Case Study Series

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Cases in the Management of Polycythemia Vera: The Importance of Strict Hematocrit Control

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Case 2 of a 3-Part Series

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Cases in the Management of Polycythemia Vera: The Importance of Strict Hematocrit Control

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Patient Case

A 68-year-old man presented with elevated levels of hemoglobin and hematocrit, as well as an elevated platelet count (Table 1). His white blood cell count was 18 × 10^9/L, his hemoglobin was 20.1 g/dL, his hematocrit level was 63%, and his platelet count was 988 × 10^9/L. At the time of presentation, he reported significant fatigue and pruritus. A diagnosis of polycythemia vera (PV) was suspected based on an elevated hematocrit level and identification of a Janus kinase 2 (JAK2) V617F mutation. The diagnosis was confirmed by a bone marrow biopsy.

Based on the patient's age, he was considered to be at high risk for thrombosis. His physician initiated treatment with hydroxyurea at a dose of 500 mg twice daily. The patient also underwent therapeutic phlebotomy at the time of diagnosis.

Throughout the first month of therapy, the patient continued to require phlebotomy every 2 weeks owing to a hematocrit level above 45%. Consequently, the dose of hydroxyurea was doubled to 1000 mg twice daily. During the ensuing 3 months, the patient continued to require intermittent phlebotomy once every 4 to 6 weeks. He had some improvement in fatigue. Treatment with hydroxyurea did not relieve pruritus. The patient began to develop intermittent oral ulcers, which caused discomfort while eating. These ulcers self-resolved, but then recurred. On examination, the patient was noted to have palpable splenomegaly as well, which was a new finding.

Given that the patient was still receiving therapeutic phlebotomies based on his hematocrit levels, the dose of hydroxyurea was further titrated up to a total of 2500 mg daily, divided as a 1500-mg dose in the morning and a 1000-mg dose in the evening. Despite this increase, the patient continued to require phlebotomy every 4 to 6 weeks during the next 3 months. His platelet count was controlled, but his white blood cell count began to decrease in response to the increased dose of hydroxyurea.

The physician concluded that the patient was exhibiting resistance, and some intolerance, to hydroxyurea. This assessment was based on the continued requirement for phlebotomy, the side effect of mucositis, and the declining white blood cell count. As a result, the decision was made to switch therapies.

The primary options for second-line treatment for this patient included pegylated interferon, based on the MPD-RC 111 trial,[1] and ruxolitinib, based on the RESPONSE trial.[2] The physician discussed these options with the patient. Given the patient's age, he was not considered to be a good candidate for interferon. The physician described the results of the RESPONSE trial, which demonstrated that ruxolitinib was superior to best available therapy for the control of peripheral blood cell counts and reduction in spleen volume.[2] Consequently,

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 68-year-old man presented with fatigue and pruritus • White blood cell count, 18 × 10^9/L; hemoglobin, 18 g/dL; hematocrit level, 63%; platelet count, 88 × 10^9/L • A diagnosis of polycythemia vera was based on the presence of a *JAK2* V617F mutation and findings on a bone marrow biopsy
Initial Treatment	• Therapeutic phlebotomies • Hydroxyurea (initial dose of 500 mg twice daily) • Low-dose aspirin
Early Response	• Continued requirement for phlebotomy every 2 weeks owing to a hematocrit level above 45% • As a result, the hydroxyurea dose was increased (to 1000 mg twice daily)
Response After First Dose Increase	• Some symptom improvement, but ongoing fatigue and pruritus • Development of recurrent oral ulcers • New palpable splenomegaly • Phlebotomy needed every 4-6 weeks • As a result, the hydroxyurea dose was increased again (to 2500 mg daily)
Response After Second Dose Increase	• Continued requirement for phlebotomy every 4-6 weeks • Better control of the platelet count, but the white blood cell count decreased
Next Treatment	• Ruxolitinib
Response	• The patient experienced rapid improvement in symptoms of pruritus and fatigue • The spleen was no longer palpable • Blood cell counts began to normalize within the first 3 months • No phlebotomies were required throughout the first 6 months

the patient began treatment with ruxolitinib at a starting dose of 10 mg twice daily.

