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Ruxolitinib Versus Best Available Therapy for Polycythemia Vera Intolerant or Resistant to Hydroxycarbamide in a Randomized Trial

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ABSTRACT

PURPOSE Polycythemia vera (PV) is characterized by JAK/STAT activation, thrombotic/hemorrhagic events, systemic symptoms, and disease transformation. In high-risk PV, ruxolitinib controls blood counts and improves symptoms.

PATIENTS AND METHODS MAJIC-PV is a randomized phase II trial of ruxolitinib versus best available therapy (BAT) in patients resistant/intolerant to hydroxycarbamide (HC-INT/RES). Primary outcome was complete response (CR) within 1 year. Secondary outcomes included duration of response, event-free survival (EFS), symptom, and molecular response.

RESULTS One hundred eighty patients were randomly assigned. CR was achieved in 40 (43%) patients on ruxolitinib versus 23 (26%) on BAT (odds ratio, 2.12; 90% CI, 1.25 to 3.60; $P = .02$). Duration of CR was superior for ruxolitinib (hazard ratio [HR], 0.38; 95% CI, 0.24 to 0.61; $P < .001$). Symptom responses were better with ruxolitinib and durable. EFS (major thrombosis, hemorrhage, transformation, and death) was superior for patients attaining CR within 1 year (HR, 0.41; 95% CI, 0.21 to 0.78; $P = .01$); and those on ruxolitinib (HR, 0.58; 95% CI, 0.35 to 0.94; $P = .03$). Serial analysis of *JAK2*V617F variant allele fraction revealed molecular response was more frequent with ruxolitinib and was associated with improved outcomes (progression-free survival [PFS] $P = .001$, EFS $P = .001$, overall survival $P = .01$) and clearance of *JAK2*V617F stem/progenitor cells. *ASXL1* mutations predicted for adverse EFS (HR, 3.02; 95% CI, 1.47 to 6.17; $P = .003$). The safety profile of ruxolitinib was as previously reported.

CONCLUSION The MAJIC-PV study demonstrates ruxolitinib treatment benefits HC-INT/RES PV patients with superior CR, and EFS as well as molecular response; importantly also demonstrating for the first time, to our knowledge, that molecular response is linked to EFS, PFS, and OS.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by erythrocytosis, thromboembolic, hemorrhagic events, myelofibrosis, and AML transformation.[1] PV is driven by *JAK2* mutations, typically *JAK2*V617F, constitutively active JAK-STAT signaling, and hematopoietic hyperproliferation.[2] Management requires aspirin and cytoreductive treatment in high-risk patients to normalize blood counts and reduce vascular events.[3,4] Hydroxycarbamide (HC) is standard first-line treatment but some patients become intolerant or resistant[5] (HC-INT/RES), and have poorer prognosis[6] with limited options.[1,3,4]

Clinical trials of ruxolitinib versus best available therapy (BAT) in HC-INT/RES PV demonstrated improved control of blood counts, splenomegaly, and disease-associated symptoms,[7-9] but allowed crossover to ruxolitinib, precluding longer-term assessment for vascular events, disease progression, and survival.

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CONTEXT

Key Objective

The MAJIC polycythemia vera (PV) study was designed to assess long-term benefit of ruxolitinib and also specific clinical targets such as comprehensive blood count control and molecular response in patients with high-risk PV. In particular, the study focused upon the impact on long-term clinical end points—thrombosis, hemorrhage, disease transformation, and overall survival (OS).

Knowledge Generated

Novel data generated suggest that ruxolitinib improves event-free survival (EFS) compared with best available therapy. In addition, important new data from the study showed that controlling all of white cells, hematocrit, and platelets improved EFS. Finally, to our knowledge, for the first time in this field, achieving a 50% reduction in JAK2 variant allele frequency improved EFS, progression-free survival (PFS), and OS.

Relevance *(S. Lentzsch)*

The MAJIC-PV study demonstrates that ruxolitinib treatment results in superior complete response, EFS, and molecular response and should be the preferred treatment of patients with PV resistant/intolerant to hydroxycarbamide. The link between molecular response and EFS, PFS, and OS supports the benefit of molecular monitoring in PV.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, PhD, MD.

MAJIC is a randomized, phase II trial evaluating the long-term comparative safety and activity of ruxolitinib versus BAT in two different populations (HC-INT/RES ET and PV). MAJIC-ET has been reported previously.[10] Here, we present the preliminary results of MAJIC-PV.

PATIENTS AND METHODS

Trial Design

MAJIC-PV is an open-label, randomized controlled trial of ruxolitinib versus BAT (ISRCTN61925716) conducted at 38 UK sites (trial schema; Data Supplement [Fig S1], online only). The study received research ethics committee approval, and all patients provided written informed consent. Patients age 18 years and older with high-risk PV meeting criteria for HC-INT/RES (Data Supplement [Table S1]) were recruited, stratified by sex and randomly assigned 1:1 to either ruxolitinib (starting 10 mg twice daily; 5 mg twice daily for baseline platelets 100-200 $\times 10^9$/L) or BAT.

Outcome Measures

Primary outcome was complete response (CR) rate within 12 months by European LeukemiaNet (ELN) criteria: hematocrit <45% without venesection for 3 months; platelets ≤400 $\times 10^9$/L; WBC count ≤10 $\times 10^9$/L, and normal spleen size.[11] Secondary outcomes included partial response (PR) rates, duration, safety profile, histologic and molecular responses, quality of life (QoL), progression-free survival (PFS; transformation into myelofibrosis, myelodysplastic syndrome, or AML, or death from any cause), overall survival (OS), and event-free survival (EFS, a composite of major thrombosis, major hemorrhage, transformation, or death). Adverse events were graded according to National Cancer Institute's Common Toxicity Criteria v.4.

