ORIGINAL ARTICLE

Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

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ABSTRACT

BACKGROUND

Ruxolitinib, a Janus kinase (JAK) 1 and 2 inhibitor, was shown to have a clinical benefit in patients with polycythemia vera in a phase 2 study. We conducted a phase 3 open-label study to evaluate the efficacy and safety of ruxolitinib versus standard therapy in patients with polycythemia vera who had an inadequate response to or had unacceptable side effects from hydroxyurea.

METHODS

We randomly assigned phlebotomy-dependent patients with splenomegaly, in a 1:1 ratio, to receive ruxolitinib (110 patients) or standard therapy (112 patients). The primary end point was both hematocrit control through week 32 and at least a 35% reduction in spleen volume at week 32, as assessed by means of imaging.

RESULTS

The primary end point was achieved in 21% of the patients in the ruxolitinib group versus 1% of those in the standard-therapy group ($P<0.001$). Hematocrit control was achieved in 60% of patients receiving ruxolitinib and 20% of those receiving standard therapy; 38% and 1% of patients in the two groups, respectively, had at least a 35% reduction in spleen volume. A complete hematologic remission was achieved in 24% of patients in the ruxolitinib group and 9% of those in the standard-therapy group ($P=0.003$); 49% versus 5% had at least a 50% reduction in the total symptom score at week 32. In the ruxolitinib group, grade 3 or 4 anemia occurred in 2% of patients, and grade 3 or 4 thrombocytopenia occurred in 5%; the corresponding percentages in the standard-therapy group were 0% and 4%. Herpes zoster infection was reported in 6% of patients in the ruxolitinib group and 0% of those in the standard-therapy group (grade 1 or 2 in all cases). Thromboembolic events occurred in one patient receiving ruxolitinib and in six patients receiving standard therapy.

CONCLUSIONS

In patients who had an inadequate response to or had unacceptable side effects from hydroxyurea, ruxolitinib was superior to standard therapy in controlling the hematocrit, reducing the spleen volume, and improving symptoms associated with polycythemia vera. (Funded by Incyte and others; RESPONSE ClinicalTrials.gov number, NCT01243944.)

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Polycythemia vera is a chronic clonal myeloproliferative neoplasm characterized by increased red-cell mass; elevated white-cell and platelet counts are also common.[1] Patients have an increased risk of thrombotic and cardiovascular events[2] and a substantial symptom burden that includes pruritus, fatigue, and night sweats.[3] Splenomegaly often develops as the disease progresses.[4]

The main goal of therapy is to prevent thrombotic events while avoiding iatrogenic harm and minimizing the risk of transformation to post–polycythemia vera myelofibrosis or acute myeloid leukemia (AML).[5,6] Most patients receive low-dose aspirin and undergo phlebotomy,[7] with a goal of maintaining hematocrit values of less than 45%. Aggressive treatment targeting a hematocrit of less than 45% lowers the risks of major thrombosis and death from cardiovascular causes.[8] Cytoreductive therapy is recommended in patients at high risk for thrombosis; those with persistent or progressive hematologic abnormalities, splenomegaly, or symptoms; and those who cannot undergo phlebotomy or who require frequent phlebotomies.[6] Phlebotomy-induced iron deficiency may lead to complications such as cognitive problems and the restless legs syndrome.[9-11]

The most commonly used first-line cytoreductive agent is hydroxyurea. However, some patients have an inadequate response to the drug or have unacceptable side effects at the doses required to consistently control the hematocrit, platelet count, white-cell count, splenomegaly, or symptom burden. Many of these patients would be classified as having resistance or intolerance to hydroxyurea according to European LeukemiaNet (ELN) criteria[12]; patients who have resistance to hydroxyurea have shorter survival than other patients with polycythemia vera.[13] In clinical practice with no approved alternatives, physicians often continue to treat these patients with hydroxyurea as long as they derive some benefit from therapy.

Ruxolitinib, a Janus kinase (JAK) 1 and 2 inhibitor, showed clinical benefit in patients with polycythemia vera in a phase 2 study, and 10 mg twice daily was established as an effective starting dose.[14] We conducted the Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor INCB018424 versus Best Supportive Care (RESPONSE), a phase 3 study, to evaluate the safety and efficacy of a JAK inhibitor in patients with polycythemia vera who have an inadequate response to or have unacceptable side effects from hydroxyurea.

