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ORIGINAL ARTICLE

Clinical outcomes of ruxolitinib treatment in 595 intermediate-1 risk patients with myelofibrosis: The RUX-MF Real-World Study

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Abstract

Background: Ruxolitinib (RUX) is a JAK1/2 inhibitor approved for the therapy of myelofibrosis (MF) based on clinical trials including only intermediate2-high risk (INT2/HIGH) patients. However, RUX is commonly used in intermediate-1 (INT1) patients, with scarce information on responses and outcome.

Methods: The authors investigated the benefit of RUX in 1055 MF patients, included in the "RUX-MF" retrospective study.

Results: At baseline (BL), 595 (56.2%) patients were at INT1-risk according to DIPSS (PMF) or MYSEC-PM (SMF). The spleen was palpable at <5 cm, between 5 and 10 cm, and >10 cm below costal margin in 5.9%, 47.4%, and 39.7% of patients, respectively; 300 (54.1%) were highly symptomatic (total symptom score ≥20). High-molecular-risk (HMR) mutations (IDH1/2, ASXL-1, SRSF2, EZH2, U2AF1^{Q157}) were detected in 77/167 patients. A total of 101 (19.2%) patients had ≥1 cytopenia (Hb < 10 g/dL: n.36; PLT <100 x 10^9/L: $n = 43$; white blood cells <4 x 10^9/L: $n = 40$).

Massimo Breccia and Filippo Branzanti contributed equally to this work.

After 6 months on RUX, IWG-MRT–defined spleen and symptoms response rates were 26.8% and 67.9%, respectively. In univariate analysis, predictors of SR at 6 months were no HMR mutations odds ratio [OR], 2.0, $p = .05$], no cytopenia (OR, 2.10; $p = .01$), and blasts <1% (OR, 1.91; $p = .01$). In multivariate analysis, absence of HMR maintained a significant association (OR, 2.1 [1.12–3.76]; $p = .01$).

Conclusions: In INT1 patients, responses were more frequent and durable, whereas toxicity rates were lower compared to INT2/high-risk patients. Presence of HMR mutations, cytopenia, and peripheral blasts identified less-responsive INT1 patients, who may benefit for alternative therapeutic strategies.

KEYWORDS
ruxolitinib, DIPSS score, myelofibrosis, JAK2 mutation, intermediate-1

INTRODUCTION

Regarding its prognosis, myelofibrosis (MF) is the most severe among the Philadelphia-negative chronic myeloproliferative neoplasms (MPNs). It may present as primary disease (PMF) or secondary to essential thrombocythemia or polycythemia vera (secondary MF [SMF]). MF is clinically characterized by spleen enlargement, systemic symptoms, and cytopenias, with substantial impact on quality of life and reduced survival.[1,2]

In recent years, several prognostic models have been developed for survival in MF. Particularly, the international prognostic scoring system (IPSS), its dynamic variant (DIPSS), and the Mutation-Enhanced International Prognostic Scoring System for Transplantation-Age Patients (MIPSS)[3] are the most frequently used in patients with PMF,[4,5] whereas the Myelofibrosis Secondary to Polycythemia Vera and Essential Thrombocythemia-Prognostic Model (MYSEC-PM)[6] is specific for patients with SMF. All scores effectively distinguish risk categories, projected to significantly different life expectancies.

Ruxolitinib is the first oral JAK1/JAK2 inhibitor that become available for the treatment of MF-related splenomegaly and symptoms. Ruxolitinib was approved based on the results of the registrative COMFORT studies, which included only intermediate-2 and high-risk patients.[7–9] However, intermediate-1 risk patients may carry a significant burden of disease and are increasingly treated with ruxolitinib in the real-life setting. Moreover, in some European countries (e.g., Germany) approval of ruxolitinib is not restricted to higher risk patients but rather to those with symptomatic disease (even when intermediate-1 or low risk).

