Original Article

Life After Ruxolitinib: Reasons for Discontinuation, Impact of Disease Phase, and Outcomes in 218 Patients With Myelofibrosis

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BACKGROUND: After discontinuing ruxolitinib, the outcome of patients with myelofibrosis reportedly has been poor. The authors investigated whether disease characteristics before the receipt of ruxolitinib may predict drug discontinuation in patients with myelofibrosis and whether reasons for drug discontinuation, disease phase at discontinuation, and salvage therapies may influence the outcome. **METHODS:** A centralized electronic clinical database was created in 20 European hematology centers, including clinical and laboratory data for 524 patients who received ruxolitinib for myelofibrosis. **RESULTS:** At 3 years, 40.8% of patients had stopped ruxolitinib. Baseline predictors of drug discontinuation were: intermediate-2–risk/high-risk category (Dynamic International Prognostic Score System), a platelet count <100 $\times 10^9$ per liter, transfusion dependency, and unfavorable karyotype. At last contact, 268 patients (51.1%) had discontinued therapy, and the median drug exposure was 17.5 months. Fifty patients (18.7%) died while taking ruxolitinib. The reasons for discontinuation in the remaining 218 patients were the lack (22.9%) or loss (11.9%) of a spleen response, ruxolitinib-related adverse events (27.5%), progression to blast phase (23.4%), ruxolitinib-unrelated adverse events (9.2%), and allogeneic transplantation during response (5.1%). The median survival after ruxolitinib was 13.2 months and was significantly better in the 167 patients who discontinued ruxolitinib in chronic phase (27.5 vs 3.9 months for those who discontinued in blast phase; $P < .001$). No survival differences were observed among patients who discontinued ruxolitinib in chronic phase because of lack of response, loss of response, or ruxolitinib-related adverse events. The use of investigational agents and/or ruxolitinib rechallenge were associated with improved outcome. **CONCLUSIONS:** The survival of patients with myelofibrosis after discontinuation of ruxolitinib is poor, particularly for those who discontinue in blast phase. Salvage therapies can improve outcome, emphasizing the need for novel therapies. ***Cancer* 2020;126:1243-1252**. *© 2019 American Cancer Society*.

KEYWORDS: investigational agents, myelofibrosis, outcome, ruxolitinib, treatment failure.

INTRODUCTION

Myelofibrosis (MF) is a rare blood cancer with an incidence of approximately 0.6 new cases per 100,000 people per year. It is characterized by a chronic and disabling course, leading to death from disease progression, disease-related complications, and/or treatment-related complications.[1] In MF, hyperactivation of the JAK-STAT pathway induces

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myeloproliferation and expression of proinflammatory cytokines.[2] This discovery raised hopes that MF may be cured by the use of *JAK* inhibitors, as in chronic myeloid leukemia, which is treated with Bcr-Abl inhibitors[3]; however, *JAK*-inhibitor treatments do not affect disease burden or the *JAK*-mutated clone to a major extent[4] because they are not *JAK2* mutation–specific.

Ruxolitinib is the first-in-class *JAK1/JAK2* inhibitor commercially available for the treatment of MF. Ruxolitinib ameliorates inflammation and proliferation, which leads to clinically relevant control of splenomegaly and symptoms in the majority of patients with MF, which may result in prolonged survival.[5-8] Nonetheless, long-term studies have demonstrated a lack of response in some patients and loss of response in the majority of patients.[9] Some patients may not tolerate ruxolitinib because of therapy-related anemia, thrombocytopenia, or nonhematologic adverse events, in particular, infectious complications.[10-12] Consequently, ruxolitinib is discontinued by most patients during the first 5 years of treatment. In the registration-enabling Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment (COMFORT)-I and COMFORT-II studies, which enrolled only intermediate-2–risk and high-risk patients, the rate of treatment discontinuation was approximately 50% at 3 years and 75% at 5 years; whereas the expanded-access JAK Inhibitor Ruxolitinib in Myelofibrosis Patients (JUMP) study, which also included intermediate-1–risk patients, reported a discontinuation rate of 35% after 3 years.[5,7,8] The outcome of patients who failed ruxolitinib within the phase 1/2 trial reportedly was poor (median survival, 14 months). Outcomes were particularly poor in patients who had molecular clonal evolution and thrombocytopenia.[13] A second study of 64 patients treated in a real-life comparison confirmed that responses to salvage treatments are rare.[14] Understanding that the outcome after ruxolitinib is important for identifying patients who may benefit from specific interventions, such as allogeneic stem cell transplantation,[15] second-generation *JAK* inhibitors,[16-18] drugs with alternative mechanisms of action,[19,20] or investigational agents in combination with ruxolitinib.[21]

Here, we report the outcome of 218 patients after ruxolitinib. Our objective was to investigate: 1) the correlations between preruxolitinib disease characteristics and the probability of drug discontinuation, 2) the effects of reasons for discontinuation and disease status at the time of discontinuation on survival, and 3) the influence of salvage therapies on outcome after ruxolitinib.