Treatment and Assessments

Change of BAT therapy was permitted. There was no per-protocol crossover of BAT patients to ruxolitinib, although a small number of patients (n = 10) received ruxolitinib treatment on the BAT arm (Data Supplement [Table S2]). Patients were analyzed on a modified intention-to-treat (mITT) basis, including all who started treatment within one year of random assignment with at least one response available. A safety population (any patient starting treatment) was used to assess toxicity profile of treatments. Events contributing to EFS were centrally adjudicated by two clinicians blinded to treatment.

Assessments were 2 weekly for 3 months, then 6 weekly until 12 months, and thereafter 4 monthly. Ruxolitinib continued beyond 1 year, provided a CR or PR was attained at 12 months. QoL was assessed using MPN Symptom Assessment Form (MPN-SAF). Paired peripheral blood or granulocyte DNA underwent allele-specific quantitative polymerase chain reaction for *JAK2*V617F variant allele fraction (VAF, %) at baseline and annually. Baseline samples underwent targeted sequencing for somatic mutations in 35 myeloid cancer–associated genes (Data Supplement). Targeted single-cell *JAK2*V617F genotyping[12] was performed on hematopoietic stem and progenitor cells

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(HSPCs) at baseline and year 4 or 5 from three ruxolitinib-treated patients with >90% reduction in *JAK2*V617F VAF to determine the corresponding reduction in *JAK2*V617F burden in HSPCs. Histologic analysis was performed on paired marrow trephine samples from baseline and 1 year by two pathologists blinded to treatment.

Statistical Analysis

$P < .10$ was considered significant for primary outcome and $P < .05$ (two-sided test) for other analyses. With the exception of analyses relating to molecular response at the last time point, time-to-event outcomes were analyzed using Kaplan-Meier survival analyses and Cox proportional hazards modeling adjusted for sex and treatment, where appropriate. The association between molecular response at the last time point and clinical outcomes were compared using chi-squared tests. Symptom changes over time and between groups used linear mixed modeling with compound symmetry covariance structure and with covariates for categorical time point, treatment arm, and interaction between time point and treatment arm. A two-sample test for proportions was used to evaluate the primary outcome. Logistic regression models assessed the effect of baseline measures on primary and secondary outcomes. Additional hypotheses testing were exploratory and not prespecified. As the mITT population included 10 patients switching to ruxolitinib, supporting analyses were performed censoring at the time they began ruxolitinib; these analyses did not affect the conclusions from mITT analysis. Analyses were performed using Stata v16.0 and v17.0, SAS v9.4, and R.

RESULTS

Patient Characteristics

One hundred ninety patients were recruited between August 2012 and August 2016, with 180 eligible for the mITT analysis (93 and 87 patients in the ruxolitinib and BAT arms, respectively; Fig 1), with a median follow-up (FU) of 4.8 years at the time of data cut (April 2022). Median age was 66 years with 105 males (58%) and 75 females (42%) enrolled, of which 54 (30%) were resistant to HC, 80 (44%) intolerant, and 46 (26%) both. Baseline characteristics were generally balanced (Table 1), with prior thrombosis more prevalent in the BAT arm, and diabetes and hypertension more prevalent in the ruxolitinib arm.

Trial Treatment

The median treatment duration on ruxolitinib was 1,568 days and 1,220 days for BAT patients. The mean dose of ruxolitinib was 10 mg twice daily with dose intensity increasing over time (Data Supplement [Fig S2]). The most frequent BATs were hydroxycarbamide (32%), interferon (15%), and combination of hydroxycarbamide and interferon (12%; Data Supplement [Table S3]).

Patient Disposition

Patient disposition at the time of analysis is shown in the CONSORT diagram (Fig 1). The causes for treatment discontinuation were similar across both arms (Data Supplement [Table S4]).

Efficacy Analysis

For patients meeting the criteria for mITT analysis, the primary outcome (CR) was achieved in 40 (43%) patients in the ruxolitinib arm versus 23 (26%; Data Supplement [Table S5]) in the BAT arm (test for proportions, $P = .02$; odds ratio [OR] from logistic regression model accounting for the stratification factor only: 2.12; 90% CI, 1.25 to 3.60; $P = .02$; Data Supplement [Table S6A]). A multivariable logistic regression model (Data Supplement [Table S6B]) was fitted, including treatment arm, sex, and the following baseline characteristics: hemoglobin at baseline, the number of previous therapies, history of thrombosis, resistance or intolerance to hydroxycarbamide, and splenomegaly. This resulted in an OR of 2.03 (90% CI, 1.09 to 3.78; $P = .06$).

A best response of PR was achieved in 50 (54%) ruxolitinib arm patients and 58 (67%) BAT arm patients during year 1. Of these, 45 in the ruxolitinib arm and 50 in the BAT arm had a hematocrit <0.45 and had been venesection-free for 3 months at their first PR. The overall response rate was 97% and 93% for ruxolitinib- and BAT-treated patients, respectively. Ruxolitinib treatment was associated with more durable CR than BAT (Fig 2A). Furthermore, patients were much more likely to switch treatment on the BAT arm compared with ruxolitinib-treated patients (Fig 2B).

