Original Article

Real-world analysis of main clinical outcomes in patients with polycythemia vera treated with ruxolitinib or best available therapy after developing resistance/intolerance to hydroxyurea

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BACKGROUND: Ruxolitinib is approved for patients with polycythemia vera (PV) who are resistant/intolerant to hydroxyurea, but its impact on preventing thrombosis or disease-progression is unknown. **METHODS:** A retrospective, real-world analysis was performed on the outcomes of 377 patients with resistance/intolerance to hydroxyurea from the Spanish Registry of Polycythemia Vera according to subsequent treatment with ruxolitinib (n = 105) or the best available therapy (BAT; n = 272). Survival probabilities and rates of thrombosis, hemorrhage, acute myeloid leukemia, myelofibrosis, and second primary cancers were calculated according to treatment. To minimize biases in treatment allocation, all results were adjusted by a propensity score for receiving ruxolitinib or BAT. **RESULTS:** Patients receiving ruxolitinib had a significantly lower rate of arterial thrombosis than those on BAT (0.4% vs 2.3% per year; $P = .03$), and this persisted as a trend after adjustment for the propensity to have received the drug (incidence rate ratio, 0.18; 95% confidence interval, 0.02-1.3; $P = .09$). There were no significant differences in the rates of venous thrombosis (0.8% and 1.1% for ruxolitinib and BAT, respectively; $P = .7$) and major bleeding (0.8% and 0.9%, respectively; $P = .9$). Ruxolitinib exposure was not associated with a higher rate of second primary cancers, including all types of neoplasia, noncutaneous cancers, and nonmelanoma skin cancers. After a median follow-up of 3.5 years, there were no differences in survival or progression to acute leukemia or myelofibrosis between the 2 groups. **CONCLUSIONS:** The results suggest that ruxolitinib treatment for PV patients with resistance/intolerance to hydroxyurea may reduce the incidence of arterial thrombosis. *Cancer* 2022;128:2441-2448. © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

LAY SUMMARY:
• Ruxolitinib is better than other available therapies in achieving hematocrit control and symptom relief in patients with polycythemia vera who are resistant/intolerant to hydroxyurea, but we still do not know whether ruxolitinib provides an additional benefit in preventing thrombosis or disease progression.
• We retrospectively studied the outcomes of 377 patients with resistance/intolerance to hydroxyurea from the Spanish Registry of Polycythemia Vera according to whether they subsequently received ruxolitinib (n = 105) or the best available therapy (n = 272).
• Our findings suggest that ruxolitinib could reduce the incidence of arterial thrombosis, but a disease-modifying effect could not be demonstrated for ruxolitinib in this patient population.

KEYWORDS: hemorrhage, myelofibrosis, myeloproliferative neoplasms, polycythemia vera, ruxolitinib, therapy, thrombosis.

Original Article

INTRODUCTION

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by an increased risk of thrombosis and bleeding and, in the long term, progression to my-elofibrosis and acute myeloid leukemia.[1,2] Hydroxyurea (HU) is the most widely used drug and achieves clinical and hematological control in most patients.[3,4] However, approximately 20% to 30% of patients develop resistance/intolerance to HU, which translates into inadequate control of the disease and an increased risk of thrombosis.[4-8] Furthermore, mutations in *TP53* or in chromatin/splicing genes are frequently found in PV patients with resistance to HU, and they confer an increased risk of transformation to acute leukemia and myelofibrosis.[9]

Ruxolitinib is a JAK1/JAK2 inhibitor approved for the treatment of patients with PV who have developed resistance/intolerance (R/I) to HU. In these patients, the RESPONSE and RESPONSE-2 studies have demonstrated the superiority of ruxolitinib over the best available therapy (BAT) in terms of hematocrit control, symptom relief, and spleen size reduction.[10,11] However, most patients assigned to BAT in these clinical trials were crossed over to ruxolitinib prematurely, and this precluded any comparison of the incidence of vascular events, disease transformation, or survival between the 2 treatment options.[11,12]

The objective of the current study was to analyze the main clinical outcomes for 377 patients with R/I to HU from the Spanish Registry of Polycythemia Vera who were subsequently treated with ruxolitinib or BAT.