MATERIALS AND METHODS

Study Cohort and Treatment

A multicenter, observational, retrospective study of patients who had MF treated with ruxolitinib was conducted in 20 European hematology centers. Participants were enrolled into the JUMP trial (clinicaltrials.gov identifier NCT01493414) or were treated off-study according to standard clinical practice, as previously described.[22] Data were extracted from an electronic database, which included consecutive patients who were treated with ruxolitinib from June 2011. All treatments for MF, baseline clinical/laboratory features, and outcome measures (including evolution into blast phase [BP], death, and spleen responses) were recorded. Diagnoses of primary MF (PMF) and postpolycythemia vera (PPV)/postessential thrombocythemia (PET) MF were made according to World Health Organization 2008 criteria or International Working Group on Myelofibrosis Research and Treatment (IWG-MRT) criteria, respectively.[23,24] All patients who received treatment with ruxolitinib in the current analysis were in chronic phase (peripheral and bone marrow blast cells <10%).

Risk category was assessed at the time patients started on ruxolitinib according to the Dynamic International Prognostic Score System (DIPSS).[25] Histologic examination was performed at local institutions; fibrosis was graded according to the European Consensus Grading System. Unfavorable karyotype was categorized as previously described.[26] Diagnosis of BP was made according to World Health Organization criteria, with a 20% bone marrow or peripheral blood blast threshold for diagnosis.[24] The burden of MF-related symptoms was assessed using the 10-item Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN10-TSS).[27]

Spleen responses were assessed according to 2013 IWG-MRT/European LeukemiaNet (ELN) criteria.[28] We acknowledge that, in many clinical situations, patients who have MF without an IWG-MRT/ELN-defined spleen response still may have a clinical benefit on splenomegaly from ruxolitinib (ie, smaller than at baseline), but we decided to use strict definitions in our analyses. The lack of a spleen response identified patients who never achieved a spleen response, whereas a loss of response was defined as any increase in spleen size compared with the patient's best recorded response. Specifically, at the time patients lost a spleen response, the spleen still may have been smaller than it was at baseline.

All adverse events were defined and graded according to Common Terminology Criteria for Adverse Events, version 4.0. Ruxolitinib-related and ruxolitinib-unrelated adverse events were considered separately.

The reasons for discontinuation and their causal relationship with the drug were assigned according to the judgment of the treating hematologist. We are aware that, in this respect, distinguishing MF-associated from ruxolitinib-induced myelosuppression may be particularly challenging. Here, ruxolitinib discontinuation was attributed to drug-related anemia and/or thrombocytopenia when cytopenias improved within 3 months after ruxolitinib was discontinued and/or could not be ascribed to other evident causes (ie, bleedings, comorbidities, BP transformation). With the objective of distinguishing ruxolitinib-induced hematologic toxicity from cytopenias caused by disease progression, if ruxolitinib discontinuation was induced by anemia/thrombocytopenia that resulted in a frank evolution to BP within 3 months after stopping the drug, then, at best, the cause of discontinuation was considered to be BP; conversely, when anemia/thrombocytopenia was concomitant to a lack or loss of response, then the cause for discontinuing ruxolitinib was considered to be a lack or loss of response. Erythrocyte transfusion dependency was defined according to IWG-MRT/ELN criteria.[28]

Comorbidities were recorded at the time of ruxolitinib start and classified according to the Charlson comorbidity index (CCI).[29] This study was approved by the Institutional Review Board of each institution and was conducted according to the Declaration of Helsinki.

Statistical Analysis

Continuous variables are expressed as medians and ranges or means and standard deviations, whereas categorical variables are presented as frequencies and percentages. We used the Wilcoxon-Mann-Whitney rank-sum test or the *t* test for comparisons between groups, and associations between categorical variables (2-way tables) were tested using the Fisher exact test or the chi-square test, as appropriate. Continuous and categorical variables at ruxolitinib start and discontinuation were compared using the Wilcoxon signed-rank test and the McNemar test, respectively.

Risk factors for ruxolitinib discontinuation and prognostic factors for survival were identified using univariate and multivariable Cox proportional hazards model. Multivariable Cox analysis was conducted on variables with *P* values <.10 at univariate analysis. To avoid the issue of multicollinearity and to remove highly correlated predictors from the model, collinearity among variables was detected using the Pearson correlation test. Variables that were associated with other factors in univariate analysis were excluded from the multivariable analysis.

Survival analyses were performed using Kaplan-Meier curves, and differences were evaluated using the log-rank test. Overall survival was calculated from the date of ruxolitinib discontinuation to either death or last contact. Tests were 2-sided, and *P* values <.05 were considered significant. Analyses were performed with using STATA software version 15 (StataCorp).

RESULTS

Study Cohort and Risk Factors Associated With Ruxolitinib Discontinuation

From 2011 to October 2018, in total, 524 patients with PMF (n = 277; 52.9%), PPV-MF (27.8%), or PET-MF (19.3%) were treated with ruxolitinib in participating centers. At time patients started on ruxolitinib, the median age was 68 years (range, 24-88 years), and 59% were men. DIPSS distribution was intermediate-1 risk (52.4%), intermediate-2 risk (40.8%), and high risk (6.8%). In total, 52 (9.9%) and 126 (24%) patients had platelet counts $<100 \times 10^9$/L or were erythrocyte transfusion-dependent, respectively. The spleen was palpable at <5 cm, at between 5 cm and 10 cm, and at >10 cm below the left costal margin in 9.4%, 37.2%, and 53.4% of patients, respectively. The median MPN10-TSS score was 20 (range, 5-100). Driver mutation distribution was as follows: *JAK2* V617F (82.9%), *CALR* mutations (11%), and *MPL* W515K/L (1.2%); and 4.9% of patients were triple-negative. Karyotype was abnormal in 93 of 348 (26.7%) evaluable patients. In 26 patients (7.4%) an unfavorable karyotype was detected, specifically: trisomy 8, complex, del7, del5, inv3, and 11q23 rearrangement.