Concerning components of hematologic response, ruxolitinib-treated patients required fewer venesections, despite slightly longer treatment and FU times: a total of 83 venesections versus 307 in the BAT arm (Data Supplement [Table S7A]). Overall, 52% of BAT-treated patients (45/87 patients) had at least one venesection versus 29% (27/93 patients) in the ruxolitinib arm (Data Supplement [Table S7B]). Hemoglobin and hematocrit levels were lower in those receiving ruxolitinib, whereas leukocytes and platelet counts were not significantly different between the arms (Data Supplement [Fig S3]). Overall, 47 paired samples (29 ruxolitinib and 18 BAT) were available for analysis of histologic response at 1 year, and no complete responses were observed.

Thrombosis, Hemorrhage, and Disease Transformation

Thromboembolic event-free, but not hemorrhage-free, survival was significantly improved with ruxolitinib (hazard ratio [HR], 0.56; 95% CI, 0.32 to 1.00; $P = .05$; Data Supplement [Figs S4A and S4B]; time to the first thrombotic event within the first 3 years on trial significantly correlated with the average number of venesections (per year; subdistribution HR, 1.20; 95% CI, 1.08 to 1.33; $P < .001$), after

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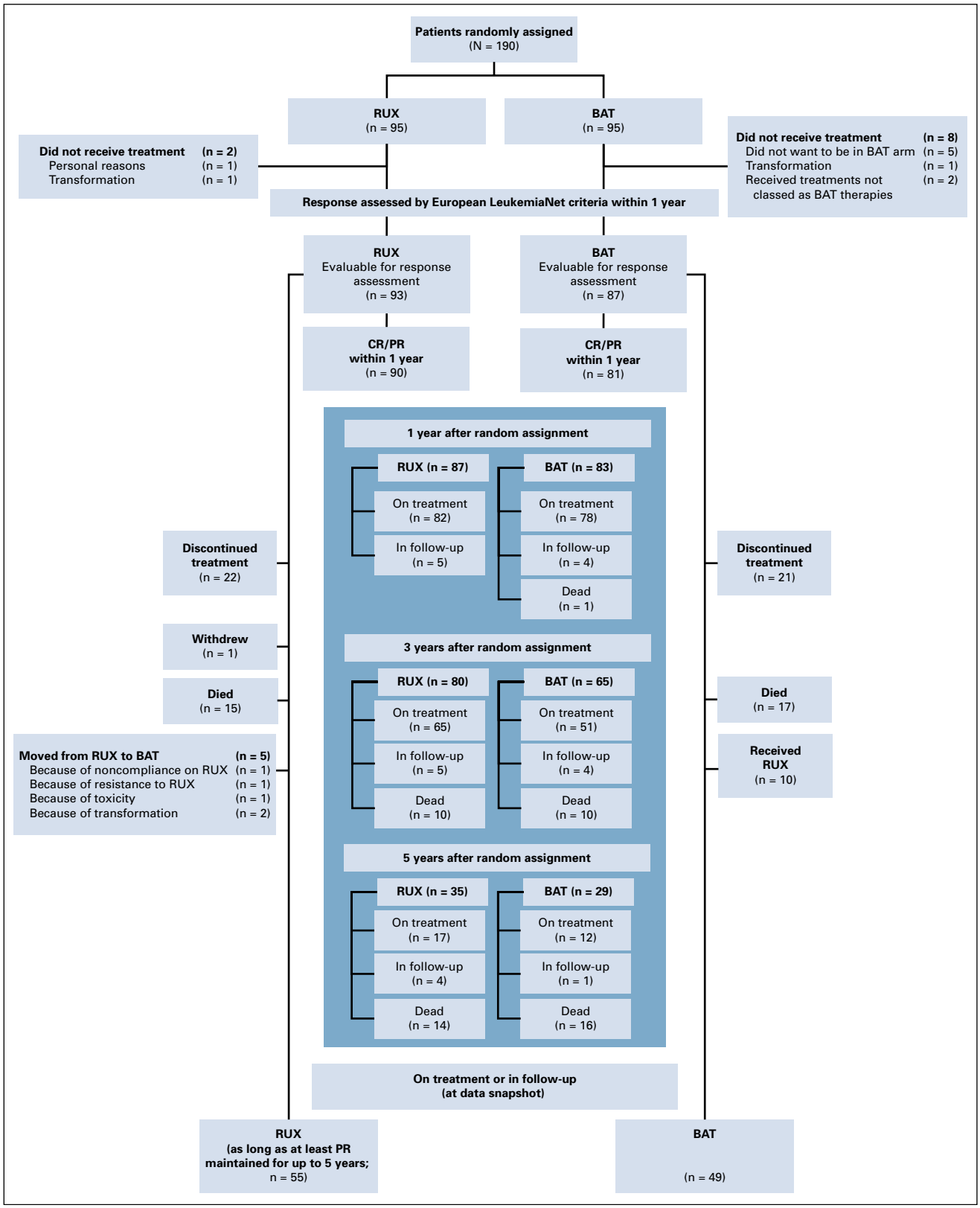

FIG 1. CONSORT diagram. BAT, best available therapy; CR, complete response; PR, partial response; RUX, ruxolitinib.