Methods

Eligibility Criteria

We enrolled adults (≥18 years of age) with polycythemia vera requiring phlebotomy for hematocrit control, a spleen volume of 450 cm^3 or more (as measured by magnetic resonance imaging [MRI] or computed tomography [CT]), and no prior treatment with a JAK inhibitor. Phlebotomy dependence was defined as two or more phlebotomies within 24 weeks before screening and at least one phlebotomy within 16 weeks before screening (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Eligible patients had resistance or intolerance to hydroxyurea according to modified ELN criteria[12] (see the Supplementary Appendix) — that is, they had had an inadequate response to or had had unacceptable side effects from hydroxyurea. Patients with a hematocrit of less than 40% or more than 45% entered a hematocrit control period before randomization; those having a hematocrit of 40 to 45% within 14 days before day 1 could proceed directly to randomization.

Study Design

RESPONSE, which is an ongoing trial, is an international, randomized, open-label, multicenter phase 3 study (see the Supplementary Appendix for a list of investigators). Patients were stratified according to status with regard to hydroxyurea therapy (inadequate response or unacceptable side effects) and were randomly assigned, in a 1:1 ratio, to receive ruxolitinib (at a starting dose of 10 mg twice daily) or single-agent therapy judged by the treating physician to be the best available therapy (standard therapy). Dose increases were intended to achieve and maintain a hematocrit of less than 45% in the absence of phlebotomy, reduce spleen size (as assessed by palpation), and normalize white-cell and platelet counts. Dose reductions or interruptions were mandated for specific cytopenias of grade 2 or higher (see the Supplementary Appendix). Standard therapy was selected by the investigator and could include 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; phosphorus-32, busulfan, and

chlorambucil were prohibited. Standard therapy could be changed owing to a lack of response or toxic effects requiring drug discontinuation. All patients received low-dose aspirin unless it was medically contraindicated.

Patients assigned to standard therapy could cross over to ruxolitinib at week 32 if the primary end point was not met or later in the case of disease progression (phlebotomy eligibility, progression of splenomegaly, or both). The data cutoff for the primary analysis occurred when all patients reached week 48 or discontinued therapy.

END POINTS

The primary end point was the proportion of patients who had both hematocrit control and a reduction of 35% or more in spleen volume from baseline at week 32, as assessed by means of centrally reviewed MRI or CT studies. Hematocrit control was defined as protocol-specified ineligibility for phlebotomy from week 8 to 32 and no more than one instance of phlebotomy eligibility between randomization and week 8; the week-32 primary end point reflects the initial 8 weeks plus an additional 24 weeks of treatment. Phlebotomy eligibility was defined as a hematocrit of more than 45% that was at least 3 percentage points higher than the baseline level or a hematocrit of more than 48%, whichever was lower (regardless of whether phlebotomy was performed). Type I error–controlled secondary end points included the proportion of patients who had a primary response (i.e., those in whom both components of the composite primary end point were achieved) at week 32 that was maintained at week 48 and the proportion of patients who had a complete hematologic remission (defined as hematocrit control, a platelet count $\leq 400\times10^9$ per liter, and a white-cell count $\leq 10\times10^9$ per liter) at week 32. Other end points included the duration of response (see the Supplementary Appendix), symptom reduction, and safety.

SYMPTOMS

Patient-reported outcomes were assessed with the use of the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) patient diary, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) (higher scores on the global health status–quality of life scale and the functioning scales indicate improvement), the Pruritus Symptom Impact Scale (higher scores indicate greater severity of itching), and the Patient Global Impression of Change (responses range from very much improved to very much worse). The MPN-SAF was used to assess 14 disease-related symptoms on a scale of 0 (absent) to 10 (worst possible). In addition to the MPN-SAF total symptom score (the sum of the scores for 14 symptoms), scores for individual symptoms and symptom clusters were determined.

SAFETY

The safety population included all patients who received at least one dose of a study drug, including those who received no drug as standard therapy, if they underwent any postrandomization procedures or assessments. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STUDY OVERSIGHT

The study was sponsored and designed by Incyte and Novartis. It was approved by the institutional review board or central ethics committee at each participating institution and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. Data were analyzed and interpreted by the sponsors in collaboration with all the authors; the sponsors were unaware of the treatment-group assignments until database lock. An independent data and safety monitoring board reviewed trial data and made recommendations regarding continuation of the study. The first author prepared the first draft of the manuscript, with assistance from a medical writer funded by Novartis, and made the final decision to submit the manuscript for publication. All the authors reviewed and amended the manuscript, vouch for the accuracy and completeness of the data, and verify that the study as reported conforms to the protocol and statistical analysis plan (both available at NEJM.org).

