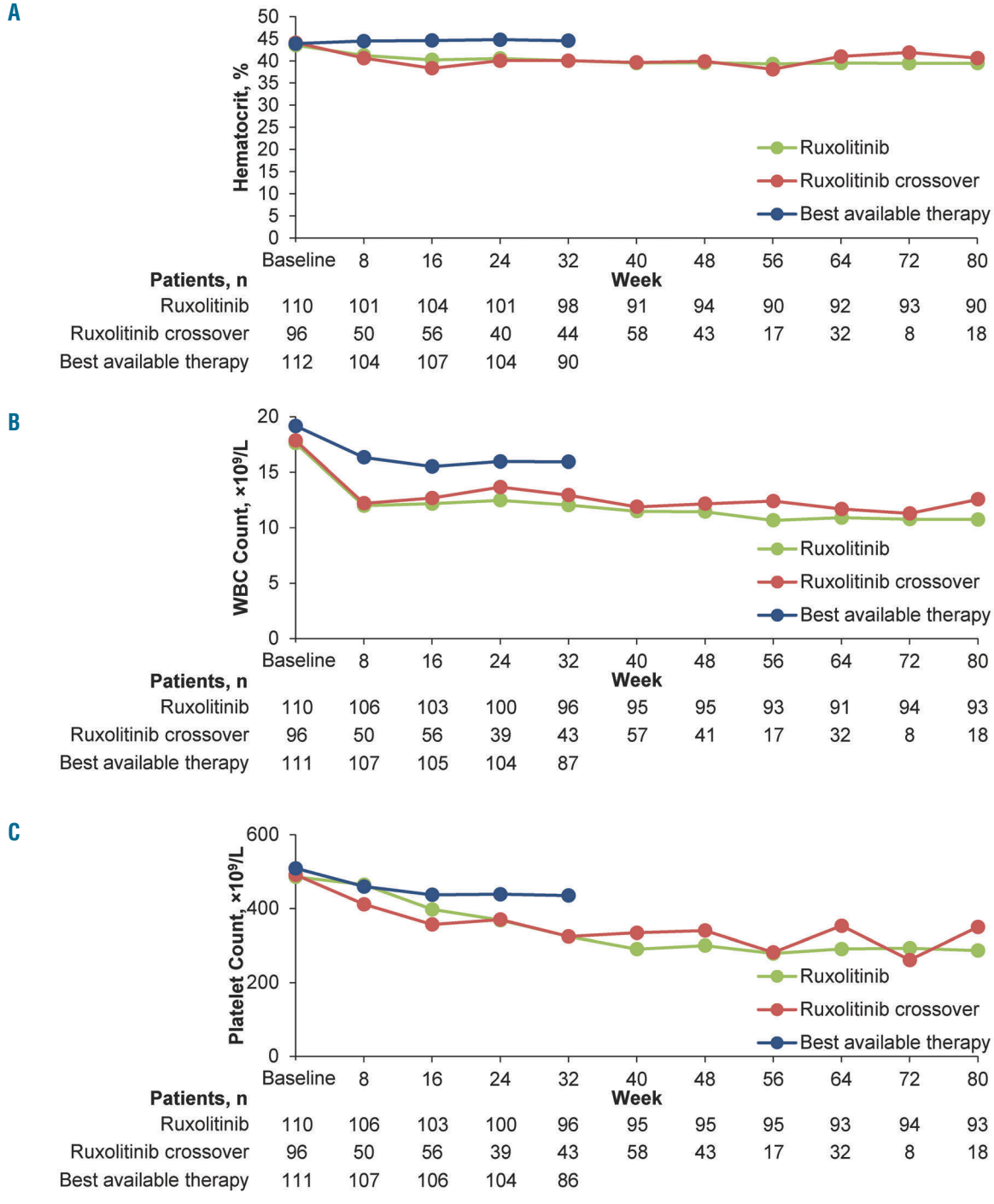


**Figure 4. Mean hematocrit levels (A), white blood cell counts (B), and platelet counts (C) over time.** Includes all data points with >5 patients. For patients in the ruxolitinib crossover group, baseline represents the date of crossover to ruxolitinib. Ruxolitinib and best available therapy arm data are from the 80-week data cutoff; ruxolitinib crossover data are from the 48-week data cutoff. WBC: white blood cell.

patients with a history of nonmelanoma skin cancer or precancer; however, exposure-adjusted rates at the time of this analysis were generally similar between the originally randomized ruxolitinib and best available therapy arms. Rates of transformation to MF and AML were consistent with published rates for similar patient populations with PV.[9,15,16] These safety and tolerability data are important because many patients require long-term therapy to manage their PV.

Hydroxyurea is often prescribed for patients who require cytoreductive treatment. Although many patients receive clinical benefits from hydroxyurea,[6-8] a considerable proportion will not tolerate therapy or may become resistant.[9] Patients who develop resistance are at increased risk of fibrotic/leukemic disease transformation and mortality,[9] with few second-line treatment options available. Ruxolitinib represents a new treatment option for this hydroxyurea-resistant or intolerant patient population that has durable responses and long-term tolerability based on the 111-week follow-up of RESPONSE.

This study had several limitations that should be considered. The design of the RESPONSE trial permitted crossover from best available therapy to ruxolitinib for patients who did not achieve the primary endpoint. Most patients crossed over to ruxolitinib shortly after they became eligible at Week 32, precluding long-term comparisons between ruxolitinib treatment and best available therapy. Many patients in the best available therapy arm received hydroxyurea (58.9%), despite established resistance or intolerance.[12] While this scenario is perhaps counterintuitive, it is not uncommon in real-world clinical practice where limited treatment options were available before the approval of ruxolitinib for patients with PV who have an inadequate response to or are intolerant of hydroxyurea.[10] In addition, although ELN criteria for hydroxyurea resistance and intolerance[17] are important for defining patient populations in clinical trials, they may not be as useful in clinical practice. Finally, because patients received hydroxyurea and other traditional treatment options before randomization to ruxolitinib, the causal relationship between ruxolitinib and adverse events such as nonmelanoma skin cancer are difficult to determine.

In conclusion, patients treated with ruxolitinib who achieved protocol-defined treatment responses for hematocrit control, spleen volume reduction, and CHR at the primary analysis[12] were likely to maintain their responses during the 111-week follow-up period of this study. Long-term follow-up with ruxolitinib did not identify new safety signs or progressively worsening toxicity. The observed adverse events were expected, and most were manageable with standard clinical monitoring and care. Taken together, these data support ruxolitinib as an effective long-term treatment option for patients with PV who are resistant to or intolerant of hydroxyurea.

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