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TABLE 1. Baseline Features at Study Entry

Parameter	BAT (n = 87)	Ruxolitinib (n = 93)	Overall (N = 180)
Age, years, median (range)	66 (28-85)	67 (34-88)	66 (28-88)
Sex, No. (%)			
Female	38 (44)	37 (40)	75 (42)
Male	49 (56)	56 (60)	105 (58)
ECOG, No. (%)			
0	59 (68)	57 (61)	116 (64)
1	27 (31)	32 (34)	59 (33)
2	1 (1)	3 (3)	4 (2)
Disease duration, months, median (range)	96 (4-388)	90 (0-365)	91 (0-388)
Previous lines of therapy. median (range)	2 (1-6)	1 (1-4)	1 (1-6)
Both resistant and intolerant to hydroxycarbamide, No. (%)	27 (31)	19 (20)	46 (26)
Intolerant to hydroxycarbamide	37 (43)	43 (46)	80 (44)
Resistant to hydroxycarbamide	23 (26)	31 (33)	54 (30)
History of thrombosis, No. (%)	38 (44)	26 (28)	64 (36)
History of hemorrhage, No. (%)	6 (7)	3 (3)	9 (5)
Migraine or erythromelalgia, No. (%)	4 (5)	6 (6)	10 (6)
Diabetes, No. (%)	3 (3)	7 (8)	10 (6)
Hypertension, No. (%)	25 (29)	33 (35)	58 (32)
Palpable splenomegaly, No. (%)	22 (25)	23 (25)	45 (25)
Spleen length by ultrasound, median (range)	14 (73; 9-30)	14 (77; 9-26)	14 (150; 9-30)
WBC count, 10^9/L, median (range)	9 (2-37)	9 (2-73)	9 (2-73)
Hemoglobin, g/L, median (range)	136 (65-163)	136 (85-173)	136 (65-173)
Hematocrit, median (range)	0.43 (0.34-0.52)	0.43 (0.28-0.57)	0.43 (0.28-0.57)
Platelets, 10^9/L, median (range)	356 (99-1,420)	401 (61-1,546)	368 (61-1,546)
JAK2 mutation status, No. (%)			
Wild-type	1 (1)	3 (3)	4 (2)
*JAK2*V617F	85 (98)	89 (96)	174 (97)
JAK2 exon 12	1 (1)	1 (1)	2 (1)

Abbreviations: BAT, best available therapy; ECOG, Eastern Cooperative Oncology Group; JAK, janus kinase.

controlling for sex and treatment. EFS was superior both for ruxolitinib treatment (HR, 0.58; 95% CI, 0.35 to 0.94; $P = .03$, Fig 2C), and those achieving CR within 12 months (HR, 0.41; 95% CI, 0.21 to 0.78; $P = .01$ Fig 2D). PFS showed a similar pattern with a trend to improved PFS for ruxolitinib (Data Supplement [Fig S4C]), with 3-year PFS of 75% (95% CI, 63 to 83) for BAT and 84% (95% CI, 74 to 90) for ruxolitinib. OS did not differ, with 3-year OS of 87% (95% CI, 77 to 93) for BAT and 88% (95% CI, 79 to 93) for ruxolitinib. Causes of death and thrombotic/hemorrhagic events are shown in the Data Supplement (Tables S8A and 8B and Table S9, respectively).

*JAK2*V617F Allele Burden Reduction and Association With Treatment

Median baseline *JAK2*V617F VAF did not differ: ruxolitinib (64%) and BAT (58%). Longitudinal quantification of *JAK2*V617F was undertaken in 127/190 patients (70 ruxolitinib and 57 BAT), after excluding 63 patients: lack of samples (n = 8), no serial samples (n = 47), treatment arm crossover (n = 4), *JAK2*V617F negativity (n = 3), and nonreproducible <0.5% VAF at baseline (n = 1). A >25% reduction in VAF at 12 months was observed in 32% (20 of 63) and 30% (15 of 50) for ruxolitinib and BAT, whereas >50% VAF reduction at 12 months was only observed in 14% (9 of 63) and 18% (9 of 50) patients, respectively (Data Supplement [Fig S5A]). By the final time point available, both more frequent and larger reductions in *JAK2*V617F VAF were observed with ruxolitinib (Fig 3A; Data Supplement [Fig S5B and S5C]), with >50% reduction observed in 56% (39 of 70, median FU 48 months) and 25% (14 of 57, median FU 36 months) of ruxolitinib and BAT, respectively ($P < .001$). We selected three ruxolitinib-treated patients with >90% reduction in *JAK2*V617F VAF at year 4 or 5 time point to analyze clonal burden in HSPCs confirming substantial (72%-100%) reduction in *JAK2*V617F+ HSPCs at FU (Fig 3B).