After a median follow-up from ruxolitinib start of 37 months, 268 patients (51.1%) discontinued ruxolitinib, with a median drug exposure of 17.5 months (range, 1-81.7 months) (Fig. 1). The percentage of patients who discontinued ruxolitinib was 22.2%, 32.4%, and 40.8% at 1 year, 2 years, and 3 years, respectively. The overall ruxolitinib discontinuation rate was 19.6 per 100 patient-years. A comparison of clinical and laboratory features at the start and end of ruxolitinib treatment showed that patients had significantly lower platelet counts and hemoglobin levels, but higher leukocytes and peripheral blast cell counts, at the time of ruxolitinib discontinuation. In addition, spleen length and symptom burden were significantly lower at discontinuation (Table 1).

In univariate analysis, PMF diagnosis, intermediate-2/high DIPSS risk, transfusion-dependent anemia, platelet count $<100 \times 10^9$/L, peripheral blasts ≥1%, splenomegaly ≥15 cm below the left costal margin, the presence of comorbidities (CCI ≥ 2), and unfavorable

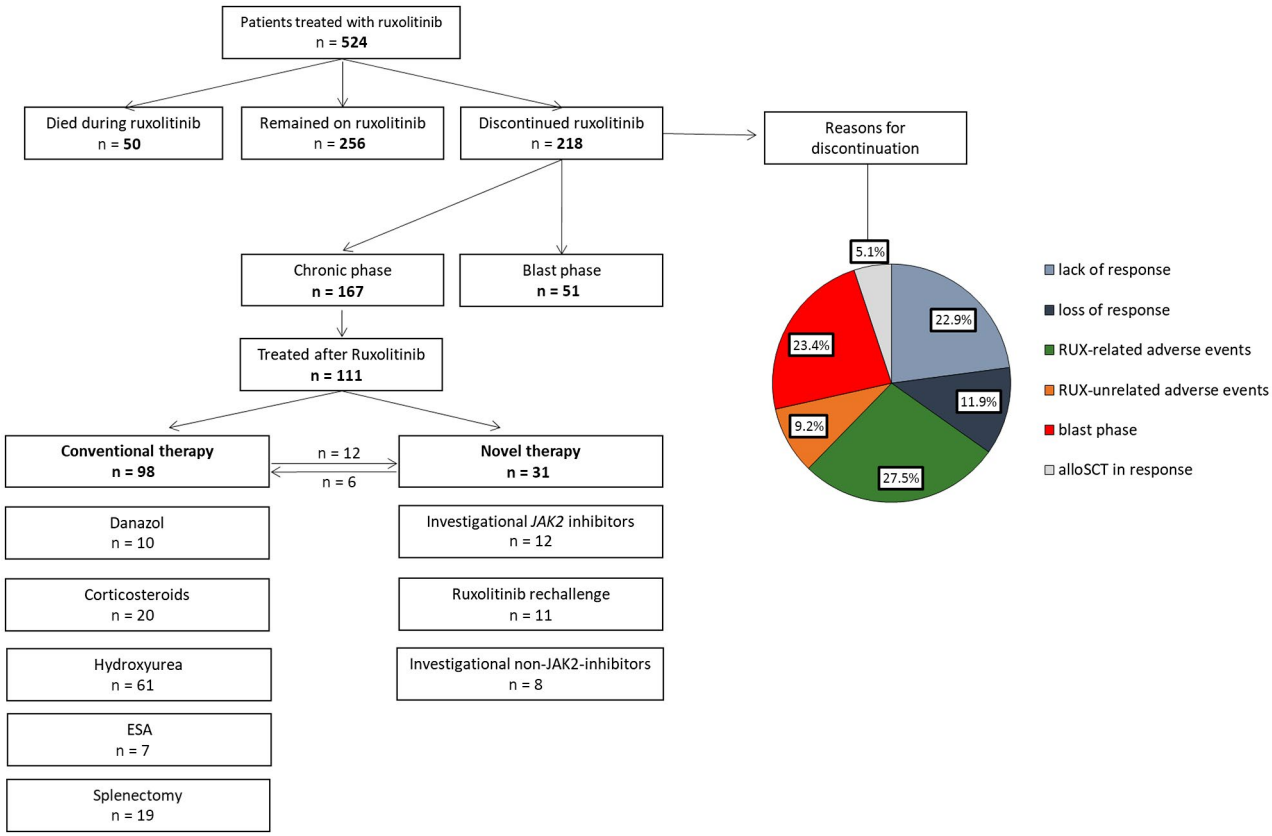

Figure 1. The disposition of all patients is illustrated. Patients received conventional and novel therapies either alone or in combination. Eighteen patients received with both conventional and novel agents. Twenty-six patients also underwent allogeneic stem cell transplantation after receiving conventional therapies. Overall, 54 patients received uniquely conventional medical therapy. The direction of the arrows between conventional and novel therapies indicates which type of therapy was received first. ESA indicates erythropoietin-stimulating agents.

karyotype were significantly associated with a greater probability of drug discontinuation. After multivariable analysis, intermediate-2/high DIPSS risk, transfusion dependency, platelet count $<100 \times 10^9$/L, and unfavorable karyotype remained significant (Fig. 2). In addition, we conducted a subanalysis after patient stratification into 3 categories according to the percentage of peripheral blasts: no peripheral blasts (61.2% of patients), from 1% to 5% peripheral blasts (34.9%) and from 6% to 9% peripheral blasts (3.9%). The probability of ruxolitinib discontinuation at 2 years was 28.6%, 43.5% and 61.5% in patients with no peripheral blasts, 1% to 5% peripheral blasts, and 6% to 9% peripheral blasts, respectively ($P = .005$).