The patient noticed rapid improvement in his symptoms of pruritus and fatigue. Throughout the next 3 months, his blood counts approached normal. The white cell count was restored to normal, and the platelets were just slightly elevated. The patient's hematocrit level remained under control. The spleen was no longer palpable. Significantly, during the first 3 months of ruxolitinib therapy, the patient did not require phlebotomy. (It should be noted that there was some initial overlap with hydroxyurea.) During the next 3 months, the patient did not require phlebotomy while he continued to receive treatment with single-agent ruxolitinib at 10 mg twice daily.

This case highlights several important aspects of management in the setting of PV. First, patients with PV can experience significant symptoms. These symptoms can persist despite treatment with phlebotomy or hydroxyurea. Second, increasing doses of hydroxyurea can lead to a range of toxicities. Myelosuppression is a well-known side effect. However, there are also physical side effects, such as mouth ulcers, that can be difficult for patients to tolerate. Third, strict hematocrit control is an important component of management for patients with PV.

Rationale for Treatment Decisions

Ruxolitinib

Ruxolitinib is a JAK1/2 inhibitor approved by the US Food and Drug Administration for the treatment of PV in adults who had an inadequate response to hydroxyurea or who were intolerant of hydroxyurea.[3] This approval was based on results from the phase 3 RESPONSE trial.[2] In guidelines from the National Comprehensive Cancer Network[4] and European LeukemiaNet,[5] ruxolitinib is recommended as a second-line treatment in patients who become resistant to hydroxyurea, are intolerant of hydroxyurea, or respond poorly to hydroxyurea.

Five-Year Follow-Up of the RESPONSE Trial. The RESPONSE trial assessed the efficacy and safety of ruxolitinib for the treatment of PV in patients who had an inadequate response to hydroxyurea or who were unable to tolerate hydroxyurea. The trial was designed as an international, randomized, open-label, multicenter phase 3 study.[2]

The trial enrolled patients with a spleen volume of 450 cm^3 or more, as assessed by magnetic resonance imaging (MRI) or computed tomography (CT). All patients