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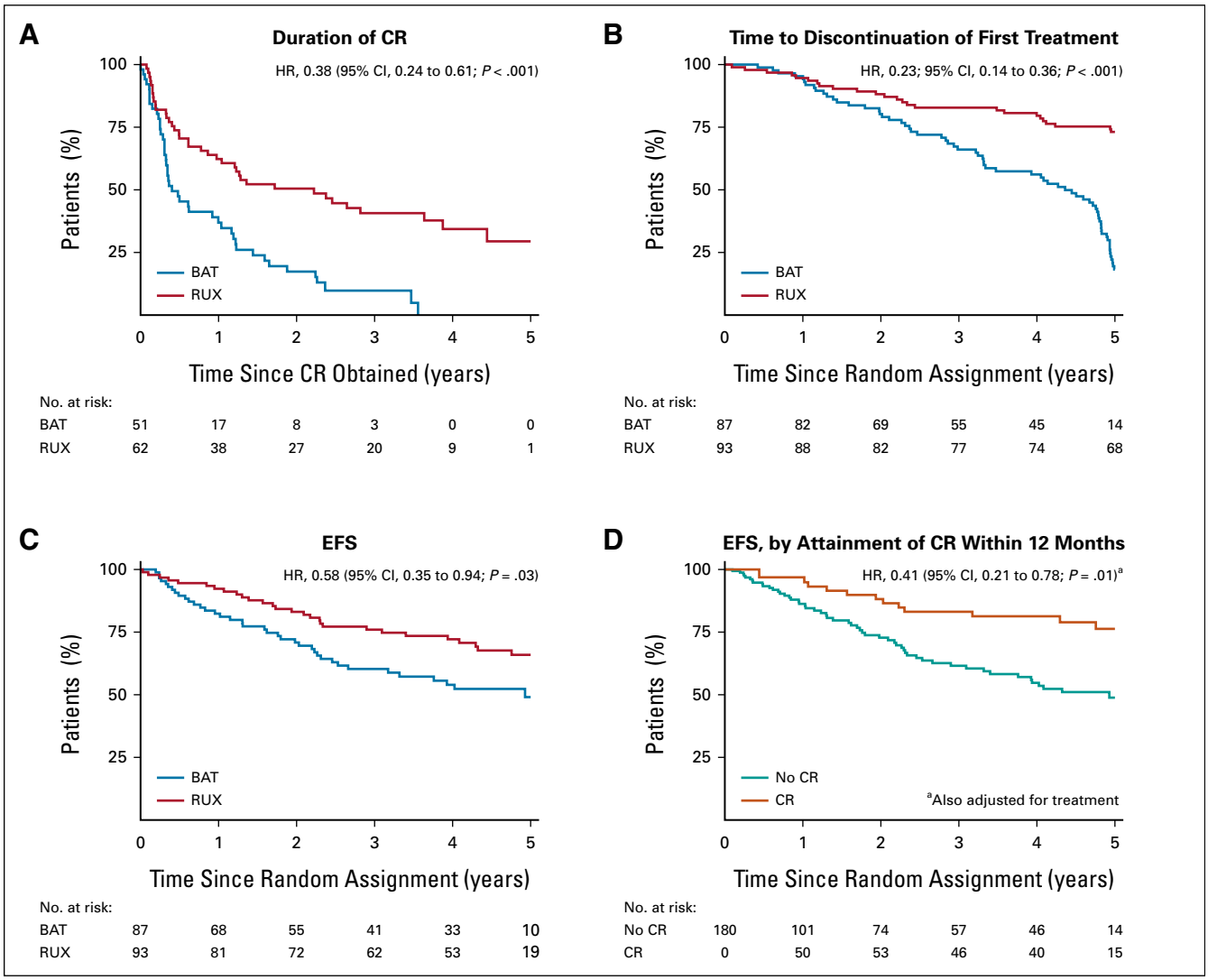

FIG 2. Ruxolitinib induces durable responses and improves major EFS in PV. Kaplan-Meier plots of (A) duration of complete remission, stratified by treatment arm; (B) time to discontinuation of first treatment, stratified by treatment arm; (C) EFS, stratified by treatment arm; and (D) EFS according to the primary end point. *P* value obtained from a Cox model adjusting for sex and, where indicated, treatment. BAT, best available therapy; CR, complete response; EFS, event-free survival; HR, hazard ratio; RUX, ruxolitinib.

Molecular Analyses and Clinical Correlation

Once patients achieved a 50% reduction in *JA2*V617F VAF, this was generally durable and termed as molecular response. The median time to molecular response was 36 months overall (36 months for ruxolitinib-treated patients, and not reached in BAT patients). Early *JAK2*V617F molecular response at 12 months was associated with improved outcome, with an event occurring in 24% of molecular responders at 12 months compared with 43% of nonresponders (P = .005; Fig 3C). ROC curve analysis did not identify that alternative (eg, 25% or 75% reductions in *JA2*V617F VAF) cutoffs defining molecular response were superior for identifying individuals likely to have reduced clinical events (Data Supplement [Fig S5D]). Molecular response at last sample tested was associated with improved outcomes for the whole cohort (PFS P = .001, EFS P = .001, OS P = .01) and for ruxolitinib (PFS P = .001, EFS P = .006, OS P = .04), but not for BAT treatment (Table 2).

Impact of Additional Cancer-Associated Driver Mutations in PV

Overall, 59% (98/167) patients had a single driver mutation (Fig 3D); additional mutations were associated with age (median 65.5 *v* 68 years; P = .04). Commonest additional driver mutations were in *TET2* and *ASXL1*. Individuals with gene panel sequencing and time-to-event data were dichotomized into single versus ≥2 driver mutations. Survival analysis demonstrated impaired EFS in patients with additional driver mutations (treatment, age- and sex-adjusted HR, 1.92; 95% CI, 1.16 to 3.19; n = 167; P = .01; Fig 3E). Specifically, mutated *ASXL1* conferred impaired EFS