Nonetheless, reports describing the use of ruxolitinib in this patient population are still limited, with small cohorts of patients and short follow-up duration. In the expanded-access JUMP trial, 163 IPSS intermediate-1 risk patients received ruxolitinib, with comparable efficacy and toxicity rates.[10,11] In the UK ROBUST prospective trial, 14 intermediate-1 patients proved high rates of spleen response at 6 months (57.1%)[12]; these features were conformed in a previous retrospective Italian study, showing 54.7% spleen response rate at 6 months in 69 intermediate-1 IPSS risk patients.[13]

The RUX-MF study is an independent retrospective clinical study that includes patients who received ruxolitinib according to approved indication from 2013 onward in Italy.

Here, we present a subanalysis of the RUX-MF study focusing on the impact of ruxolitinib on responses, toxicity, and outcomes in patients with intermediate-1 risk MF within real-world clinical practice settings. This analysis also describes data concerning ruxolitinib administration, including ruxolitinib dosing and reasons for treatment discontinuation.

MATERIALS AND METHODS

Patients and study design

After institutional review board approval, the RUX-MF retrospective study collected 1055 patients with MF (PMF: $n = 548$; SMF: $n = 507$) who received ruxolitinib outside clinical trials in hematology centers that are dedicated to the treatment of MF. All patients were in chronic phase at ruxolitinib start.

The list of the participating centers is available in Supporting Information S1: Appendix. Characteristics of the data collection have been previously detailed.[14]

All patients were followed from 2013 until death or to data cutoff (February 2, 2024).

Definitions

Diagnoses of PMF and SMF were made according to 2016 World Health Organization criteria and International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT)[15] criteria, respectively.[16]

The risk category was assessed at the time patients started on ruxolitinib according to the DIPSS for PMF[17] and to MYSEC-PM for SMF.[6] Histologic examination was performed at local institutions; fibrosis was graded according to the European Consensus Grading

System.[18] Unfavorable karyotype was categorized as previously described.[17] Triple-negative patients had no mutations in the three driver genes (*JAK2*, *CALR*, and *MPL*). Blast phase (BP) evolution was defined by blast cells ≥20% in peripheral blood or bone marrow.[19] MF-related symptoms were assessed using the 10-item Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (TSS).[20] Spleen and symptom responses were routinely assessed by spleen palpation and by TSS evaluation, according to 2013 IWG-MRT criteria.[16] High-molecular-risk (HMR) mutations were defined according to MIPSS70-plus version 2.0 (*IDH1/2*, *ASXL-1*, *SRSF2*, *EZH2*, *U2AF1*^{Q157R}).[21]

Anemia and thrombocytopenia were graded according to Common Terminology Criteria for Adverse Events.[22] Treatment-emergent anemia and thrombocytopenia are defined as worsening of anemia/thrombocytopenia grade compared to baseline. Particularly, treatment-emergent anemia and thrombocytopenia grade 3-4 could occur only in patients with hemoglobin >8 g/dL in absence of red blood cell transfusion requirement and platelets >50 x 10^9/L at ruxolitinib start.

Ethical aspects

The RUX-MF study was performed in accordance with the guidelines of the institutional review boards of the participating centers and the standards of the Helsinki Declaration. The promoter of this study was the IRCCS Azienda Ospedaliero-Universitaria S. Orsola-Malpighi, Bologna, which obtained approval from the Area Vasta Emilia Centro Ethics Committee (approval file number: 048/2022/Oss/AOUBo). The study was approved by the local ethics committee of participating centers (protocol code: RUX-MF) and has no commercial support.

Statistical analysis

Statistical analysis was performed at the biostatistics laboratory of the MPN Unit at the Institute of Hematology "L. and A. Seràgnoli," IRCCS Azienda Ospedaliero-Universitaria di Bologna.

Continuous variables have been summarized by their median and range, and categorical variables by count and relative frequency (%) of each category. Comparisons of quantitative variables between anemia groups were performed by Wilcoxon-Mann-Whitney rank-sum test, whereas association between categorical variables was tested by the χ^2 test.

Spleen and symptom responses were assessed by palpation and by routine 10-item Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score evaluation, respectively, according to 2013 IWG-MRT/ELN criteria.[23]

Event-free survival (EFS) and overall survival (OS) were calculated by Kaplan–Meier curves from the date of ruxolitinib start to the date of BP evolution, drug discontinuation, death, or last contact (EFS) or to the date of death or last contact (OS), whichever came first. A log-rank test was applied to compare survival times. Patients who underwent allogeneic stem cell transplantation (ASCT) were censored at the time of transplant. In addition, EFS and OS were calculated using Cox proportional hazards regression survivor plot adjusted for patients age at ruxolitinib start.