STATISTICAL ANALYSIS

The efficacy analysis for the primary and secondary end points was performed according to the intention-to-treat principle, with data from all patients who underwent randomization. Assessments of change and percentage change from baseline included all patients with baseline measurements; changes in individual symptom scores included only patients with baseline values greater than 0. Patients with missing assessments that

prevented the evaluation of the primary and secondary end points were considered not to have had a response.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From November 29, 2010, to February 13, 2013, a total of 222 patients underwent randomization, of whom 110 were assigned to ruxolitinib and 112 were assigned to standard therapy. No significant differences between the two treatment groups were noted with respect to baseline characteristics and disease history (Table 1).

Initial standard therapy included hydroxyurea (in 58.9% of the patients), interferon (in 11.6%), anagrelide (in 7.1%), immunomodulators (in 4.5%), and pipobroman (in 1.8%); no medication was administered in 15.2% of the patients. Six patients received more than one standard therapy.

A total of 10 of the 98 patients in the ruxolitinib group who had assessments at week 32 were receiving doses of less than 10 mg twice daily, 33 were receiving 10 mg twice daily, 32 were receiving 15 mg twice daily, 15 were receiving 20 mg twice daily, and 8 were receiving 25 mg twice daily. The mean total daily dose increased over time (Fig. 1 in the Supplementary Appendix); most dose adjustments occurred during the first 8 weeks of treatment.

At the time of data cutoff (median exposure to therapy, 81 weeks in the ruxolitinib group and 34 weeks in the standard-therapy group), 17 patients in the ruxolitinib group (15.5%) and 108 patients in the standard-therapy group (96.4%) had discontinued randomized treatment (Fig. 1, and Table S1 in the Supplementary Appendix); the most frequent reasons for discontinuation included protocol-defined lack of efficacy (0% in the ruxolitinib group and 87.5% in the standard-therapy group), the patient's decision (5.5% and 4.5%, respectively), and adverse events (3.6% and 1.8%, respectively). Overall, 96 patients assigned to standard therapy (85.7%) crossed over to ruxolitinib at or after week 32, with most crossovers occurring at or immediately after the week-32 visit.

EFFICACY

The composite primary end point of both hematocrit control and at least a 35% reduction in spleen volume occurred in a significantly higher proportion of patients in the ruxolitinib group than in the standard-therapy group (20.9% vs. 0.9%, P<0.001) (Fig. 2A). Response rates with ruxolitinib were similar among patients who had unacceptable side effects from hydroxyurea and those who had an inadequate response to hydroxyurea (22.0% and 19.6%, respectively), and there was no relationship between response and age, sex, or baseline spleen volume (see the Results section in the Supplementary Appendix). Higher proportions of patients in the ruxolitinib group than in the standard-therapy group had hematocrit control through week 32 (60.0% vs. 19.6%) and a reduction of 35% or more in spleen volume from baseline at week 32 (38.2% vs. 0.9%) (Fig. 2A). At least one component of the primary end point occurred in 77.3% of patients in the ruxolitinib group. In the standard-therapy group, 15 of 66 patients receiving hydroxyurea, 4 of 13 patients receiving interferon, and 1 of 17 patients receiving no medication had hematocrit control (Table S2 in the Supplementary Appendix); 1 patient who received hydroxyurea had at least a 35% reduction in spleen volume. Significantly more patients in the ruxolitinib group than in the standard-therapy group had a complete hematologic response (23.6% vs. 8.9%, P=0.003).

A total of 21 patients assigned to ruxolitinib (19.1%) and 1 patient assigned to standard therapy (0.9%) had a primary response (as defined above) at week 32 that was maintained at week 48 (P<0.001). The probability that a primary response to ruxolitinib would be maintained for 1 year from the time of the initial response was 94% (Fig. 2B). Responses for individual components of the primary end point were also maintained over time (Fig. S2 in the Supplementary Appendix).

The rate of phlebotomy procedures between weeks 8 and 32 was lower in the ruxolitinib group than in the standard-therapy group. A total of 19.8% of patients in the ruxolitinib group and 62.4% of patients in the standard-therapy group underwent at least one phlebotomy; 2.8% and 20.2%, respectively, underwent three or more phlebotomies (Fig. S3 in the Supplementary Appendix).