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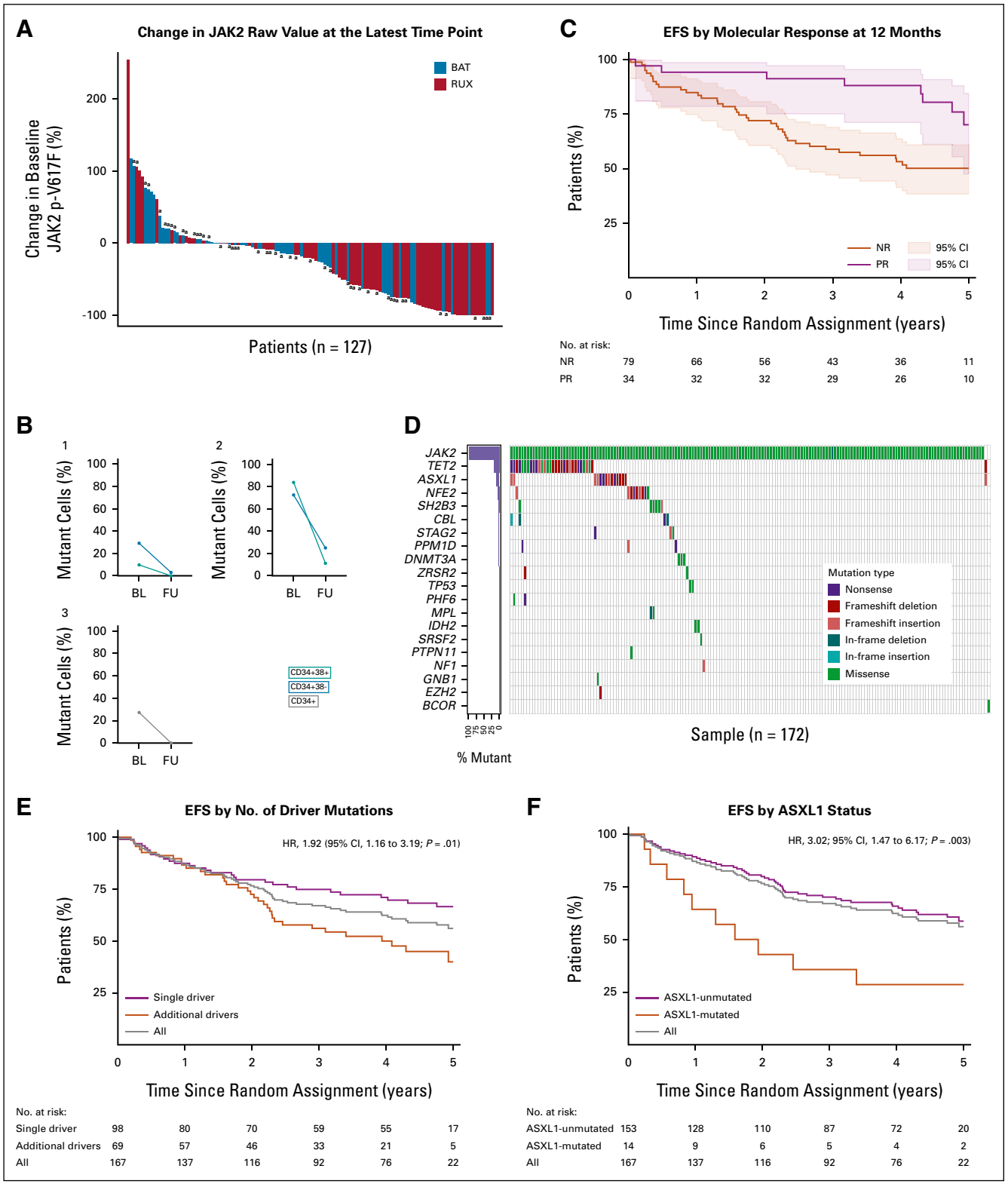

FIG 3. Molecular analysis and clinical correlates. (A) Waterfall plot displaying the percentage change in JAK2V617F VAF at the latest time point in comparison with baseline. Bars are colored according to BAT (blue) and ruxolitinib (red). [a]Patients with additional driver mutations. (B) The percentage of HSPCs that were *JAK2*V617F+ by single-cell genotyping at BL and latest FU. Three ruxolitinib-treated patients showing a >90% reduction in *JAK2*V617F VAF in peripheral blood at the latest time point were selected for analysis. For patients (1) and (2), CD34+CD38+ (n = 237 and n = 218 cells analyzed, respectively) and CD34+CD38− (n = 70 and n = 90 cells analyzed, respectively) HSPCs are shown separately. For patient (3), total CD34+ cells (n = 125) are shown. (C) EFS with patients stratified according to molecular response at 12 months (orange, NR defined as <50% *JAK2* VAF reduction; purple, partial responder defined as >50% *JAK2* VAF reduction). Shaded areas represent 95% CIs. (D) Heatmap of extended gene panel mutation analysis of baseline samples. The rows in the graph represent individual gene mutations colored by the type of mutation together with the VAF for mutant *JAK2*, and the columns represent (continued on following page)

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FIG 3. (Continued). patients in the study. (E) EFS for patients stratified according to presence or absence of additional driver mutations (gray, all patients; purple, patients with a single driver mutation; orange, those with additional driver mutations). (F) EFS stratified according to presence or absence of an *ASXL1* mutation (gray, all patients; purple, *ASXL1*-unmutated; orange, *ASXL1*-mutated). BAT, best available therapy; BL, baseline; EFS, event-free survival; FU, follow-up; HR, hazard ratio; HSPCs, hematopoietic stem and progenitor cells; NR, nonresponder; PR, partial response; VAF, variant allele fraction.