To assess factors associated with spleen/symptoms response, OS, and EFS, the following baseline variables, selected on the basis of clinical plausibility, have been explored using a logistic regression (spleen and symptom responses) and a Cox regression (OS and EFS) model[1]: hemoglobin (Hb) < 10 g/dL[2]; platelet count (PLT) <100 × 10^9/L[3]; white blood cells (WBC) >25 × 10^9/L[4]; peripheral blasts ≥1%[5]; age ≥70 years[6]; TSS ≥20[7]; spleen palpable at > 10 cm below left costal margin (BLCM)[8]; presence of HMR mutations[9]; presence of cytopenia (defined as at least one of Hb < 10 g/dL; PLT <100 x 10^9/L; WBC <4 x 10^9/L)[10]; lower than expected ruxolitinib dose, based on platelet count. In addition,[11] absence of spleen response at 6 months was explored in the evaluation of OS and EFS. Pearson's correlation test was performed to investigate a relationship between these factors. Because data on HMR mutations were available only in a fraction of patients, all analyses have been performed with and without this variable. Separate analyses for PMF and SMF patients were also performed.

Logistic regression and Cox proportional hazard models were used to evaluate in univariate and multivariate analysis predictors of spleen response at 6 months and outcomes, respectively.

A Poisson regression model was applied to calculate the incidence rate ratio (IRR) of blast phase evolution and ruxolitinib discontinuation. The IRR was described as the number of events per 100 patient-years (%p-y).

For all tested hypotheses, two-tailed p values < .05 were considered significant. Statistical analyses were performed using STATA Software, 15.1 (StataCorp LP, College Station, Texas).

RESULTS

Study cohort

At baseline, 595 (56.2%) patients were at intermediate-1 risk according to DIPSS or MYSEC-PM: 291 PMF patients (of 548 PMF, 53.1%) and 304 SMF patients (of 507 SMF, 60.1%). Overall, 460 (43.8%) patients were intermediate-2/high risk. Notably, the percentage of patients at intermediate-1 risk was almost superimposable using the DIPSS in all patients (PMF and SMF) (54.8%), whereas it decreased significantly using the IPSS score (34.9%).

In the 595 intermediate-1 patients, spleen was palpable at <5 cm, between 5 and 10 cm, and >10 cm BLCM in 5.9%, 54.4%, and 39.7% of patients, respectively; 300 (54.1%) patients were highly symptomatic (TSS ≥20) at baseline. HMR mutations were detected in 77/167 evaluable patients. Overall, 101 (19.2%) patients presented at least one cytopenia (Hb < 10 g/dL: n.36; PLT <100 x 10^9/L: $n = 43$; WBC <4 x 10^9/L: $n = 40$).

As expected, the baseline clinical-laboratory features including anemia, thrombocytopenia, circulating blasts, splenomegaly, and symptoms were significantly worse in intermediate-2/high risk

compared to the intermediate-1 risk patients. Also, HMR mutations were significantly more frequent in higher-risk patients (60.8% vs 46.1%, $p = .02$). (Table 1).

The dosing of ruxolitinib was overall comparable in the two cohorts in terms of median initial dose and percentage of patients who required ruxolitinib dose reductions at the 3- and 6-month timepoints and any reductions during the first 12 months.

More specifically, 28.1% intermediate-1 and 24.2% intermediate-2 patients ($p = .16$) had a dose decrease at 3 months; these figures were 35.5% and 29.8%, respectively, at 6 months. At baseline, ruxolitinib was underdosed compared to platelet count in 42.1% and 39.3% of intermediate-1 and intermediate-2/high-risk patients, respectively ($p = .36$).

Spleen and symptom response by risk category

In intermediate-1 risk patients, spleen and symptom response rates at 6 months were 26.8% and 67.9%, respectively (Table 1).

Factors associated with spleen response at 6 months were evaluated separately in PMF and SMF patients and with/without HMR mutations (Supplemental Table S1).