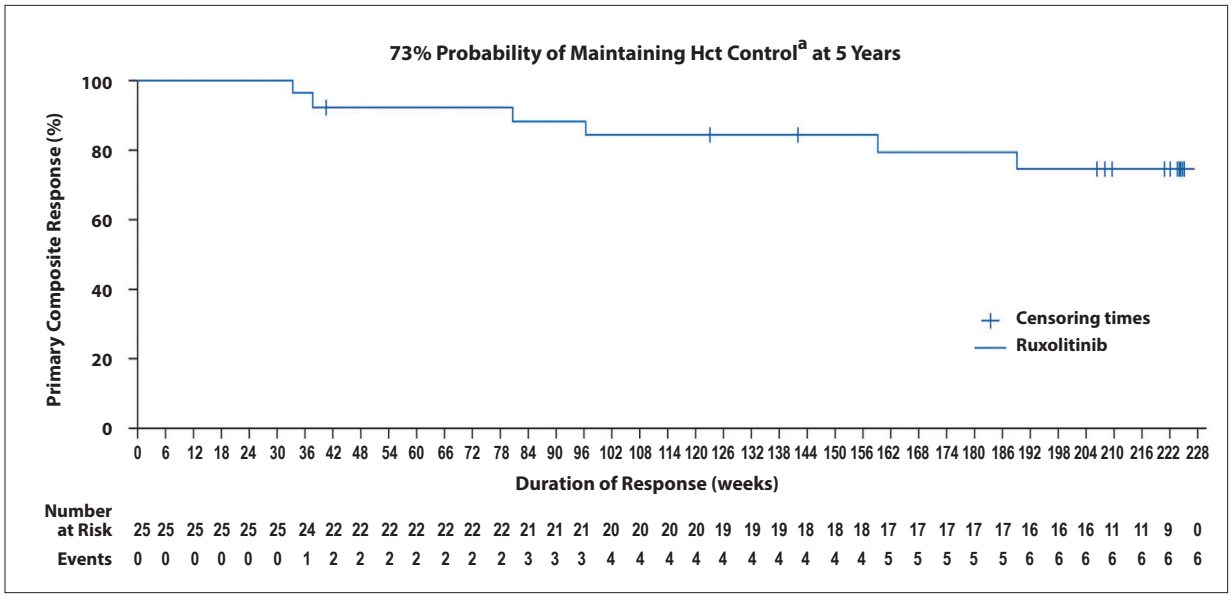

Figure 1. In a 5-year analysis of the phase 3 RESPONSE trial, the median duration of primary response (patients who achieved both Hct control without phlebotomy and ≥35% reduction from baseline in spleen volume) was not reached. Twenty-five patients responded. There were 6 events. Nineteen patients were 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.[6]

required phlebotomy to achieve hematocrit control. The patients had undergone at least 2 phlebotomies within 24 weeks before screening, as well as at least 1 phlebotomy within 16 weeks before screening. An inadequate response to hydroxyurea was defined according to modified criteria from the European LeukemiaNet.[5] Exclusion criteria included prior use of JAK inhibitor therapy.

The patients were randomly assigned to treatment with either ruxolitinib (at a starting dose of 10 mg administered twice daily) or standard single-agent therapy. The only stratification factor was response to hydroxyurea therapy (inadequate response vs unacceptable side effects). The dose of ruxolitinib could be increased so that patients could achieve and maintain a hematocrit level below 45% in the absence of phlebotomy, a decrease in palpated spleen size, and normal white blood cell and platelet counts. In the ruxolitinib arm, patients who developed specific grade 2 or higher cytopenias underwent mandated dose reductions or interruptions of treatment. The standard therapy consisted of the best available treatment as determined by the treating physician. This therapy could be changed if the patient did not respond or experienced intolerable toxicity. Standard therapy could include hydroxyurea (at a dose that did not cause unacceptable side effects), interferon or pegylated interferon, pipobroman, anagrelide, immunomodulators (lenalidomide or thalidomide), or no medication. Crossover to the ruxolitinib arm was permitted at week 32. Patients in both arms received low-dose aspirin, unless contraindicated.[2]

The primary endpoint of the RESPONSE trial was the proportion of patients who achieved both hematocrit control (defined as phlebotomy ineligibility from week 8 to 32 and ≤1 instance of phlebotomy eligibility prior to week 8) and a reduction of 35% or more in spleen volume from baseline to week 32 (as assessed by centrally reviewed MRI or CT). At the time of the primary analysis, when all patients had either reached week 48 of treatment or discontinued therapy, the composite primary endpoint was met by 20.9% of patients in the ruxolitinib arm vs 0.9% of the standard-therapy arm (P<.001).[2]

A recent report provided data from a planned analysis conducted after all patients had completed approximately 5 years (224 weeks) of treatment (or had discontinued therapy).[6] After the primary analysis, 88% of patients originally randomly assigned to the standard-therapy arm had crossed over to receive ruxolitinib. No patient remained on standard therapy after week 80. At the 5-year analysis, 66% of patients in the ruxolitinib arm and 65% of patients in the standard-therapy arm who had crossed over to ruxolitinib had completed 5 years of treatment.[6]

At the 5-year study completion, 24% of patients who had responded at the primary analysis developed disease progression, as evidenced by eligibility for phlebotomy, spleen enlargement, or both. From week 32, a total of 74% (95% CI, 51-88) of patients maintained a primary response at the 5-year analysis (Figure 1). At the time of study completion, the median duration of primary response had not been reached.[6]