SYMPTOMS AND OTHER PATIENT-REPORTED OUTCOMES

At week 32, a total of 36 of 74 patients in the ruxolitinib group (49%) and 4 of 81 patients in the standard-therapy group (5%) had at least a 50% reduction in the 14-item MPN-SAF total symptom score (Fig. 3A). In addition, ruxolitinib-treated patients had greater reductions in all symp-

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Ruxolitinib (N=110)	Standard Therapy (N=112)
Age — yr		
Median	62.0	60.0
Range	34–90	33–84
Sex — no. of patients (%)		
Male	66 (60.0)	80 (71.4)
Female	44 (40.0)	32 (28.6)
Time since diagnosis of polycythemia vera — yr		
Median	8.2	9.3
Range	0.5–36	0.5–23
Duration of previous hydroxyurea therapy — yr		
Median	3.1	2.8
Range	<0.1–20.9	<0.1–20.9
ECOG performance status — no. of patients (%)†		
0	76 (69.1)	77 (68.8)
1	31 (28.2)	34 (30.4)
2	3 (2.7)	1 (0.9)
Status with regard to previous hydroxyurea therapy — no. of patients (%)		
Unacceptable side effects	59 (53.6)	61 (54.5)
Inadequate response	51 (46.4)	51 (45.5)
Previous thromboembolic event — no. of patients (%)	39 (35.5)	33 (29.5)
Positive status for *JAK2* V617F mutation — no. of patients (%)	104 (94.5)	107 (95.5)
Allele burden — %	76.2±17.8	75.0±22.6
Spleen length		
Below costal margin — cm		
Median	7.0	7.0
Range	0.0–24.0	0.0–25.0
<10 cm — no. of patients (%)	71 (64.5)	67 (59.8)
>20 cm — no. of patients (%)	2 (1.8)	4 (3.6)
Spleen volume — cm^3		
Median	1195	1322
Range	396–4631	254–5147
Hematocrit — %‡		
Mean	43.6±2.2	43.9±2.2
Median	43.3	44.0
Range	39.2–50.5	37.6–50.5
Hematocrit category — no. of patients (%)		
40–45%	79 (71.8)	83 (74.1)
>45%	28 (25.5)	25 (22.3)
White-cell count — $\times 10^{-9}$/liter	17.6±9.6	19.0±12.2
Platelet count — $\times 10^{-9}$/liter	484.5±323.3	499.4±318.6
No. of phlebotomies within 24 wk before screening		
Median	2.0	2.0
Range	1–8	0–16

* Plus–minus values are means ±SD.
† The Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing disability.
‡ Shown is the value at the end of the hematocrit control period before randomization. Patients who had a hematocrit of 40 to 45% within 14 days before their day 1 visit could proceed to randomization; however, the hematocrit at baseline may have been higher or lower.

tom clusters (Fig. 3A); they reported a decrease in almost all individual symptoms, whereas patients receiving standard therapy had an increase in many symptoms (Fig. 3B). Reductions in scores on the Pruritus Symptom Impact Scale were consistent with the MPN-SAF results (Fig. S4 in the Supplementary Appendix). Improvements were also observed in scores on the EORTC QLQ-C30 global health status–quality of life scale and functioning scales and in the Patient Global Impression of Change for ruxolitinib-treated patients, whereas little or no improvement was observed with standard therapy (Fig. S5 and S6 in the Supplementary Appendix).

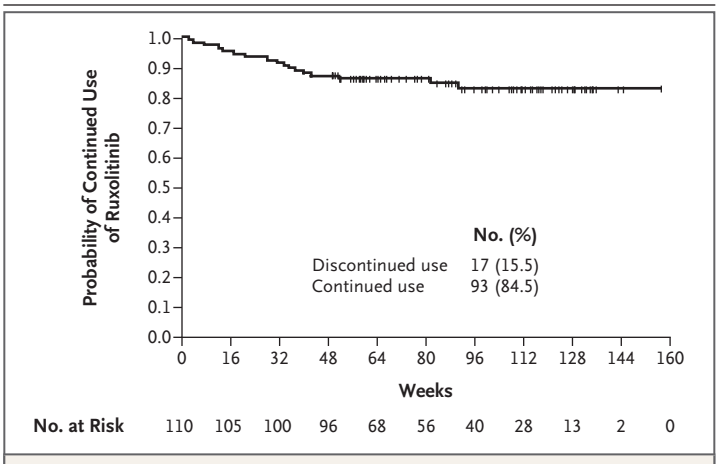

Figure 1. Ruxolitinib Discontinuations.
Shown are Kaplan–Meier estimates of the probability of continued use of ruxolitinib therapy after randomization.