(adjusted HR, 3.02; 95% CI, 1.47 to 6.17; n = 167; P = .003; Fig 3F) after correcting for age, sex, and the presence of mutations in *TET2*. Moreover, *ASXL1* mutations (n = 14, of which eight had *JAK2*V617F molecular response data) were over-represented in *JAK2*V617F molecular nonresponders at 12 months (n = 8).

Impact of Therapy Upon Disease Symptom Burden

Overall, 147 patients (76 ruxolitinib and 71 BAT) completed at least baseline symptom assessment and 39 patients completed 60 months (Data Supplement [Table S10]). Baseline symptom scores were similar between arms; only MPN-SAF weight loss was different (BAT 0.7 [standard deviation {SD} 1.7] *v* ruxolitinib 1.7 [SD 2.8], P = .02). Durable improvements in total symptom score (TSS) were noted for ruxolitinib patients lasting a mean of 52 months. BAT patients experienced a worsening of their symptom burden improving to baseline at 56 months (Fig 4). Dwindling numbers of patients influence data from 36 months. Of the 115 patients with MPN-SAF TSS scores at baseline and at least one additional time point, 17/56 (30%) BAT and 36/59 (61%) ruxolitinib patients had TSS reduction of 50% or greater in at least one time point (P = .001). Regarding specific symptoms, there was statistically significant symptom reduction for ruxolitinib compared with BAT at >5 time points for fatigue, early satiety, night-sweats, itching, bone pain, and weight loss (Data Supplement [Table S10]).

Safety

Adverse events are summarized in the Data Supplement (Tables S11A and S11B). Infections, GI disorders, and vascular disorders were most frequent. Overall, infections were more common for ruxolitinib-treated patients, in particular, respiratory, genitourinary, and cutaneous herpes zoster (27 *v* 12 grade 3/4 events in ruxolitinib and BAT, respectively). There were no infection-related deaths or atypical infections. Concerning malignancy, squamous cell skin cancer was reported more commonly in ruxolitinib-treated patients (11 *v* 0 events in ruxolitinib and BAT, respectively).

DISCUSSION

In previous studies of HC-INT/RES PV patients, ruxolitinib demonstrated improved hematocrit control and reduced spleen volume in comparison with BAT.[7-9] In MAJIC-PV, there was no preplanned crossover to ruxolitinib and patients were followed for 60 months, which enabled important novel clinical and biological outcome data to be assessed. The primary end point of our study was CR, selected a priori on the basis of ELN recommendations, and although biologically logical, to our knowledge, our study is the first to demonstrate a correlation between attaining a CR and EFS (P = .01) in HC-INT/RES PV patients. We also demonstrate a relationship between ruxolitinib therapy and improved thrombosis-free survival (P = .05) and EFS

TABLE 2. Comparison of Molecular Response (JAK2 variant allele fraction reduction of >50%) at Last Recorded Time Point With Key Trial Outcomes

	Any Treatment				Ruxolitinib			BAT		
Outcome	Whole Trial (n = 127), No. Events, (%)	NR[a] (n = 74), No. Events, (%)	PR[b] (n = 53), No. Events, (%)	P	NR[a] (n = 31), No. Events, (%)	PR[b] (n = 39), No. Events, (%)	P	NR[a] (n = 43), No. Events, (%)	PR[b] (n = 14), No. Events, (%)	P
Thromboembolic event[c]	38 (30)	28 (38)	10 (19)	.02	10 (32)	7 (18)	.17	18 (42)	3 (21)	.17
Hemorrhagic event[c]	28 (22)	23 (31)	5 (9)	.004	9 (29)	4 (10)	.04	14 (33)	1 (7)	.06
Progression-free survival[c]	35 (28)	29 (39)	6 (11)	.001	13 (42)	3 (8)	.001	16 (37)	3 (21)	.28
EFS[c]	53 (42)	40 (54)	13 (25)	.001	16 (52)	8 (21)	.006	24 (56)	5 (36)	.19
OS[c]	22 (17)	18 (24)	4 (8)	.01	8 (26)	3 (8)	.04	10 (23)	1 (7)	.18
CR achieved at 1 year	49 (39)	22 (30)	27 (51)	.02	10 (32)	22 (56)	.04	12 (28)	5 (36)	.58

NOTE. P value results from chi-squared testing.

Abbreviations: BAT, best available therapy; CR, complete response; EFS, event-free survival; NR, no response; OS, overall survival; PR, partial response.

[a]No molecular response defined as <50% reduction in *JAK2* variant allele fraction.

[b]Partial molecular response defined as ≥50% response in *JAK2* variant allele fraction.

[c]These comparisons include any event that contributes to EFS outcome.