MATERIALS AND METHODS

Study Design

The Spanish Registry of Polycythemia Vera was started in July 2011 and is periodically updated. It is sponsored by the Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas. By April 2021, a total of 2245 patients from 60 Spanish hospitals had been included in the registry, and 1784 of them had been treated with HU. Patients were eligible for inclusion in the current study if they had developed R/I to HU. R/I was assessed according to the modified European LeukemiaNet criteria as described by Barosi et al.[13]

A total of 431 patients (24%) developed R/I to HU and were stratified into 2 groups according to the treatment received subsequently. Patients never exposed to ruxolitinib (n = 272) were assigned to the BAT group, and those who received ruxolitinib within the first year after R/I to HU made up the ruxolitinib group (n = 105). Fifty-four additional patients who started ruxolitinib more than 1 year after R/I development were excluded from the study. The indication of ruxolitinib was decided by local physicians according to the clinical guidelines and prevailing recommendations at that time.

The diagnosis of PV was established according to the World Health Organization criteria.[14] Informed consent was obtained for scientific use of patients' clinicohematological data. The study was approved by the Hospital del Mar institutional review board.

Outcomes

The main outcomes of the study were survival, major thrombosis (total, arterial, and venous [including superficial thrombophlebitis]), hemorrhage (total, major, and minor), disease progression to acute myeloid leukemia, myelofibrosis, and the occurrence of a second primary cancer. Relevant symptomatology and hematological values at the time of R/I to HU and later were retrospectively reviewed. For details, see the Supporting Methods.

Statistical Methods

Rates of thrombosis, bleeding, myelofibrosis, acute myeloid leukemia, and second cancers were calculated with the incidence rate method. The time at risk ranged from the date of R/I to the last follow-up or death. Outcomes were compared according to treatment (BAT vs ruxolitinib). Periods on anticoagulants and on antiplatelet agents were evaluated as time-varying covariates. Multivariable analyses of factors influencing the incidence rates were performed by Poisson regression. A propensity score (PS) was calculated from the binary logistic regression of initial clinical features predicting ruxolitinib therapy, and it was forced into the Poisson models to control for confounding. Overall survival and time to event curves were drawn by the Kaplan-Meier method (see the Supporting Methods).

RESULTS

Patient Characteristics

The main clinical and hematological characteristics at the time of R/I to HU are shown in Table 1. The median age of the overall series was 73 years (interquartile range, 63-75 years). Patients in the ruxolitinib group had been exposed to HU for a longer time before R/I, with 54% of them exposed for more than 3 years in contrast to 43% in the BAT group ($P = .04$).

Table 2 summarizes the distributions of the patients according to the different criteria of R/I, symptomatic burden, and hematological values at the time of R/I to HU. Progressive splenomegaly was more frequent in

TABLE 1. Main Clinical Characteristics of 377 Patients With Resistance/Intolerance to Hydroxyurea According to the Subsequent Treatment

	Ruxolitinib (n = 105)	BAT (n = 272)	P
Age, median (IQR), y	71 (63-75)	74 (66-80)	.0006
Male sex, No. (%)	55 (53)	132 (49)	.45
Time from diagnosis, median (IQR), y	6.3 (2.5-10.1)	2.8 (0.6-6.6)	.001
Cardiovascular risk factors, No. (%)			
Smoking	15 (14)	42 (15)	.8
Diabetes	21 (15)	42 (20)	.3
Hypertension	55 (52)	163 (60)	.2
Hypercholesterolemia	32 (30)	66 (24)	.2
Atrial fibrillation	5 (5)	15 (5.5)	.8
Prior thrombosis, No. (%)			
Arterial	18 (17)	59 (22)	.3
Venous	12 (11)	25 (9)	.5
Prior bleeding, No. (%)	14 (13)	28 (10)	.4

Abbreviations: BAT, best available therapy; IQR, interquartile range.

ruxolitinib-treated patients, whereas cytopenia and extrahematological toxicity were more frequent in the BAT cohort.

Therapy

BAT consisted of HU (in 60% of the patients), interferon (4%), anagrelide (9%), busulfan (15%), melphalan (2%), radioactive phosphorus (1%), other treatments (2%), and no medication (8%). By logistic regression, the use of ruxolitinib was significantly associated with age (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.94-0.98; $P = .002$), longer disease duration (OR, 1.10; 95% CI, 1.05-1.15; $P < .0001$), and less cytopenia (OR, 0.23; 95% CI, 0.08-0.71; $P = .01$). The predicted probability of starting on ruxolitinib for each of the 377 patients, conditional on the aforementioned clinical features, ranged from 0.035 to 0.838, and it was used as a PS in subsequent analyses. The median duration of ruxolitinib treatment was 2 years (range, 0.1-8 years), with 27, 24, 25, and 29 patients receiving ruxolitinib for less than 1, 1 to 2, 2 to 3, and >3 years, respectively. Permanent discontinuation of ruxolitinib was recorded in 17 patients (16%) because of an inadequate response (n = 4), hematological toxicity (n = 1), extrahematological toxicity (n = 6), severe infections (n = 2), and a second primary cancer (n = 4).