In the overall cohort, in multivariable analysis including HMR mutations, absence of HMR maintained significant association (odds ratio [OR], 1.91 [95% CI, 1.02–4.12]; $p = .05$) (Figure 1a). Whereas in multivariable analysis excluding HMR mutations, peripheral blasts <1% remained significant (OR, 1.91 [95% CI, 1.90–3.16]; $p = .01$) (Figure 1b).

The only predictor of symptoms response at 6 months was the use of correct starting ruxolitinib dose (OR, 1.70 [95% CI, 1.14–2.56]; $p = .01$).

In intermediate-2/high-risk patients, the rate of spleen response was only numerically lower compared to intermediate-1 patients (23.3% vs 26.8%, $p = .24$); however, the duration of spleen response was significantly shorter (0.46 vs 2.1 years, respectively; $p = .004$). The rate of symptoms response at 6 months was 59.1%, and significantly lower compared to intermediate-1 risk patients ($p = .01$).

Considering a 30% spleen length reduction in all patients as a spleen response, the global percentage of spleen response at 6 months was 61.8%.

Ruxolitinib safety according to risk category

In intermediate-1 patients, all grades anemia rate at 6 months was 35.6%, whereas treatment-emergent anemia rate was 29.4%. Thrombocytopenia rate was 19.2% (overall) and 14.3% (treatment-emergent).

Hematological toxicity at 6 months was significantly higher in intermediate-2 patients, including anemia/thrombocytopenia overall and treatment-emergent. Treatment-emergent grade 3-4 anemia and thrombocytopenia were also significantly higher in intermediate-2/high risk patients (anemia: 39.8% vs 15.2%, $p < .001$; thrombocytopenia: 4.8% vs 2.3%, $p = .04$).

A total of 166 infectious complications ≥grade 2 occurred after a median time of 1.32 years from ruxolitinib start (range, 0.02–10.37). Frequently diagnosed infections include respiratory tract infections (73 cases, including 29 COVID-19 infections), herpes zoster reactivations (23 cases), urinary tract (21 cases) and gastrointestinal tract (19 cases) infections, herpes simplex mucosal infections, and *Mycobacterium tuberculosis* infections (three cases each). The IRR of infections was 5.45%p-y and was significantly higher in intermediate-2/high risk compared to intermediate-1 patients (7.40 vs 4.33%p-y, $p < .001$). Overall, 49 (29.5%) infections were fatal.

Outcome by risk category

With a median observation time from ruxolitinib start of 4193.8 p-y, 150 (14.2%) of 1055 patients had a blast phase evolution, 543 (51.4%) died, and 692 (65.6%) discontinued ruxolitinib; IRR of these events were 3.7, 12.9, and 21.1%p-y, respectively. As shown in Table 1, IRR of all events were significantly more favorable in intermediate-1 patients.

Ruxolitinib discontinuation rates at 1 and 3 years were 14.8% and 34.6% in intermediate-1 patients and 30.7% and 59.7%, respectively, in intermediate-2/high risk patients. Among the 692 patients who discontinued ruxolitinib, 254 (36.7%) discontinued because of MF persistence/progression, including lack/loss of response; 106 (15.3%) because of blast phase evolution; 181 (26.2%) discontinued because of ruxolitinib-related toxicity (hematological, $n = 111$; nonhematological, $n = 70$); 50 (7.2%) received ASCT; 101 (14.6%) discontinued for causes unrelated to MF or treatment. Notably, in 196 (28.3%) patients, the date of ruxolitinib discontinuation coincided with the date of death; death on therapy was significantly higher in intermediate-2/high-risk patients.

OS rate at 5 years was significantly lower in intermediate-2/high-risk patients compared to intermediate-1 (38.1% vs 66.9%, $p < .001$), with a median OS of 3.82 (95% CI, 3.13–4.33) and 7.97 (95% CI, 7.11–9.31) years, respectively (Figure 2a). Likewise, EFS rate at 5 years was significantly lower in intermediate-2/high-risk patients compared to intermediate-1 (19.5% vs 47.8%, $p < .001$), with a median EFS of 1.97 (95% CI, 1.66–2.32) and 4.56 (95% CI, 3.92–5.38), respectively (Figure 2b). These figures remained significant after adjustment for older (≥70 years) age (Supplemental Figure 1a and 1b, respectively).