Outcome According to the Reason for Ruxolitinib Discontinuation

Fifty patients (18.7%) died while taking ruxolitinib because of MF (34%), infections (24%), bleedings/thrombosis (12%), secondary neoplasms (10%), or other unrelated causes (20%). In these 50 patients, the median ruxolitinib exposure was 22.3 months (range, 1.0-81.7 months). Notably, BP was always preceded by or coincided with the discontinuation of ruxolitinib; therefore, no patient died from BP-MPN or secondary AML during therapy. Follow-up data are available for 218 patients who were observed for a total of 286.8 patient-years after ruxolitinib discontinuation.

The reason for ruxolitinib discontinuation was the lack or loss of a spleen response in 50 (22.9%) and 26 (11.9%) patients, respectively. Fifty-one patients (23.4%) discontinued because of progression to BP. In total, 60 patients (27.5%) discontinued because of ruxolitinib-related adverse events, namely: anemia (n = 23; 10.5%), thrombocytopenia (n = 15; 6.9%), infections (n = 20; 9.2%), and neurologic side effects (n = 2; 0.9%). An additional 20 patients (9.2%) discontinued because of ruxolitinib-unrelated adverse events, namely: second solid neoplasms (n = 10), thrombosis (n = 7), heart failure (n = 2), and pleural effusion

TABLE 1. Clinical and Laboratory Characteristics at the Start and End of Ruxolitinib Treatment[a]

Characteristic	No. of Patients (%) of Mean ± SD					
	At the Start of Ruxolitinib	At Discontinuation of Ruxolitinib	With Increased Continuous Values or With Shift of a Dichotomous Value From "No" to "Yes"	With Decreased Values or With Shift of a Dichotomous Value From "Yes" to "No"	With Stable Values	*P*
Hemoglobin in 259 evaluable patients, g/dL	10.4 ± 2.1	9.4 ± 1.8	80 (30.9)	173 (66.8)	6 (2.3)	<.001
Hemoglobin <10 g/dL	138 (51.5)	181 (69.9)	66 (25.5)	20 (7.7)	173 (66.8)	<.001
Leucocytes in 249 evaluable patients, $\times 10^9$ L	16.6 ± 17.6	26.3 ± 1.0-37.8	124 (49.8)	122 (49.0)	3 (1.2)	.02
Leukocytes > 25 $\times 10^9$ L	48 (18.5)	72 (28.4)	38 (15.3)	14 (5.6)	197 (79.1)	.001
Circulating blasts in 2017 evaluable patients, %	1.2 ± 1.87	9.4 ± 1.8	81 (39.1)	44 (21.3)	82 (39.6)	<.001
Circulating blasts ≥1%	109 (44.9)	117 (51.8)	38 (18.3)	25 (12.1)	144 (69.6)	.13
Platelets in 260 evaluable patients, $\times 10^9$/L	296 ± 253.8	163.9 ± 147.9	49 (18.8)	211 (81.2)	0 (0.0)	<.001
Platelets < 100 $\times 10^9$/L	33 (12.5)	113 (43.5)	86 (33.1)	5 (1.9)	169 (65.0)	<.001
Spleen length, in 250 evaluable patients, cm BLCM	12.8 ± 7.5	10.6 ± 8.6	76 (30.4)	153 (61.2)	21 (8.4)	<.001
Spleen ≥ 10 cm BLCM	173 (65.5)	128 (51.2)	14 (5.6)	49 (19.6)	187 (74.8)	<.001
TSS in 233 evaluable patients	23.6 ± 14.4	14.3 ± 18.5	37 (15.9)	180 (77.2)	16 (6.9)	<.001
TSS ≥ 20	166 (65.1)	63 (26.8)	13 (5.6)	100 (42.9)	120 (51.5)	<.001
BMI in 245 evaluable patients, kg/m^2	23.8 ± 3.3	24 ± 3.6	126 (51.4)	87 (35.5)	32 (13.1)	.08
BMI > 25 kg/m^2	84 (32.9)	87 (34.9)	25 (10.2)	16 (6.5)	204 (83.3)	.45

Abbreviations: BMI, body mass index; BLCM, below the left costal margin; TSS, total symptoms score.
[a]Continuous variables at the time of ruxolitinib start and discontinuation were compared using the Wilcoxon signed-rank test, and dichotomous variables at the 2 time points were compared using the McNemar test statistic.

(n = 1). Eleven patients (5.1%) patients stopped ruxolitinib while in response to undergo allogeneic stem cell transplantation.