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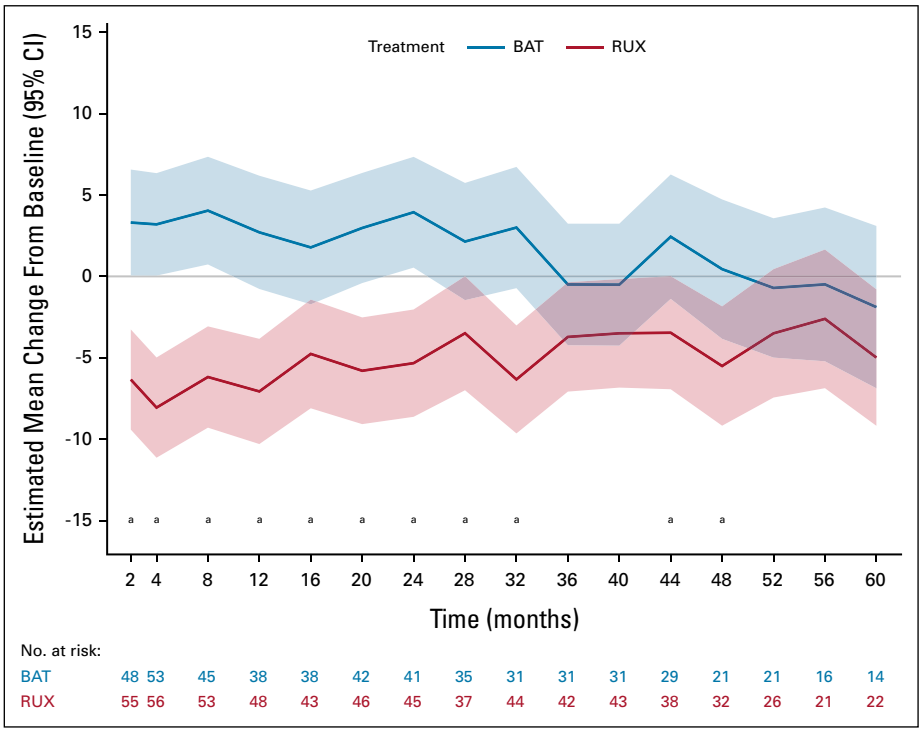

FIG 4. Symptom responses. Change in MPN TSS, blue is BAT, red is ruxolitinib. Shaded areas indicate 95% CIs. [a]Significant difference between the arms. BAT, best available therapy; MPN, myeloproliferative neoplasm; RUX, ruxolitinib; TSS, total symptom score.

(P = .03), which could reflect higher CR rates in ruxolitinib treated patients, or potential disease-modifying activity.

Patients with PV often have high *JAK2* V 617F VAF (>50%) because of the emergence of a dominant clone with concurrent loss of wild-type *JAK2*, which in turn is associated with increased risk of vascular events and transformation to myelofibrosis.[3,13–16] In MPN, unlike other hematologic malignancies, for example, chronic myeloid leukemia and AML, where molecular response to therapy correlates with improved outcome and directs patient management, the clinical importance of molecular response has been unclear despite the efficacy of several therapies at reducing *JAK2*V617F VAF.[17] This includes recent data with pegylated interferon alpha-2b where despite showing the superiority of molecular response with this agent, correlation with clinical benefit has not yet been feasible, perhaps because of lower event rates in the frontline population, and has been explored in studies, for example, those involving MDM inhibitors.[18,19]

Here, we observed that ruxolitinib was associated with more frequent molecular responses, defined as 50% reduction in VAF, (P < .001) at their final FU. Importantly, *JAK2*V617F molecular responders at 12 months were more likely to have CR at 12 months (P = .09), and those responding at their last time point demonstrated improved PFS (P = .001 all patients and P = .001 ruxolitinib-treated), EFS (P = .001 all and P = .006 for ruxolitinib), and OS (P = .01 all and P = .04 ruxolitinib). Similar to other myeloid malignancies, additional somatic mutations were associated with higher rates of events independent of age and sex, with mutated ASXL1 conferring a specific risk of major events (adjusted HR, 3.02; 95% CI, 1.47 to 6.17; n = 167; P = .003). Upon evaluating molecular responses at a stem/progenitor cell level, a substantial reduction in the clonal burden of *JAK2*V617F HSPCs in ruxolitinib-treated patients achieving a molecular response was demonstrated, consistent with ruxolitinib-induced clearance of *JAK2*V617F stem cells.[2]

Patterns of adverse events with ruxolitinib were similar to those previously reported, with more frequent infections and hematologic toxicities, and no new events emerged with longer FU.

Limitations of our study include that although treatment discontinuation rates were similar across arms, patients receiving BAT were permitted to change therapy, which could attenuate any difference between treatment arms. In addition, as with other studies in this field,[7,8] a significant proportion of patients (66%; 57 of 87 patients) continued with HC as BAT in the absence of alternative therapies for patients with high-risk PV. Although our data support further exploration of adding allele burden assessment into routine practice, this will require considerations such as standardization, DNA source, and cost.

Overall, MAJIC-PV confirms evidence that ruxolitinib is associated with improved treatment efficacy, for

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hematologic control and symptom responses, and significantly extends currently available data demonstrating novel benefits for ruxolitinib improving thrombosis-free survival and EFS in high-risk HC-INT/RES PV. Furthermore, to our knowledge, embedded preplanned analyses demonstrate for the first time that attainment of a 50% reduction in *JAK2*V617F VAF, which occurred more frequently with ruxolitinib, was associated with important clinical benefits (attaining CR, improved PFS, EFS, and OS) and clearance of MPN stem cells. These data confirm and challenge the current therapeutic algorithm, supporting the benefit of targeted therapy and molecular monitoring in PV.

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DATA SHARING STATEMENT

Participant data and the associated supporting documentation will be available within 6 months after the publication of the outcome measures. Scientifically sound proposals addressed to Claire.harrison@gstt.nhs.uk will be considered for data sharing.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Ruxolitinib Versus Best Available Therapy for Polycythemia Vera Intolerant or Resistant to Hydroxycarbamide in a Randomized Trial

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