Symptoms and Hematological Response

The proportion of patients with pruritus and microvascular and constitutional symptoms decreased over time among patients receiving ruxolitinib, whereas it remained stable among those treated with BAT (Supporting

TABLE 2. Type of Resistance/Intolerance to Hydroxyurea, Symptomatic Burden, and Hematological Values in 377 Patients With Polycythemia Vera According to the Subsequent Treatment

	Ruxolitinib (n = 105)	BAT (n = 272)	P
Type of resistance/intolerance, No. (%)[a]			
Need for phlebotomies	16 (15)	49 (18)	.5
Progressive splenomegaly	9 (9)	5 (2)	.002
Myeloproliferation	12 (11)	24 (9)	.4
Cytopenia	4 (4)	39 (14)	.004
Extrahematological toxicity[b]	66 (63)	199 (73)	.05
Symptomatic burden, No. (%)			
Constitutional symptoms[c]	30 (31)	17 (10)	<.0001
Microvascular symptoms[d]	18 (18)	8 (5)	.001
Pruritus[e]	47 (47)	26 (16)	<.0001
Symptomatic splenomegaly[f]	7 (7)	5 (3)	.2
Hematological values, median (IQR)			
Hemoglobin, g/L	141 (126-153)	141 (121-155)	.97
Leukocyte count, ×10⁹/L	8.7 (5.9-13)	7.2 (5.1-11.2)	.01
Platelet count, ×10⁹/L	371 (252-601)	328 (194-499)	.02

Abbreviations: BAT, best available therapy; IQR, interquartile range.
[a]Resistance/intolerance to hydroxyurea was defined according to the modified European LeukemiaNet criteria.
[b]Extrahematological toxicity included the following: leg ulcers (n = 112), other mucocutaneous toxicity (n = 106), hydroxyurea-related fever (n = 16), gastrointestinal toxicity (n = 23), and other (n = 17).
[c]Available in 261 cases.
[d]Available in 253 cases.
[e]Available in 257 cases.
[f]Available in 263 cases.

Table 1). As for hematological values, ruxolitinib resulted in significantly better hemoglobin values and hematocrit control than BAT (Supporting Table 1). Supporting Table 2 summarizes the cumulative incidence of the main events defining the natural history of PV.

Survival

After a median follow-up of 3.8 years (interquartile range, 2.0-7.0 years), a total of 92 patients (24%) had died. Causes of death are shown in Supporting Table 3. Figure 1 shows the expected survival after R/I to HU according to the treatment group. Death occurred in 10 and 82 patients in the ruxolitinib and BAT cohorts, respectively. The incidence rate of death was 4.2 per 100 patient-years in the ruxolitinib group and 6.4 per 100 patient-years in the BAT group. The PS-adjusted incidence rate ratio (IRR) of death associated with the use of ruxolitinib was 0.8 (95% CI, 0.4-1.5; $P = .4$).