The median cumulative ruxolitinib dose was significantly higher in patients who discontinued because of the lack or loss of a spleen response, with 44.7% of patients receiving a median daily dose ≥15 mg twice daily (vs 18.4% of patients who discontinued because of ruxolitinib-related hematologic toxicity; $P = .006$); notably, the median drug exposure was comparable in the 2 groups (16.5 vs 17.5 months, respectively; $P = .14$). More specifically, we observed that the cumulative ruxolitinib dose was comparable in patients who discontinued ruxolitinib because of thrombocytopenia or anemia ($P = .06$).

The median survival after ruxolitinib discontinuation for the entire cohort of 218 patients was 13.2 months (95% CI, 8.0-22.7 months). The median survival was of 32.4, 27.9, 13.2, 3.9, and 3.6 months for patients who discontinued because of the loss of a spleen response, the lack of a spleen response, ruxolitinib-related adverse events, BP, and ruxolitinib-unrelated adverse events, respectively. Overall, a significant difference in survival between the groups was detected (log-rank test; $P < .001$). This difference was caused in particular by those who developed BP and those who stopped ruxolitinib for drug-unrelated adverse events, who had the worst outcomes, whereas overall survival was comparable in patients who discontinued because of the lack or loss of a response or ruxolitinib-related adverse events (Fig. 3). The death rates among patients who discontinued because of BP, drug-unrelated adverse events, ruxolitinib-related adverse events, the lack of a spleen response, or the loss of a spleen response were 10.5 per 100 patient-months (95% CI, 7.9-14.1 per 100 patient-months), 6.8 per 100 patient-months (95% CI, 4.0-11.7 per 100 patient-months), 3.2 per 100 patient-months (95% CI, 2.3-4.5 per 100 patient-months), 2.9 per 100 patient-months (95% CI, 2.1-4.3 per 100 patient-months), and 2.1 per 100 patient-months (95% CI, 1.1-3.8 per 100 patient-months), respectively.

Outcome of Patients Who Discontinued in Chronic Phase

In total, 167 patients discontinued ruxolitinib while in chronic phase and had a median survival after discontinuation of 27.5 months. Causes of death in this cohort included progression of MF (35.2%), infections (12.5%), bleedings/thrombosis (12.5%), second solid neoplasia (11.4%), heart disease (5.7%), and other MF-unrelated causes (21.6%). Among clinical and laboratory parameters at ruxolitinib discontinuation, Cox univariate analysis

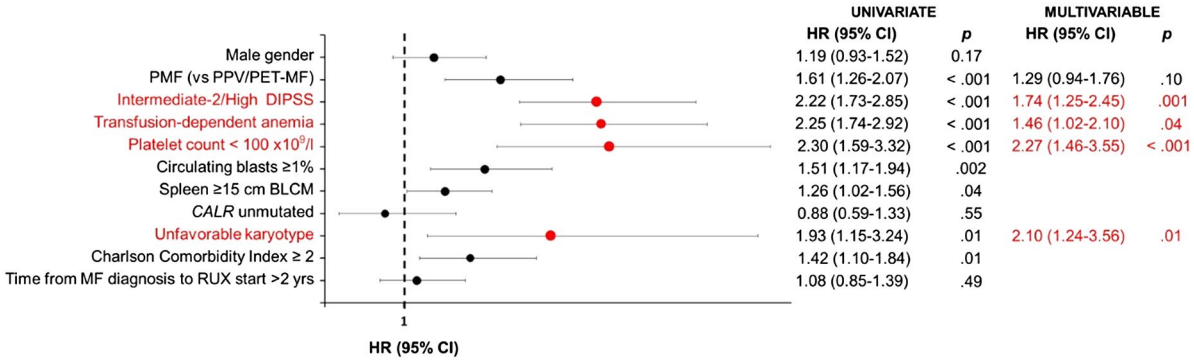

Figure 2. Univariate Cox analysis is illustrated of the baseline risk factors that were predictive for discontinuation of ruxolitinib (RUX). Variables with *P* values <.10 in univariate analysis were considered for multivariable analysis, and collinearity among variables was detected by using the Pearson correlation test. Because the ruxolitinib starting dose was based on the platelet count, this variable was not included in the analysis. In addition, peripheral blasts from 6% to 9% were associated with a greater probability of ruxolitinib discontinuation in univariate analysis (hazard ratio, 1.84; 95% CI, 1.01-3.36; *P* = .049). Peripheral blasts (using cutoff levels of both ≥1% and 6%-9%) were correlated with the Dynamic International Prognostic Score System (DIPSS) (Pearson correlation test) and were not included in multivariable analysis. Four variables (indicate in red) remained significantly associated with ruxolitinib discontinuation after multivariable analysis. The Harrell C concordance index was 0.75, and the Gronnesby and Borgan goodness-of-fit test reported a *P* value = .9. BLCM indicates below the left costal margin; PMF, primary myelofibrosis; PPV/PET-MF, postpolycythemia vera/postessential thrombocythemia myelofibrosis.