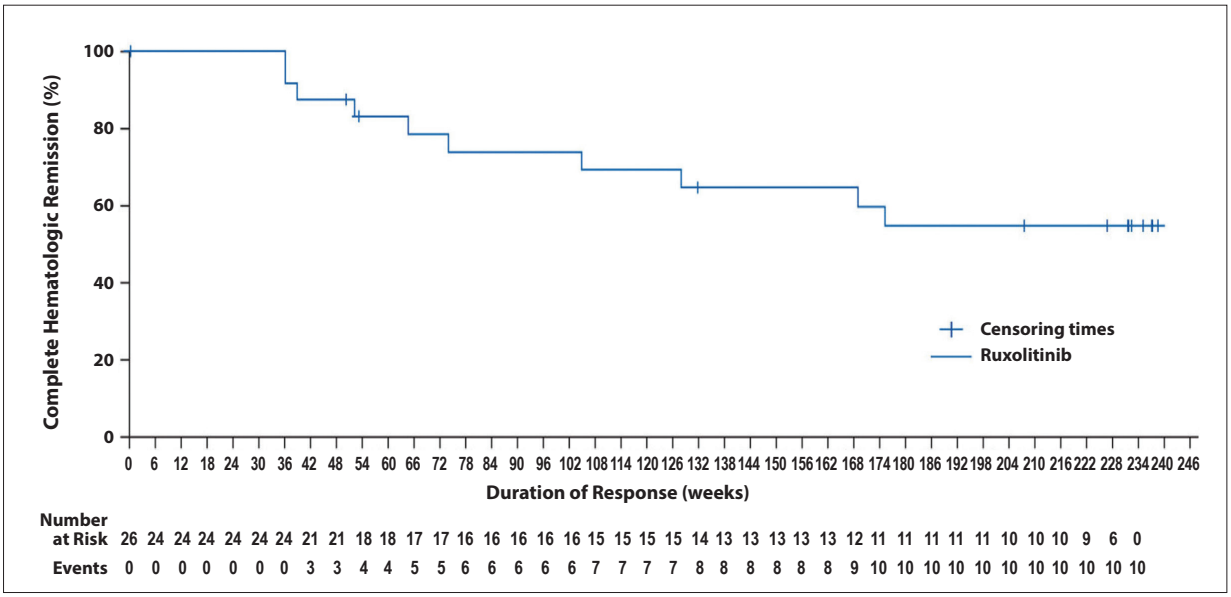

Figure 2. Complete hematologic remission among patients in a 5-year analysis of the RESPONSE trial. Twenty-six patients responded. There were 10 events. Sixteen patients were censored. The crosses indicate patients who were censored. Adapted from Kiladjian JJ et al. *Lancet Haematol*. 2020;7(3):e226-e237.[6]

The duration of complete hematologic remission was also assessed in the 5-year analysis. A complete hematologic remission was defined as hematocrit control, a platelet count of 400 × 10^9 cells/L or less, and a white blood cell count of 10 × 10^9 cells/L or less. A durable complete hematologic remission was reported in 55% (95% CI, 32-73) of patients at 5 years (Figure 2). Among the 26 patients (24%) with a complete hematologic remission at week 32, 10 patients (38%) had progressed by week 256. Among the 66 patients (60%) with hematocrit control at week 32, 16 patients (24%) had progressed by week 256. At week 224, hematocrit control was reported in 73% (95% CI, 60-83) of patients. Among the 98 patients who crossed over to ruxolitinib, 63 patients (64%) achieved hematocrit control after 32 weeks.[6]

Overall, the requirement for phlebotomy was lower among patients who received ruxolitinib, whether they had been randomly assigned to the ruxolitinib arm or had crossed over from the standard-therapy arm to receive ruxolitinib. Among patients randomly assigned to ruxolitinib, 83% of 94 evaluable patients did not require any phlebotomies. Only 6 patients (6%) required 3 or more phlebotomies between weeks 80 and 256. Among the 79 evaluable patients who crossed over to ruxolitinib, 69 patients (87%) did not require any phlebotomies. Six patients (8%) required 3 or more phlebotomies by week 224 of crossover.[6]