In a subgroup analysis, there was no difference in mortality between the ruxolitinib and BAT groups when the analysis was restricted to patients with either resistance
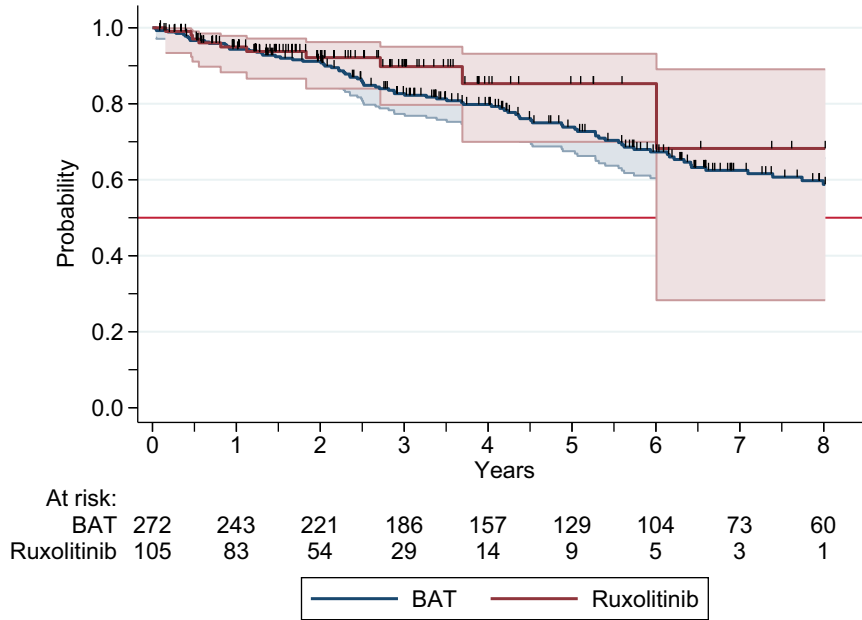
FIGURE 1. Survival after resistance/intolerance to hydroxyurea according to therapy in 377 patients with polycythemia vera. The red line corresponds to ruxolitinib (n = 105). The blue line corresponds to BAT (n = 272). The hazard ratio was 0.8 (95% confidence interval, 0.4-1.7; *P* = .6). The Cox regression included the type of therapy and the propensity score for ruxolitinib. BAT indicates best available therapy.
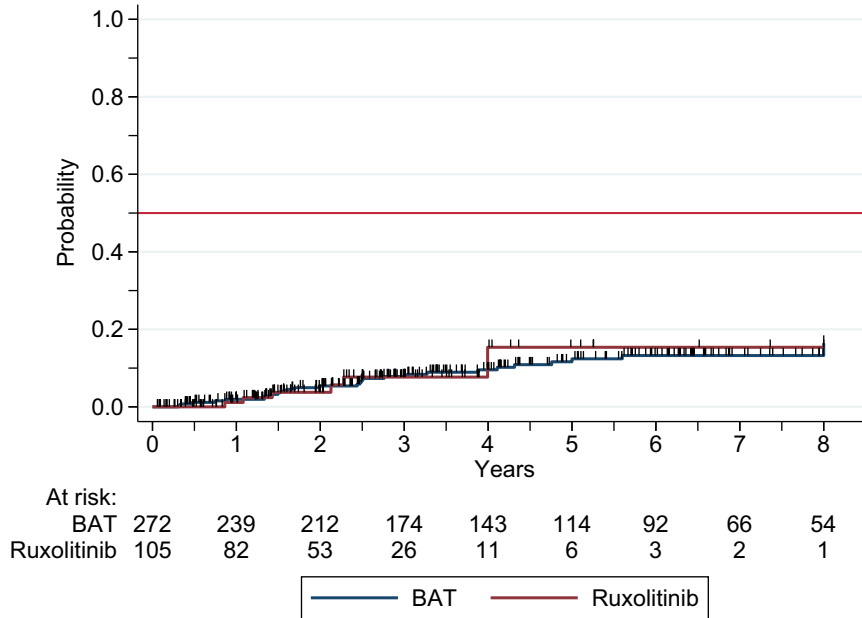

FIGURE 2. Time to myelofibrosis after resistance/intolerance to hydroxyurea according to therapy in 377 patients with polycythemia vera. The red line corresponds to ruxolitinib (n = 105). The blue line corresponds to BAT (n = 272). The hazard ratio was 0.8 (95% confidence interval, 0.4-2.3; *P* = .9). The Cox regression included the type of therapy and the propensity score for ruxolitinib. BAT indicates best available therapy.

TABLE 3. Incidence of Thrombosis and Major Bleeding in 377 Patients With Polycythemia Vera Who Were Treated With Ruxolitinib or BAT After Developing Resistance/Intolerance to Hydroxyurea

	Ruxolitinib (251 Person-y)		BAT (1272 Person-y)		
	No. of Events	Incidence Rate[a]	No. of Events	Incidence Rate[a]	P
Arterial thrombosis[b]	1	0.4	29	2.3	.03
Venous thrombosis[c]	2	0.8	14	1.1	.7
Major bleeding[d]	2	0.8	11	0.9	.9

Abbreviations: BAT, best available therapy; CI, confidence interval; IRR, incidence rate ratio.
[a]Events per 100 person-years.
[b]IRR, 0.18; 95% CI, 0.02-1.3; P = .09 (adjusted by propensity score).
[c]IRR, 1.1; 95% CI, 0.3-3.9; P = .9 (adjusted by propensity score).
[d]IRR, 0.9; 95% CI, 0.2-4.9; P = .9 (adjusted by propensity score).