Focusing on the intermediate-1 cohort, HMR mutations and age ≥70 years were the strongest predictors for poorer OS (HMR, hazard ratio [HR], 2.14, $p = .02$; older age, HR, 2.69; $p < 0.001$) and EFS (HMR, HR, 2.00; $p = .002$; older age, HR, 1.50; $p < .001$].

In transplant-age (<70 years) intermediate-1 patients, in multivariable analysis including HMR mutations, hemoglobin <10 g/dL maintained significance for poorer EFS (HR, 3.43 [95% CI, 1.15–10.3], $p = .03$), whereas absence of spleen response at 6 months preserved

TABLE 1 Baseline characteristics and outcome measures according to DIPSS/MYSEC-PM risk.

	Intermediate-1 (n = 595)	Intermediate-2/high (n = 460)	p-value
Age, median (range), years	65.3 (24.0–88.2)	71.8 (39.4–92.6)	<.001[a]
Male, *n* (%)	332 (55.8%)	267 (58.0%)	.47
Type of MF, *n* (%)			
PMF	291 (48.9%)	257 (55.9%)	.03[a]
SMF	304 (51.1%)	203 (44.1%)	
RUX daily dose, n. (%)			.22
5–10 mg twice daily	221 (37.1%)	188 (40.8%)	
15–20 mg twice daily	374 (62.9%)	272 (59.2%)	
Lower dose than prescribing, *n* (%)	248/589 (42.1%)	180/458 (39.3%)	.36
≥1 dose reduction during the first 12 months of therapy, *n* (%)	134/285 (47.0%)	104/253 (37.7%)	.17
Driver mutation, *n* (%)			.006[a]
JAK2	467 (81.6%)	323 (73.9%)	
CALR	72 (12.6%)	64 (14.7%)	
MPL	10 (1.8%)	17 (3.9%)	
TN	23 (4.0%)	33 (7.6%)	
Unfavorable karyotype, *n* (%)	23/291 (7.9%)	22/237 (9.3%)	.57
HMR mutations, *n* (%)	77/167 (46.1%)	65/107 (60.8%)	.02[a]
Platelet count < 100 x 10^9/L, *n* (%)	43 (7.2%)	63 (13.7%)	<001[a]
Leukocyte count >25 x 10^9/L, *n* (%)	51 (8.6%)	107 (23.3%)	<0.001[a]
Hemoglobin <10 g/dL, *n* (%)	36 (6.1%)	357 (77.6%)	<.001[a]
Transfusion requirement, *n* (%)	30/585 (5.1%)	170/456 (37.3%)	<.001[a]
Blasts ≥ 1%, *n* (%)	141/568 (24.8%)	245 (53.9%)	<.001[a]
Spleen length, median (range), cm BLCM	9 (0–35)	11 (0–31)	<.001[a]
Spleen > 10 cm, *n* (%)	231/590 (39.2%)	233/454 (51.3%)	<.001[a]
TSS, mean (range)	23.5 (0–100)	29.3 (0–100)	<.001[a]
TSS ≥ 20, *n* (%)	300 (54.1%)	304 (70.4%)	<.001[a]
Time to RUX start from MF diagnosis, median (range), years	0.8 (0–32.9)	0.9 (0–31.7)	.79
Spleen response at 6 months, *n* (%)	135/503 (26.8%)	88/337 (23.3%)	.24
Spleen response duration, median (range), years	2.1 (0.1-11.3)	0.46 (0.1-8.8)	.004[a]
Symptoms response at 6 months, *n* (%)	296/436 (67.9%)	207/350 (59.1%)	.01[a]
Any grade hematological toxicity at 6 months			
Overall anemia, *n* (%)	188/528 (35.6%)	292/397 (73.6%)	<.001[a]
Treatment-emergent anemia, *n* (%)	146/497 (29.4%)	39/90 (43.3%)	.009[a]
Overall thrombocytopenia, *n* (%)	101/527 (19.2%)	114/397 (28.7%)	.001[a]
Treatment-emergent thrombocytopenia, *n* (%)	71/495 (14.3%)	78/359 (21.7%)	.005[a]
Blast phase evolution, *n* (%)	73 (12.3%)	77 (16.7%)	.04[a]
Incidence rate of leukemic transformation (%p-y)	2.9	5.0	<.001[a]