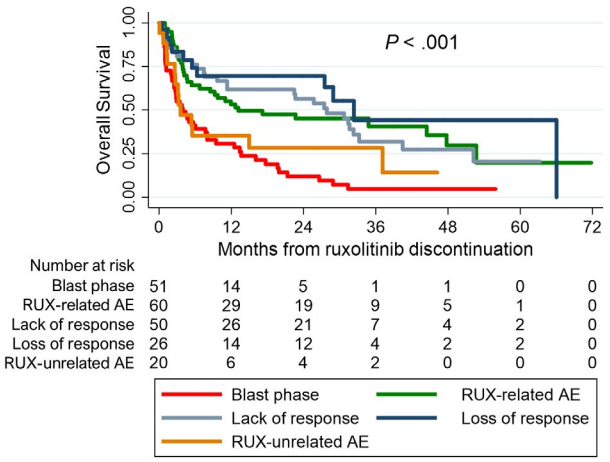

Figure 3. Overall survival is illustrated according to the reason for ruxolitinib (RUX) discontinuation. The 11 patients who discontinued ruxolitinib to undergo allogeneic stem cell transplantation while in response were excluded from this survival analysis. The *P* value reported on the figure results from the log-rank test for the overall difference between all Kaplan-Meier curves. Pairwise log-rank tests between all curves were conducted and confirmed that patients who discontinued because of a lack or loss of response had statistically comparable survival distributions compared with those who discontinued because of ruxolitinib-related adverse events (AEs) (*P* = .93 and *P* = .34, respectively) and that the patients who had significantly worse survival that had a major effect on the overall difference (*P* < .001) were those who discontinued because of ruxolitinib-unrelated events and blast phase.

showed that hemoglobin <10 g/dL (*P* = .03; hazard ratio [HR], 1.70; 95% CI, 1.05-2.76), circulating blast count ≥1% (*P* = .02; HR, 1.72; 95% CI, 1.09-2.71), and platelet count <100 ×10^9/L (*P* = .04; HR, 1.63; 95% CI, 1.04-2.42) correlated significantly with worse survival. Multivariable analysis confirmed that hemoglobin <10 g/dL (*P* = .01; HR, 1.92; 95% CI, 1.19-3.11) and circulating blast count ≥1% (*P* = .01; HR, 1.75; 95% CI, 1.11-2.74) at the time of ruxolitinib discontinuation correlated with worse survival.

In total, 111 patients (66.5%) received at least 1 additional line of therapy after ruxolitinib discontinuation. Among the 56 patients who did not receive further treatment, 46 (82.1%) were considered unfit to receive further therapy because of: poor performance and/or health status (60.9%), cytopenias and/or recurrent infections (30.4%), and co-occurrence of significant adverse events (heart failure, thrombosis; 8.7%). In 3 patients (5.4%), the diagnosis of a second malignancy prevented salvage treatment after ruxolitinib. In 7 patients (12.5%), no available drug was considered potentially effective by the treating hematologist. Overall, patients who did not receive further therapy after ruxolitinib discontinuation were characterized by older age (mean age, 66.2 vs 72.2 years; *P* < .001) and higher CCI (mean CCI, 1.5 vs 1.0; *P* = .02) compared with patients who did receive further therapy. In addition, patients who discontinued because of a lack or loss of response were treated more frequently compared with those who discontinued because of ruxolitinib-related or ruxolitinib-unrelated adverse events (*P* < .001) (see Supporting Table 1).

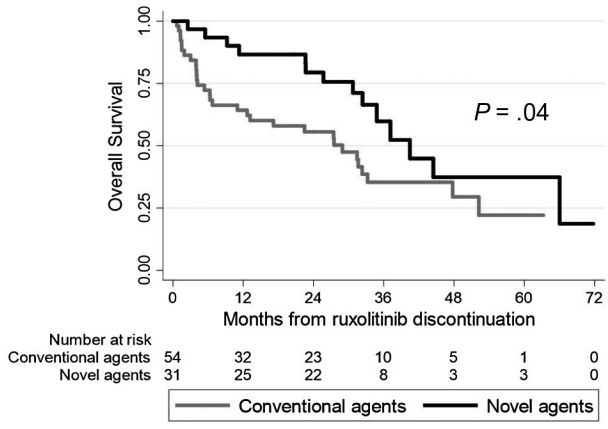

Figure 4. The overall survival of patients who discontinued ruxolitinib in chronic phase is illustrated according to the type of salvage treatment they received after discontinuation. Patients were not randomized between the 2 groups. Novel agents include ruxolitinib rechallenge, investigational *JAK2* inhibitors, and investigational non-*JAK2* inhibitors. Conventional therapies include hydroxyurea, danazol, erythropoiesis-stimulating agents, corticosteroids, and splenectomy. The 26 patients who underwent allogeneic stem cell transplantation were excluded from this survival analysis. The 18 patients who received both conventional and novel therapies were included only in the "novel agents" cohort.

Overall, patients who were treated after ruxolitinib discontinuation had significantly better outcomes than those who were not treated after discontinuing the drug (median survival, 34.8 vs 3.6 months, respectively; $P < .001$). The median time from ruxolitinib discontinuation to the start of a salvage therapy was 1 month (range, 0-45 months).

The treatments received after ruxolitinib discontinuation are summarized in Figure 1. Overall, 31 patients received salvage therapies, including ruxolitinib rechallenge and/or investigational agents, whereas 54 patients received exclusively conventional therapies. More specifically, 11 patients had a ruxolitinib rechallenge after a median of 16 months from ruxolitinib discontinuation (range, 3-70 months). The causes of discontinuation in these 11 patients were the lack or loss of a spleen response (n = 6), infectious events (n = 2), anemia (n = 1), and ruxolitinib-unrelated adverse events (pleural effusion and heart failure). Ruxolitinib rechallenge was used as the first salvage option or after another line of treatment in 3 and 8 patients, respectively. At rechallenge, the ruxolitinib dose was the same as before the discontinuation in all but 1 patient who rechallenged ruxolitinib at a lower dose.