(IRR, 0.55, 95% CI.16-1.80; P = .32) or intolerance to HU (IRR, 0.88; 95% CI, 0.40-1.89; P = .71).

Disease Progression

Eleven cases progressed to acute myeloid leukemia (n = 9) or myelodysplastic syndrome (n = 2), and all were in the BAT cohort (Supporting Table 4). The time to acute transformation is shown in Supporting Figure 1. The incidence rate of acute transformation in the BAT cohort was 0.86 events per 100 person-years (P = .1 for the comparison with the ruxolitinib group).

Thirty-four patients progressed to myelofibrosis: 6 in the ruxolitinib group and 28 in the BAT cohort (Fig. 2). The incidence rate of myelofibrosis was 2.5 and 2.3 events per 100 person-years in the ruxolitinib and BAT cohort, respectively (IRR, 0.98; 95% CI, 0.4-2.3; P = .9 [adjusted for PS]).

Thrombosis and Bleeding

A total of 46 thrombotic events (30 arterial and 16 venous) were registered in 1523 person-years of follow-up. The incidence rates of arterial and venous thrombosis according to the treatment group are shown in Table 3. Patients receiving ruxolitinib had a significantly lower rate of arterial thrombosis after adjustment for the time on anticoagulation and antiplatelet drugs. This lower rate remained a statistically nonsignificant trend after adjustment for PS (IRR, 0.18; 95% CI, 0.02-1.30; P = .09). There were no significant differences between the 2 study groups in rates of venous thrombosis and major bleeding after adjustment for being or not being on anticoagulants or antiplatelet agents at the time of the event (Table 3).

Second Primary Cancer

Table 4 summarizes the incidence rates for all second primary cancers and specifically for nonmelanoma skin cancer and noncutaneous cancer. Ruxolitinib exposure was not associated with a higher rate of second cancers either when all tumors were considered or after noncutaneous carcinoma and nonmelanoma skin cancer were disaggregated (Table 4). Male sex was associated with a higher rate of second neoplasia (P < .0001), especially for cutaneous basal cell carcinoma (P = .002) and cutaneous squamous cell carcinoma (P = .005). The duration of HU exposure before R/I was associated with a trend for a higher rate of cutaneous basal cell carcinoma (P = .06).

DISCUSSION

The outcomes of PV patients after R/I to HU who were treated with ruxolitinib or BAT were described in the RESPONSE and RESPONSE-2 trials, which showed the superiority of ruxolitinib over BAT in achieving hematocrit control and improving symptoms and quality of life.[10-12] However, other relevant clinical outcomes could not be explored because of early crossover, which resulted in short follow-up in the BAT arms of the RESPONSE trials.[10-12] In the current retrospective study, the outcomes of 272 patients on BAT followed for a total of 1272 person-years were compared with those of 105 patients receiving ruxolitinib for R/I to HU. The treatment modalities in the BAT group, ruxolitinib exposure, and reasons for discontinuation were similar to the ones reported in the RESPONSE trials and 2 real-world studies.[11,12,15,16]

We observed only 1 arterial thrombotic event in the ruxolitinib group; this resulted in a rate of 0.4 events per 100 patient-years, which was 5 times below the incidence observed in patients treated with BAT. In contrast, the incidence of venous thrombosis was quite similar in the 2 treatment groups. Notably, the rates of total thrombosis in our study (1.2 and 3.4 per 100 patient-years in the ruxolitinib and BAT groups, respectively) were comparable to the figures reported in the 5-year update of the RESPONSE trial and in a recent meta-analysis of patients with PV treated with HU.[12,17]

TABLE 4. Incidence of Second Cancers in 377 Patients With Polycythemia Vera Who Were Treated With Ruxolitinib or BAT After Developing Resistance/Intolerance to Hydroxyurea

	Ruxolitinib (251 Person-y)		BAT (1272 Person-y)		
	No. of Events	Incidence Rate[a]	No. of Events	Incidence Rate[a]	P
Total cancer[b]	6	2.4	34	2.7	.8
Noncutaneous cancer[c]	3	1.2	12	0.9	.7
Cutaneous carcinoma					
Basal cell[d]	1	0.4	8	0.6	.7
Squamous cell[e]	2	0.8	9	0.7	.8

Abbreviations: BAT, best available therapy; CI, confidence interval; IRR, incidence rate ratio.
All IRRs were adjusted by propensity score.
[a]Events per 100 person-years.
[b]IRR, 1.1; 95% CI, 0.5-2.8; *P* = .8.
[c]IRR, 1.72; 95% CI, 0.46-6.4; *P* = .4.
[d]IRR, 0.8; 95% CI, 0.1-5.9; *P* = .8.
[e]IRR, 1.3; 95% CI, 0.25-6.6; *P* = .7.