JAK2 V617F ALLELE BURDEN

The mean change in the *JAK2* V617F allele burden from baseline to week 32 was –12.2% in the ruxolitinib group and 1.2% in the standard-therapy group. The allele burden decreased steadily over time in the ruxolitinib group (maximal mean change, –34.7% at week 112).

SAFETY

Most patients in the standard-therapy group crossed over to receive ruxolitinib immediately after week 32; therefore, adverse-event rates were evaluated through week 32, when the duration of exposure to therapy was similar in the two study groups. Through week 32, both ruxolitinib and standard therapy were associated with few grade 3 or 4 nonhematologic adverse events (Table 2). Herpes zoster infections, all of grade 1 or 2, occurred in seven patients in the ruxolitinib group (6.4%) as compared with no patients receiving standard therapy. Overall, the rate of infections of any grade was 41.8% in the ruxolitinib group and 36.9% in the standard-therapy group; the rate of grade 3 or 4 infection was 3.6% and 2.7% in the respective groups.

Four patients in the ruxolitinib group and two patients in the standard-therapy group had newly diagnosed nonmelanoma skin cancer (basal-cell or squamous-cell carcinoma); all but one patient (in the standard-therapy group) had a history of nonmelanoma skin cancer or precancerous skin lesions. One patient in the standard-therapy group received a diagnosis of melanoma (at day 155). Low-grade elevations in cholesterol, triglyceride, alanine aminotransferase, and aspartate aminotransferase levels were observed with ruxolitinib but were not associated with clinical outcomes; there was a higher rate of hyperuricemia with standard therapy (Table S3 in the Supplementary Appendix). Hematologic laboratory abnormalities (Table 2) primarily included low-grade anemia and thrombocytopenia with ruxolitinib and low-grade neutropenia with standard therapy.

Rates of adverse events were also evaluated, with adjustment for cumulative exposure through data cutoff (170.0 patient-years in the ruxolitinib group and 72.8 patient-years in the standard-therapy group) (Table S4 in the Supplementary Appendix). The rate of grade 3 or 4 adverse events per 100 patient-years was lower in the ruxolitinib group than in the standard-therapy group (28.8 vs. 44.0).

Through week 32, thromboembolic events occurred in one patient in the ruxolitinib group versus six patients in the standard-therapy group (Table S5 in the Supplementary Appendix). There was one additional thromboembolic event in the ruxolitinib group after week 32.

At the time of data cutoff, myelofibrosis had developed in three patients assigned to ruxolitinib (at approximately 5, 9, and 19 years after a diagnosis of polycythemia vera and at 120, 182, and 469 days after randomization), and one patient had received a diagnosis of AML (at day 56). Myelofibrosis had developed in one patient assigned to standard therapy (diagnosed at day 101). In addition, two patients assigned to standard therapy received a diagnosis of myelofibrosis on days 308 and 378 after crossover, one of whom had progression to AML. No patient died while receiving the randomly assigned treatment. Two patients died after crossing over: one owing