(Continues)

TABLE 1 (Continued)

	Intermediate-1 (n = 595)	Intermediate-2/high (n = 460)	p-value
RUX discontinuation	326 (54.8%)	366 (79.6%)	<.001[a]
Incident rate of RUX discontinuation (% p-y)	15.3	30.9	<.001[a]
Death, n (%)	229 (38.5%)	314 (68.3%)	<.001[a]
Overall survival at 3 years	80.0%	47.4%	<.001[a]
Event-free survival at 3 years	60.1%	36.9%	<.001[a]

Abbreviations: BLCM, below left costal margin; DIPSS, international prognostic scoring system, dynamic variant; HMR, high molecular risk; MF, myelofibrosis; MYSEC-PM, Myelofibrosis Secondary to Polycythemia Vera and Essential Thrombocythemia-Prognostic Model; PMF, primary myelofibrosis; RUX, ruxolitinib; TSS, Total Symptoms Score; %p-y, percent person-years.

[a]Indicates the statistically significant of the p-values.

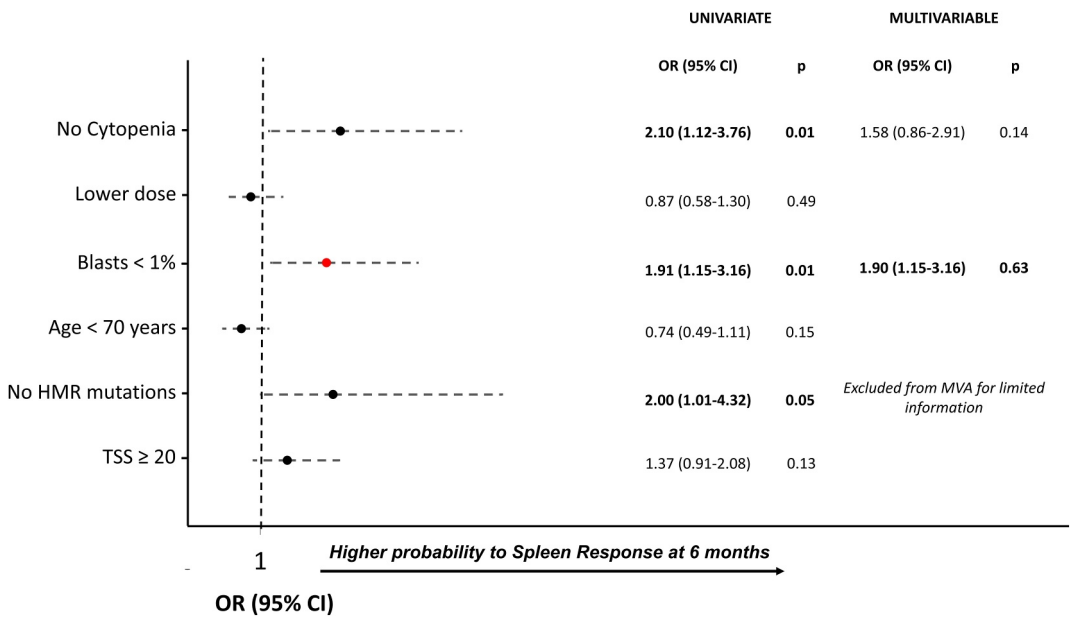

FIGURE 1 Characteristics associated to spleen response at 6 months in intermediate-1 patients.* *Using Pearson's correlation test: white blood cell (WBC) count <25 x 10^9/L correlates with blasts <1%; platelet (PLT) count <100 x 10^9/L; and hemoglobin (Hb) <10 g/dL correlate with no cytopenia. (a) Including high-molecular risk (HMR) mutations; (b) excluding HMR mutations.