At baseline, 87 patients had a white blood cell count above 10 × 10^9 cells/L. Among these patients, 36 (41%) achieved a white blood cell count below 10 × 10^9 cells/L at week 256. Similarly, among 25 patients (46%) with platelet counts above 400 × 10^9 cells/L at baseline, platelet counts decreased to below 400 × 10^9 cells/L at week 256.[6]

An overall clinicohematologic response at week 32 was reported in 70 patients (64%). Among these patients, 21 (30%) progressed by week 256. Therefore, the probability of maintaining a clinicohematologic response from week 32 to week 224 was 67% (95% CI, 54-77). The median duration of clinicohematologic response was not reached.[6]

More patients treated with ruxolitinib, in both the randomized treatment arm (89%) and the crossover population (86%), showed a decrease in spleen volume at some point during the study. In comparison, 49% of the patients treated with standard therapy showed a reduction in spleen volume. Among patients treated with ruxolitinib, the probability of maintaining a reduction in spleen volume of 35% or higher from week 32 to week 224 was 72% (95% CI, 34-91).[6]

Kaplan-Meier estimates for overall survival were calculated for the intention-to-treat population. Not accounting for crossover, the 5-year overall survival rate was 91.9% (95% CI, 84.4-95.9) in the ruxolitinib arm vs 91.0% (95% CI, 82.8-95.4) in the standard-therapy arm. The corresponding hazard ratio was 0.95 (95% CI, 0.38-2.41). Because most patients had left the study at or before their individual week 256 visit and were censored, there was a substantial decrease in the number of patients at risk after week 256, after which the estimates became highly variable.[6]

Most patients were positive for the *JAK2* V617F

mutation at baseline, with a mean allele burden of 76%. The mean allele burden decreased consistently throughout the study period among patients treated with ruxolitinib. By week 256, patients in the ruxolitinib group showed a mean percentage change of –38% (standard deviation [SD], 38.64) in the allele burden from baseline. At this same time point, patients who had crossed over to receive ruxolitinib had a mean percentage change in allele burden of –23% (SD, 40.5) from baseline. In comparison, among the standard-therapy group at week 32, the mean percentage change from baseline in allele burden was 1.18 (SD, 25.33).[6]

A similar trend was noted in quality-of-life measures. Improvements in quality of life reported by week 32 were maintained by week 256 among patients in the ruxolitinib arm. A total of 40% of the patients treated with ruxolitinib maintained "very much improved" or "much improved" responses in pruritus (as measured by the Pruritus Symptom Impact Scale) through week 256. Sustained improvements in the European Organization for the Research and Treatment of Cancer quality-of-life questionnaire global health status–quality-of-life scale were maintained through week 256.[6]

The 5-year follow-up analysis also evaluated safety. Importantly, this analysis included patients who had crossed over from the standard-therapy arm to receive ruxolitinib. The median time to crossover was 34.7 weeks (95% CI, 33.9-35.3). The investigators noted that there was no relevant increase in the exposure-adjusted rates of adverse events at this 5-year analysis compared with prior studies. No new or unexpected adverse events were identified. Serious adverse events were reported at a frequency of 10.3 per 100 patient-years of exposure in the ruxolitinib group compared with 13.6 per 100 patient-years of exposure in the standard-therapy group. Serious adverse events occurred at a rate of 13.0 per 100 patient-years of exposure in the crossover population. The most frequent adverse events that required a dose adjustment or interruption of ruxolitinib were anemia, thrombocytopenia, and pruritus.[6]