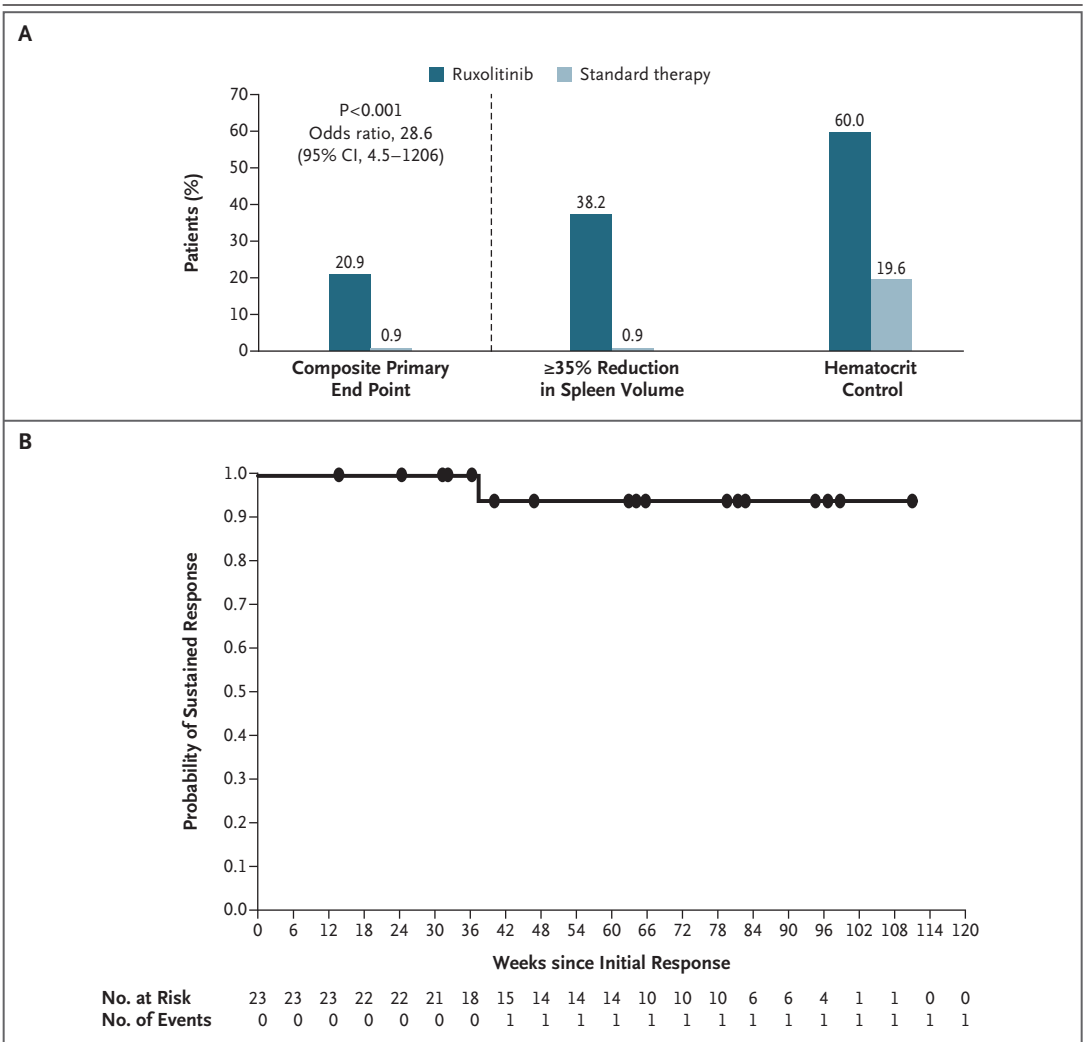

Figure 2. Primary Response and Duration of Response.

Panel A shows the percentage of patients who met the composite primary end point of hematocrit control through week 32 and at least a 35% reduction in spleen volume at week 32 (primary response). Individual components of the primary end point are also shown. To have hematocrit control, patients could not be eligible for phlebotomy on the basis of protocol-defined hematocrit values (with eligibility defined as a hematocrit >45% and ≥3 percentage points higher than the baseline level or a hematocrit >48%). Patients who discontinued therapy or had missing data or assessments outside protocol-defined windows were considered not to have had a response. Panel B shows the duration of the primary response, defined as the time from the initial documented response to the loss of response (event).

to central nervous system hemorrhage in the context of long-standing, poorly controlled hypertension and the other owing to multiorgan failure and hypovolemic shock with a precipitous and unexplained drop in the hemoglobin level in association with a positive fecal occult-blood test.

DISCUSSION

RESPONSE showed that ruxolitinib was effective in achieving both the composite primary end point and its individual components (hematocrit control and a reduction in spleen volume) and in reducing symptoms in patients with polycythemia vera who had an inadequate response to or had unacceptable side effects from hydroxyurea.

Although many patients with polycythemia vera have an adequate response to hydroxyurea, a subgroup of patients (approximately 25%) have unacceptable side effects or an inadequate response,[13] and alternative treatment options are needed for these patients.[15,16] In addition, some patients have