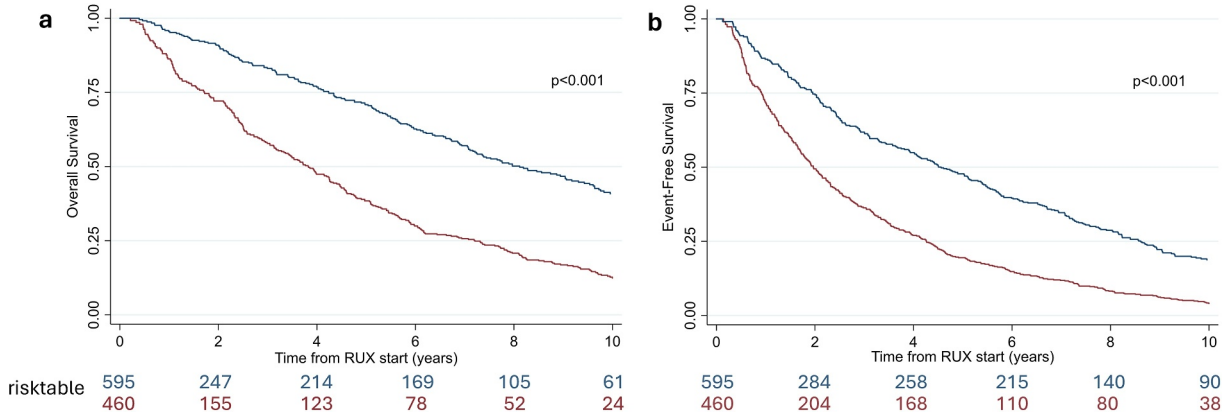

FIGURE 2 Overall survival (a) and event-free survival (b) of intermediate-1 (blue line) compared to intermediate-2/high-risk patients (red line).

significant association with both outcomes (OS, HR, 5.68 [95% CI, 1.71–19.09], $p = .005$; EFS, HR, 2.00 [95% CI. 1.06–3.75], $p = .03$).

In multivariable analysis excluding HMR mutations, hemoglobin <10 g/dL retained significance for both outcomes (OS, HR, 2.36 [95% CI, 1.33–4.18, $p = .003$; EFS, HR, 2.19 [95% CI, 1.39–3.48], p = 0.001), whereas absence of spleen response at 6 months maintained association with poorer EFS (HR, 1.81 [95% CI, 1.24–2.66], $p = .002$).

Data on predictors of OS/EFS in PMF and SMF patients, and with/without including HMR mutations, have been reported in Supplemental Table 1.

DISCUSSION

The first finding of this analysis, which includes a very large cohort of intermediate-1 patients homogeneously treated with ruxolitinib, is that splenomegaly and symptoms may be extremely burdensome also in lower risk patients, with approximately 40% of such patients starting ruxolitinib with a large splenomegaly and a high symptom score. This finding again supports how the clinical phenotype of MF should guide the medical therapeutic approach, without being influenced by the prognostic risk category, which, in contrast, is essential instead for the transplant decision.

In intermediate-1 patients, spleen and symptoms responses were more frequent and/or durable compared to intermediate-2/high-risk patients. Improved efficacy was not related to higher ruxolitinib doses, which was comparable across risk categories, despite intermediate-1 patients displaying better baseline hematological features. However, rates of spleen responses at 6 months (26% in the overall cohort) were lower compared to previous reports both from prospective trials (COMFORT-1: 41.9%; COMFORT-2: 32%; JUMP: 56.5%)[24–26] and retrospective observations with fewer patients included.[27,28] Multiple reasons may explain this difference in spleen response rates. First, in the present analysis, spleen response is assessed according to IWG-MRT criteria, which require different spleen length reductions based on degree of baseline splenomegaly. In our cohort, 6% of patients had no spleen palpable at >5 cm BLCM: these patients could have been included in clinical studies using magnetic resonance imaging for splenomegaly assessment, possibly having a spleen volume >450 cm^3, and are likely to respond well, but have been excluded by the efficacy analysis in this paper. Almost 40% of patients had spleen >10 cm BLCM and are less likely to respond.[29] Second, the direct correspondence between spleen volume responses of at least 35% from baseline (which does not take into account the magnitude of baseline splenomegaly and is based on imaging rather than physical palpation) and IWG-MRT–defined spleen response has never been fully validated and may not be confirmed for all spleen categories (5-10 cm BLCM and >10 cm BLCM). In fact, if we considered a 30% spleen reduction as a spleen response, the global percentage would increase to 61.8%. Finally, errors in spleen assessment cannot be completely excluded as this is a real-world study. Nonetheless, similar spleen volume responses of at least 35% from baseline rates at 24 weeks were observed in the prospective randomized Simplify-1 study comparing momelotinib (27%) and ruxolitinib (29%) in the front-line setting..[30,31]