Anemia was the most frequently reported adverse event among ruxolitinib-treated patients (in both the randomized treatment arm and in patients who crossed over). Most cases were mild or moderate. A total of 4 ruxolitinib-treated patients developed new or worsening grade 3/4 hemoglobin abnormalities from baseline. Patients in the standard-therapy arm experienced a higher exposure-adjusted rate of thrombocytopenia (16.3 per 100 patient-years) as compared with patients in the randomized ruxolitinib arm (4.4 per 100 patient-years) and patients in the crossover group (1.2 per 100 patient-years). Lower exposure-adjusted rates of thromboembolic events were reported in the ruxolitinib arm (1.2 per 100 patient-years) and the crossover population (2.7 per 100 patient-years) compared with the standard-therapy arm (8.2 per 100 patient-years).[6]

Overall, nonhematologic adverse events occurred at a lower frequency among ruxolitinib-treated patients compared with patients who received standard therapy. The most frequently reported nonhematologic adverse events (exposure-adjusted rate ≥5 per 100 patient-years) among patients in the ruxolitinib arm and the crossover population 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). Most infections were reported at a lower rate among patients who received ruxolitinib, with the exception of herpes zoster infection.[6]

Secondary malignancies were reported in this 5-year analysis. Among patients in the ruxolitinib arm, the rate of secondary malignancies was 7.0 per 100 patient-years, compared with 4.5 per 100 patient-years in the crossover population and 4.1 per 100 patient-years in the standard-therapy arm. Rates of nonmelanoma skin cancer were 5.1 per 100 patient-years in patients originally assigned to ruxolitinib, 2.7 per 100 patient-years in the crossover arm, and 2.7 per 100 patient-years in the standard-therapy arm.[6]

The rate of transformation to myelofibrosis was 2.1 per 100 patient-years in the ruxolitinib arm, 0.6 per 100 patient-years in the crossover population, and 1.8 per 100 patient-years in the standard-therapy arm. The rates of transformation to acute myeloid leukemia were 0.6 per 100 patient-years, 0 per 100 patient-years, and 1.4 per 100 patient-years, respectively. In the crossover population, 1 patient was diagnosed with grade 2 lymphoplasmacytoid lymphoma or immunocytoma 35 days after the final dose of ruxolitinib. This diagnosis was considered a serious adverse event unrelated to the study treatment.[6]

Two on-treatment deaths were reported in the ruxolitinib arm. A death from gastric adenocarcinoma was considered related to ruxolitinib. A death from a malignant neoplasm was not considered related to ruxolitinib. In the crossover population, 4 patients experienced fatal adverse events leading to on-treatment deaths (2 from pneumonia, 1 from central nervous system hemorrhage, and 1 from hypovolemic shock). None of these events were considered related to ruxolitinib. No patients died while receiving standard therapy.[6]

Five-Year Follow-Up of the RESPONSE-2 Trial. The RESPONSE-2 trial was a similarly designed, open-label, randomized phase 3b study performed in patients with PV without splenomegaly. The patients were intolerant of or resistant to hydroxyurea. They were randomly assigned to treatment with either ruxolitinib (starting dose of 10 mg twice daily) or best available standard therapy. Crossover was permitted at week 28 if the primary endpoint