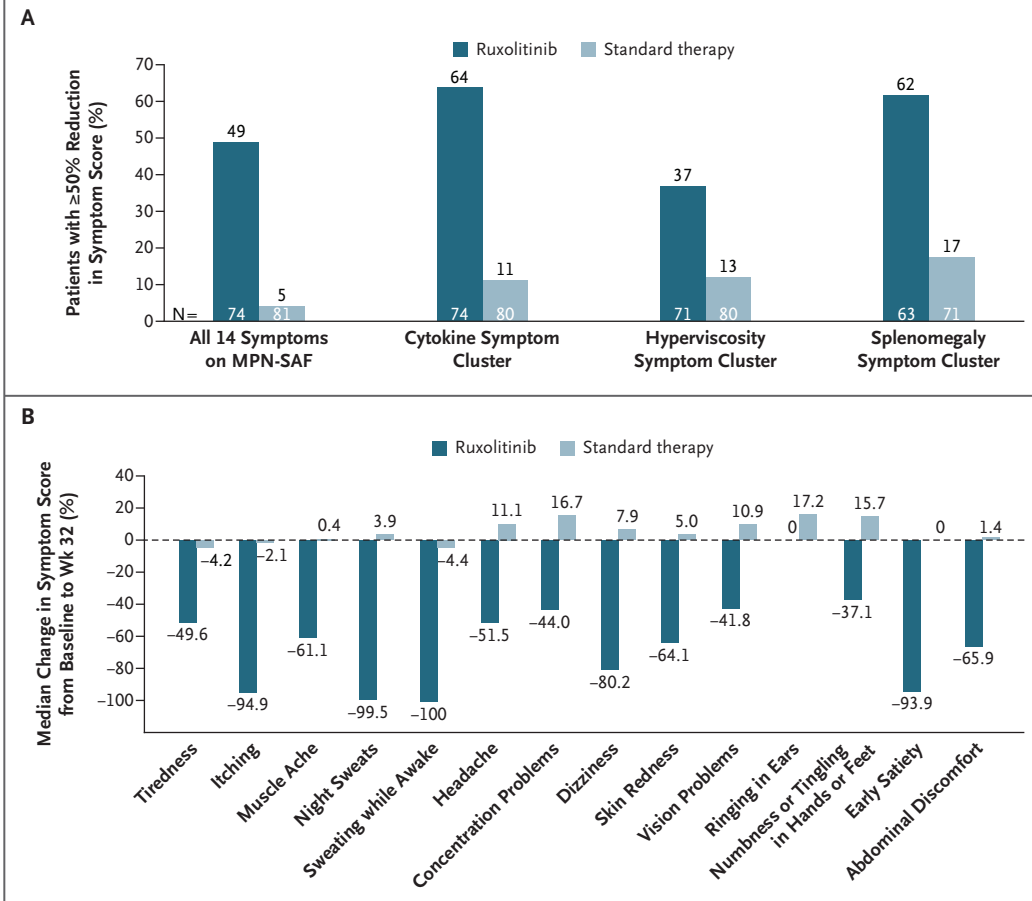

Figure 3. Symptom Assessments.

Panel A shows the percentage of patients who had at least a 50% reduction in the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) total symptom score (with regard to 14 symptoms; higher scores indicate greater severity of symptoms) and in total scores for the cytokine symptom cluster (tiredness, itching, muscle ache, night sweats, and sweating while awake), the hyperviscosity symptom cluster (vision problems, dizziness, concentration problems, headache, numbness or tingling in the hands or feet, ringing in the ears, and skin redness), and the splenomegaly symptom cluster (abdominal discomfort and early satiety) at week 32. Panel B shows the median percentage change from baseline to week 32 in the score for each of the 14 symptoms on the MPN-SAF. Patients with data at both baseline (value >0) and week 32 were included in the analyses for both panels. Negative values indicate a reduction in the severity of symptoms.

a symptom burden that is as high as that in myelofibrosis,[3,17,18] including itching, fatigue, and night sweats, which respond poorly to standard therapies. Although phase 2 studies have shown that interferon treatment can result in hematologic and molecular responses,[19-22] interferon is not approved in most countries and may have unacceptable side effects,[21,23] and other cytotoxic drugs, such as busulfan and other alkylating agents (not recommended for patients <75 years of age[24]), may be associated with an increased risk of leukemia.[25,26]

The limited number of therapeutic alternatives for these subgroups of patients with polycythemia vera is indirectly supported by the fact that a large percentage of patients continue to receive hydroxyurea, despite having an inadequate response or unacceptable side effects. Indeed, in our study, investigators may have selected hydroxyurea as the best option for maintaining some degree of clinical benefit, eventually lowering the dosage to the highest dose that did not cause unacceptable side effects in the case of patients who had had unacceptable side effects. Regardless, this approach led to unsatisfactory results, as suggested by the 85.7% of patients in the standard-therapy group who crossed over to receive ruxolitinib therapy.

A conservative approach was used to define

Table 2. Adverse Events from Start of Study Drug to Week 32, Regardless of Whether They Were Related to the Study Drug.