Two meta-analyses have reported a lower incidence of thrombosis in patients with PV treated with ruxolitinib in comparison with controls.[18,19] Samuelson et al,[18] in a study including patients with myelofibrosis from the COntrolled MyeloFibrosis Study With ORal JAK Inhibitor Treatment Trial (COMFORT) and patients with PV from the RESPONSE trials, observed a significant reduction of thrombotic events in the ruxolitinib-treated patients (risk ratio, 0.46; 95% CI, 0.23-0.88). This lower risk was driven by a larger reduction in the rate of arterial events (risk ratio, 0.42; 95% CI, 0.14-1.01) versus venous events (risk ratio, 0.46; 95% CI, 0.14-1.48). Masciulli et al,[19] in a meta-analysis of 663 patients from the RESPONSE, RESPONSE-2, A RandoMised study of best Available therapy versus JAK Inhibition in patients with high risk Polycythaemia Vera or Essential Thrombocythaemia who are resistant or intolerant to HydroxyCarbamide (MAJIC), and RELIEF clinical trials, observed a nonsignificantly lower number of thrombotic events with ruxolitinib in comparison with controls (IRR, 0.56; 95% CI, 0.28-1.11; *P* = .09). There is a biological basis to support these clinical observations. Indeed, ruxolitinib inhibits both platelet function[20] and hyperplasia of the arterial intimal layer[21]; levels of inflammatory cytokines are higher in myeloproliferative neoplasms than the general population,[22-24] and they decrease after exposure to ruxolitinib, at least in patients with myelofibrosis.[25] Finally, there is a correlation between the serum levels of C-reactive protein, the risk of thrombosis, and the *JAK2*V617F allele burden in PV and essential thrombocythemia.[26,27] Taken together, our results and the aforementioned clinical and biological observations allow us to speculate on a possible role for the anti-inflammatory effects of ruxolitinib in decreasing the risk of arterial thrombosis, a hypothesis that would be worth investigating in future studies.

A post hoc analysis of the RESPONSE trial has shown that ruxolitinib reduces the *JAK2*V617F allele burden in parallel with a reduction of the spleen size.[28] This finding has led to speculation about a potentially beneficial effect of the drug in decreasing the risk of disease progression to myelofibrosis, which is particularly increased in patients with R/I to HU.[4,7] However, our data showed similar rates of progression to myelofibrosis in patients treated with ruxolitinib and patients treated with BAT. Nevertheless, the absence of cases progressing to acute myeloid leukemia in the ruxolitinib group was striking, and this finding could be partially explained by a lower frequency of cytopenia as a criterion for R/I to HU.[7,29] In addition, we were unable to demonstrate a survival benefit in patients treated with ruxolitinib after adjustment for the propensity to be started on this drug instead of BAT. Although there was some trend for better survival with ruxolitinib when the analysis was restricted to the resistance group, it should be noted that patients who received ruxolitinib were significantly younger and had less frequent cytopenia than their counterparts in the BAT group.

There is growing concern about a potential carcinogenetic effect of ruxolitinib, which could be especially relevant in patients with PV because of their prolonged survival with potentially longer drug exposures in comparison with patients with myelofibrosis. Notably, both the RESPONSE and MPN-K (Secondary Cancers in Myeloproliferative Neoplasms) studies have reported an increased risk of nonmelanoma skin cancer in patients treated with ruxolitinib.[12,30] The RESPONSE trial showed a higher incidence of nonmelanoma skin cancer in patients on ruxolitinib (5.1% and 2.7% for ruxolitinib and BAT, respectively), with the incidence being markedly higher in patients with a history of nonmelanoma skin cancer. In contrast, the incidence of nonmelanoma skin cancer was clearly

lower in our study (1.2% and 0.9% for ruxolitinib and BAT, respectively). Several factors, including a longer disease duration in the RESPONSE series in comparison with our patients (8 vs 6 years), a higher proportion of patients with a history of nonmelanoma skin cancer (11% in RESPONSE vs 3% in our study), and longer ruxolitinib exposure in RESPONSE (428 vs 251 person-years), may account for this discrepancy. Furthermore, ruxolitinib exposure was not associated with an increased risk of second malignancies in another real-world study including 289 patients with PV, 95 of whom were treated with ruxolitinib.[31]