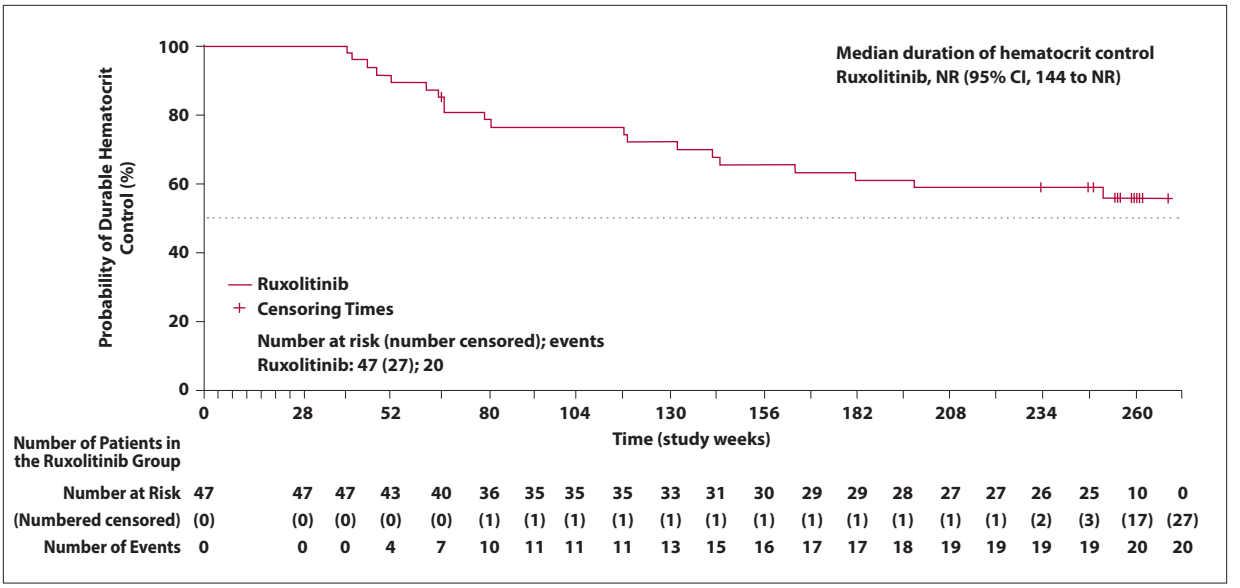

Figure 3. Hematocrit control in a 5-year analysis among patients treated with ruxolitinib in the phase 3b RESPONSE-2 trial of patients with polycythemia vera without splenomegaly. NR, not reached. Adapted from Passamonti F et al. *Lancet Haematol.* 2022:S2352-3026(22)00102-8.[8]

was not met, or after week 28 and up to week 80 if the best available therapy was not effective or not tolerated. The trial randomly assigned 149 patients to treatment. At the primary analysis, hematocrit control was achieved in 62% of patients randomly assigned to ruxolitinib vs 19% of those randomly assigned to best available therapy (odds ratio, 7.28; 95% CI, 3.43-15.45; *P*<.0001).[7]

A 5-year analysis of this study was recently published.[8] The median follow-up was 67 months (interquartile range, 65-70). A total of 77% of patients crossed over to ruxolitinib between weeks 28 and 80. Per protocol, no patients continued best available therapy after week 80. By week 260, 22% (95% CI, 13-33) of patients in the ruxolitinib group had achieved durable hematocrit control. The estimated median duration of hematocrit control was not reached in these patients (95% CI, 144 to not reached; Figure 3). Owing to the small number of responders by week 80 in the control arm, the median duration of hematocrit control was not reported for these patients.[8]

The median hematocrit level among patients who received ruxolitinib was maintained below 45%. At 260 weeks, phlebotomies were required by 60 patients in the ruxolitinib arm vs 106 patients in the best-available-therapy arm. At this long-term follow-up analysis, the 5-year overall survival rates were 96% (95% CI, 87-99) in the ruxolitinib arm and 91% (95% CI, 80-96) in the best-available-therapy arm.[8]

At the 5-year follow-up, the most frequently reported grade 3/4 exposure-adjusted adverse events in the ruxolitinib arm vs the control arm included hypertension (2.4% vs 5.6%, respectively), thrombocytopenia (0.3% vs 5.6%), and thrombocytosis (0 vs 7.5%). Exposure-adjusted rates of any-grade thromboembolic events were 1.5% per 100 person-years in the ruxolitinib arm vs 3.7% per 100 person-years in the control arm.[8]

Disclosure

Dr Rampal is a consultant to Constellation, Incyte, Celgene/BMS, Novartis, Promedior, CTI, Jazz Pharmaceuticals, Blueprint, Stemline, Galecto, PharmaEssentia, AbbVie, Sierra Oncology, Disc Medicines, and Sumitomo Dainippon. He has received research funding from Zentalis, Incyte, Constellation, and Stemline.

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