Adverse Event	Ruxolitinib (N=110)			Standard Therapy (N=111)*		
	All Grades	Grade 3 or 4		All Grades	Grade 3 or 4	
	number of patients (percent)					
Nonhematologic†						
Headache	18 (16.4)	1 (0.9)		21 (18.9)	1 (0.9)	
Diarrhea	16 (14.5)	0		8 (7.2)	1 (0.9)	
Fatigue	16 (14.5)	0		17 (15.3)	3 (2.7)	
Pruritus	15 (13.6)	1 (0.9)		25 (22.5)	4 (3.6)	
Dizziness	13 (11.8)	0		11 (9.9)	0	
Muscle spasms	13 (11.8)	1 (0.9)		5 (4.5)	0	
Dyspnea	11 (10.0)	3 (2.7)		2 (1.8)	0	
Abdominal pain	10 (9.1)	1 (0.9)		13 (11.7)	0	
Asthenia	8 (7.3)	2 (1.8)		12 (10.8)	0	
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic‡						
Anemia	48 (43.6)	1 (0.9)	1 (0.9)	34 (30.6)	0	0
Thrombocytopenia	27 (24.5)	5 (4.5)	1 (0.9)	21 (18.9)	3 (2.7)	1 (0.9)
Lymphopenia	48 (43.6)	17 (15.5)	1 (0.9)	56 (50.5)	18 (16.2)	2 (1.8)
Leukopenia	10 (9.1)	1 (0.9)	0	14 (12.6)	2 (1.8)	0
Neutropenia	2 (1.8)	0	1 (0.9)	9 (8.1)	1 (0.9)	0

* One patient withdrew consent and did not receive study treatment.
† Shown are events occurring in at least 10% of patients in either treatment group.
‡ These were new or worsening abnormalities, as assessed on the basis of laboratory values.

hematocrit control in the primary end point (on the basis of phlebotomy eligibility, regardless of whether phlebotomy was performed), and patients with missing assessments that prevented the evaluation of hematocrit control were considered not to have had a response. The benefit of ruxolitinib over standard therapy was more pronounced as measured by the actual phlebotomy rate; fewer patients in the ruxolitinib group underwent one or more phlebotomies.

The rate of thromboembolic events in the ruxolitinib group (1.2 events per 100 patient-years) was lower than expected in this high-risk population (2.8 and 3.5 events per 100 patient-years for patients with polycythemia vera that responds to hydroxyurea and for those without a response, respectively[13]). The benefits of maintaining a hematocrit of less than 45% were established by the Cytoreductive Therapy in Polycythemia Vera study,[8] which showed that a target hematocrit of less than 45%, as compared with a target of 45 to 50%, reduced the rates of major thrombosis and death from cardiovascular causes by a factor of almost 4. These data may also reflect the effect of ruxolitinib on white-cell counts (Fig. S7 in the Supplementary Appendix) and inflammatory markers such as C-reactive protein (see the Results section in the Supplementary Appendix), which have been reported to be associated with the risk of thrombosis.[27-29]

Nearly 85% of patients assigned to ruxolitinib continued to receive it at a median follow-up of 81 weeks. Most patients were receiving 10 or 15 mg twice daily at week 32, indicating appropriate dose selection. The rates of grade 3 or 4 cytopenias were low in both study groups. The rate of herpes zoster infection was higher in the ruxolitinib group than in the standard-therapy group. These events were generally low grade and did not lead to discontinuation of therapy, but rates of these and other infections will continue to be followed with long-term use of ruxolitinib. A higher rate of basal-cell and squamous-cell carcinomas was reported with ruxolitinib than with standard therapy, and a higher proportion of patients assigned to ruxolitinib had a history of nonmelanoma skin cancer or precancerous skin conditions; no patients discontinued treatment because of the development of basal-cell or squamous-cell carcinoma. Rates of transformation to myelofibrosis and AML were consistent

with those expected in a high-risk population of patients with polycythemia vera[30,31] and in those with resistance to hydroxyurea[13] but will continue to be monitored going forward.

In conclusion, this phase 3 study showed that ruxolitinib was effective in controlling the hematocrit, reducing spleen size, and improving symptoms in patients with polycythemia vera who had an inadequate response to or had unacceptable side effects from hydroxyurea, whereas existing therapies offered little or no benefit. Most patients assigned to ruxolitinib were still receiving therapy at the time of this analysis in this ongoing but not recruiting study.

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