Although the current study constitutes a good representation of real practice in patients with R/I to HU, several limitations should be taken into account when the results are interpreted. First, the patient cohorts were not contemporaneous. Most patients in the BAT group developed R/I to HU before the approval of ruxolitinib and had, therefore, a longer follow-up than patients who received ruxolitinib. We dealt with this potential source of bias by considering only the first 8 years after R/I to HU. Second, the observational design of our study precluded us from establishing causal associations. Indeed, despite adjustments for the PS to be in the ruxolitinib group, unaccounted confounders or imperfect adjustments may have influenced the results. Additionally, the ability to assess the impact of ruxolitinib on disease modification may have been eroded by the relatively short follow-up (a median of 3.8 years) and the longer disease duration in patients receiving ruxolitinib. Nevertheless, it should be noted that most of the events that shape the natural history of PV occur within the first years after R/I to HU.

In conclusion, the results of the current study suggest that ruxolitinib may reduce the risk of arterial thrombosis in patients with PV who have developed R/I to HU. On the other hand, with the limitations derived from a short follow-up and a retrospective design, we have been unable to demonstrate a disease-modifying effect of ruxolitinib in this patient population.

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CONFLICT OF INTEREST DISCLOSURES

AUTHOR CONTRIBUTIONS

Alberto Alvarez-Larrán: Study design, data collection, statistical analysis, analysis and interpretation of the results, and writing of the manuscript. **Marta Garrote:** Data collection, interpretation of the results, and writing of the manuscript. **Francisca Ferrer-Marín:** Data collection, interpretation of the results, and approval of the final version. **Manuel Pérez-Encinas:** Data collection, interpretation of the results, and approval of the final version. **M. Isabel Mata-Vazquez:** Data collection, interpretation of the results, and approval of the final version. **Beatriz Bellosillo:** Data collection, interpretation of the results, and approval of the final version. **Eduardo Arellano-Rodrigo:** Data collection, interpretation of the results, and approval of the final version. **Montse Gómez:** Data collection, interpretation of the results, and approval of the final version. **Regina García:** Data collection, interpretation of the results, and approval of the final version. **Valentín García-Gutiérrez:** Data collection, interpretation of the results, and approval of the final version. **Mercedes Gasior:** Data collection, interpretation of the results, and approval of the final version. **Beatriz Cuevas:** Data collection, interpretation of the results, and approval of the final version. **Anna Angona:** Data collection, interpretation of the results, and approval of the final version. **María Teresa Gómez-Casares:** Data collection, interpretation of the results, and approval of the final version. **Clara M. Martínez:** Data collection, interpretation of the results, and approval of the final version. **Elena Magro:** Data collection, interpretation of the results, and approval of the final version. **Rosa Ayala:** Data collection, interpretation of the results, and approval of the final version. **Rafael del Orbe-Barreto:** Data collection, interpretation of the results, and approval of the final version. **Raúl Pérez-López:** Data collection, interpretation of the results, and approval of the final version. **Maria Laura Fox:** Data collection, interpretation of the results, and approval of the final version. **José-María Raya:** Data collection, interpretation of the results, and approval of the final version. **Lucía Guerrero:** Data collection, interpretation of the results, and approval of the final version. **Carmen García-Hernández:** Data collection, interpretation of the results, and approval of the final version. **Gonzalo Caballero:** Data collection, interpretation of the results, and approval of the final version. **Ilda Murillo:** Data collection, interpretation of the results, and approval of the final version. **Blanca Xicoy:** Data collection, interpretation of the results, and approval of the final version. **M. José Ramírez:** Data collection, interpretation of the results, and approval of the final version. **Gonzalo Carreño-Tarragona**: Data

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collection, interpretation of the results, and approval of the final version. **Juan Carlos Hernández-Boluda:** Data collection, interpretation of the results, and writing of the manuscript. **Arturo Pereira:** Statistical analysis, analysis and interpretation of the results, and writing of the manuscript.

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