Causes of discontinuation and disease burden at discontinuation of ruxolitinib (specifically, DIPSS distribution, spleen length, TSS, and hemoglobin/leukocyte/platelet/peripheral blast values) were comparable between patients who received conventional therapies only and patients those were received ruxolitinib rechallenge and/or investigational agents. Overall survival seemed to be longer in this latter cohort (40.5 vs 28.9 months; $P = .04$) (Fig. 4).

Outcome of Patients Who Discontinued Because of Transformation Into BP-MPN

Overall, 51 patients (23.4%) patients discontinued ruxolitinib because of progression to BP-MPN. Twenty-eight patients (54.9%) received a salvage treatment, specifically: hydroxyurea (n = 14), hypomethylating agents (azacytidine/decitabine; n = 7), chemotherapy (n = 6), and allogeneic stem cell transplantation (n = 5).

After a median of 3.2 months from ruxolitinib discontinuation, 46 patients died (90.2%). The median survival was significantly longer for patients who received therapy after ruxolitinib (7.9 months vs 2 months in untreated patients; $P = .005$). The type of therapy received after ruxolitinib did not significantly influence survival ($P = .17$). In multivariate analysis, only anemia (hemoglobin < 10 g/dL) at ruxolitinib discontinuation was correlated significantly with worse survival.

DISCUSSION

The management of patients with MF after ruxolitinib represents a major challenge in real-life clinical practice. Here, we observed that higher DIPSS risk category, lower platelet count, unfavorable karyotype, and erythrocyte transfusion dependency at ruxolitinib start were associated with a greater probability of drug discontinuation. These parameters correlated with those already related to inferior survival in the DIPSS-plus score; specifically, the role of cytogenetics in predicting ruxolitinib discontinuation supports the importance of karyotype in the prognostic assessment of patients with MF. In addition, the association of an elevated circulating blast cell count with increased treatment failure is in agreement with recent data suggesting its negative effect on survival.[30]

Importantly, we noticed that the 3 top clinical reasons for stopping ruxolitinib in patients with MF in chronic phase inadequately controlled splenomegaly (including the lack or loss of a spleen response; 34.8%), anemia/thrombocytopenia (17.4%), and infectious events (9.2%). First, failure to achieve or maintain a significant spleen response was the main cause of discontinuation, probably because ruxolitinib is initiated in most patients to target this specific clinical need. However, we observed

a counterintuitive decrease in baseline symptoms and splenomegaly at ruxolitinib discontinuation, indicating that ruxolitinib had some degree of efficacy, even in patients who finally discontinued the drug. Second, almost 20% of patients discontinued because of hematologic toxicity. This result matches with the greater frequency of anemia and thrombocytopenia that we detected at the time of ruxolitinib discontinuation. Third, the current study points out that infections may lead to discontinuation in a substantial fraction of ruxolitinib-treated patients, reinforcing the recommendation for close infectious monitoring before and during therapy.[31] Finally, we observed that the cumulative ruxolitinib dose was significantly higher in patients who discontinued because of the lack or loss of a spleen response compared with those who discontinued because of ruxolitinib-related hematologic toxicity but was comparable in those who discontinued because of anemia or thrombocytopenia.

This finding reflects the adherence of treating hematologists to prescribing information, according to which the ruxolitinib dose should be reduced in case of thrombocytopenia.[32] Conversely, we observed that both anemia and thrombocytopenia comparably triggered reductions of the ruxolitinib dose. This observation probably reflects that anemia is managed in real life with great caution and provides new insights into the practical management of ruxolitinib.

The main predictor of outcome after ruxolitinib, as expected, was disease status (chronic phase vs BP). Indeed, among patients in chronic phase, the median overall survival exceeded 24 months and was almost 35 months if at least 1 salvage therapy was attempted. In addition, the use of investigational agents and/or ruxolitinib rechallenge possibly may be associated with improved survival compared with conventional treatments, excluding allogeneic stem cell transplantation, raising the median survival beyond 40 months. This comparison has well known limitations (mainly, its retrospective and nonrandomized nature, the number of patients involved, the possible role of additional factors, such as willingness to participate in a clinical trial, and the heterogeneity of therapeutic approaches). Nevertheless, this may support the finding that participation in clinical trials after ruxolitinib discontinuation has the potential to significantly improve outcome. From a practical point of view, even with no innovative clinical trials available, ruxolitinib rechallenge may be a valuable therapeutic option in routine clinical practice and previously was associated with significant clinical responses.[33] Also, we observed that survival was significantly worse in patients who did not receive any treatment after ruxolitinib, suggesting indeed that all possible patients should receive therapy after ruxolitinib. Finally, although patients who lack or lose a spleen response are clinically (and probably biologically) heterogeneous, we unexpectedly noted that survival was comparable in these 2 cohorts. This observation may further highlight that patients who do not achieve official IWG-MRT responses may derive benefit from ruxolitinib.

Also, we did not detect any significant difference in survival between patients who discontinued ruxolitinib because of the lack or loss of a response and those who discontinued because of drug-related toxicity. Conversely, patients who experienced ruxolitinib-unrelated adverse events had significantly poorer projected outcomes, mainly because of the detrimental effect of second solid neoplasia. Overall, these observations may indicate that ruxolitinib-induced toxicity is not predictive of inferior survival, as noted previously for anemia during ruxolitinib therapy. In addition, these findings highlight the importance of strictly monitoring ruxolitinib-exposed patients in oncologic practice.[34,35] However, despite the absence of statistical significance, the difference in median survival between patients who lacked or lost a spleen response and those who had ruxolitinib-related adverse events may be clinically relevant (approximately 30 vs 13.2 months) and may have been caused in part by the lower likelihood of receiving further treatments in patients who discontinued ruxolitinib because of cytopenias or infections. From a clinical point of view, the latter patients are certainly the most vulnerable, with extremely limited therapeutic possibilities after ruxolitinib, and thus should require special attention and research.

This study does not provide the dynamics of nondriver mutations, which are not recommended in a real-life context but were previously identified as very informative,[13] but we did identify clinical and laboratory features that can easily be assessed in everyday clinical practice and may be associated with ruxolitinib discontinuation and outcome.

Despite the well known limitations inherent in retrospective studies, the objective of the current analysis was to provide valuable information not only about the risk factors for ruxolitinib discontinuation (which were found to correspond to higher risk disease) but also about the reasons for discontinuation and long-term outcomes after discontinuation. The latter data are extremely relevant to guide clinical practice and could hardly be extrapolated from further analyses of prospective studies. Overall, we observed that outcomes were extremely poor for patients who had MF in BP regardless of treatment, whereas, for those in chronic phase, receiving a salvage therapy and particularly entering a clinical trial possibly may improve

survival. Overall, the outcome of patients with MF after ruxolitinib discontinuation remains dismal, urging the need for new treatment strategies.

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CONFLICT OF INTEREST DISCLOSURES

Francesca Palandri reports personal fees from Novartis outside the submitted work. Massimo Breccia reports personal fees from Bristol-Myers Squibb, Incyte, Novartis, and Pfizer outside the submitted work. Massimiliano Bonifacio reports grants from Novartis and personal fees from Amgen, Bristol-Myers Squibb, Incyte, Novartis, and Pfizer outside the submitted work. Giulia Benevolo reports personal fees from Amgen, Bristol-Myers Squibb, Incyte, Janssen, and Novartis outside the submitted work. Mario Tiribelli reports personal fees from Bristol-Myers Squibb, Incyte, Novartis, and Pfizer outside the submitted work. Elisabetta Abruzzese reports personal fees from Amgen, Celgene, Incyte, Novartis, and Pfizer outside the submitted work. Alessandra Iurlo reports personal fees from Bristol-Myers Squibb, Incyte, Novartis, and Pfizer outside the submitted work. Florian H. Heidel reports grants from Novartis during the conduct of the study and personal fees from Celegene, CTI, and Novartis outside the submitted work. Monica Crugnola reports personal fees from Bristol-Myers Squibb, Celgene, Janssen, and Novartis outside the submitted work. Francesco Cavazzini reports personal fees from Incyte, Novartis, and Pfizer outside the submitted work. Alessandro Isidori reports personal fees from Gilead, Janssen, and Novartis outside the submitted work. Nicola Sgherza reports personal fees from Bristol-Myers Squibb, Incyte, Novartis, and Pfizer outside the submitted work. Roberto Latagliata reports personal fees from Bristol-Myers Squibb, Celgene, Janssen, and Novartis outside the submitted work.
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AUTHOR CONTRIBUTIONS

Francesca Palandri: Designed research, performed research, collected data, analyzed and interpreted data, performed statistical analysis, and wrote the article. **Massimo Breccia:** Designed research, performed research, collected data, analyzed and interpreted data, and wrote the article. **Massimiliano Bonifacio:** Performed research, collected data, analyzed and interpreted data, and wrote the article. **Nicola Polverelli:** Performed research, collected data, analyzed and interpreted data, and wrote the article. **Elena M. Elli:** Performed research, collected data, analyzed and interpreted data, and wrote the article. **Giulia Benevolo:** Performed research, collected data, analyzed and interpreted data, and wrote the article. **Mario Tiribelli**, **Elisabetta Abruzzese**, **Alessandra Iurlo**, **Florian H. Heidel**, **Micaela Bergamaschi**, **Alessia Tieghi**, **Monica Crugnola**, **Francesco Cavazzini**, **Gianni Binotto**, **Alessandro Isidori**, **Nicola Sgherza**, **Costanza Bosi**, **Bruno Martino**, **Roberto Latagliata**, **Giuseppe Auteri**, **Luigi Scaffidi**, **Davide Griguolo**, **Malgorzata Trawinska**, **Daniele Cattaneo**, **Lucia Catani**, **Mauro Krampera**, **Roberto M. Lemoli**, **Antonio Cuneo**, **Gianpietro Semenzato**, **Robin Foà**, **Francesco Di Raimondo**, and **Michele Cavo:** Performed research and collected data. **Daniela Bartoletti:** Performed research, collected data, analyzed and interpreted data, performed statistical analysis, and wrote the article. **Giuseppe A. Palumbo:** Designed research, performed research, collected data, analyzed and interpreted data, and wrote the article. **Nicola Vianelli:** Designed research, performed research, collected data, analyzed and interpreted data, and wrote the article.

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