Lower-than-expected ruxolitinib doses compared to prescribing information were used a not-negligible fraction of patients, regardless of risk category. Ruxolitinib underdosing may compromise efficacy and may be responsible for these results below expectations[29,32]; indeed, patients treated with full ruxolitinib doses had significantly higher rates of symptoms response.

Intermediate-1 patients also showed lower toxicity rates compared to higher risk patients. This improved safety was related both to reduced hematological and infectious adverse events. The association between ruxolitinib and infections is mainly due to down-regulation of the production of proinflammatory cytokines mediated by JAK1 inhibition, resulting in decreased immune surveillance.[33] Infectious complications are more frequent in the first months of ruxolitinib therapy and in patients with previous infections.[34] Here, we also demonstrate that disease burden and risk category may significantly influence the frequency of these events, that resulted to be fatal in 49 patients in our cohort, accounting for cause of death in 9% of cases.

Globally, BP evolution incidence was 14.2%. This figure is higher than the 10.6% reported by Mora et al.,[35] which included patients evaluated from diagnosis and not requiring ruxolitinib in most cases. Here, we analyzed a cohort of patients with highly symptomatic disease and carrying HMR mutations in approximately 50% of the cases. In addition, these patients are observed from the start of ruxolitinib, which may have been initiated many years after diagnosis. Because blast phase transformation is a late event with higher probability in patients with high disease burden, this may explain the relatively high incidence of blast phase evolution that we have observed, with a median follow-up from ruxolitinib start of 3.8 years. However, it is important to note that the IRR, which considers the impact of observation time, of blast phase evolution was 2.9 in intermediate-1 and 5%p-y in intermediate-2 high-risk patients, confirming a less aggressive disease in lower risk patients.

Notably, intermediate-1 patients had lower rates of ruxolitinib discontinuation, and better OS and EGS rates. Globally, 54.8% of intermediate-1 patients discontinued ruxolitinib. This relatively high incidence of discontinuation, which is associated with worse prognosis, may have also greatly contributed to poor EFS.[36–38]

Presence of HMR mutations, cytopenia, and peripheral blasts identified less responsive intermediate-1 patients.

These findings are aligned with previous observations and reinforces the indication for NGS evaluation and careful clinical-hematological monitoring in intermediate-1 risk patients. Indeed, lower risk patients with HMR mutations, cytopenia, and/or peripheral blasts may benefit from alternative therapeutic strategies, including allogeneic transplantation.[39] Also, in transplant-age intermediate-1 patients, baseline anemia and absence of spleen response at 6 months were the strongest predictors of worse outcome: these factors may also be useful in guiding the decision about ASCT.

CONCLUSIONS

Finally, outcome measures, including OS, EFS, and rates of ruxolitinib discontinuations were significantly better in intermediate-1 patients, even after adjustment for age. This may be mainly related to lower disease burden and better hematological status at baseline. Overall, these data confirm the benefits of ruxolitinib in patients with less advanced disease.[29,40,41]

AUTHOR CONTRIBUTIONS

Francesca Palandri: Conceptualization; Investigation; Funding acquisition; Writing - original draft; Writing - review & editing; Data curation; Resources; and Visualization. **Elena M. Elli**: Conceptualization; Investigation; Writing - original draft; Visualization; Writing - review & editing; Resources; and Data curation. **Erika Morsia**: Conceptualization; Investigation; Writing - original draft; Visualization; Writing - review & editing; Resources; and Data curation. **Giulia Benevolo**: Conceptualization; Investigation; Writing - original draft; Visualization; Writing - review & editing; Resources; and Data curation. **Mario Tiribelli**: Conceptualization; Writing - original draft; Investigation; Visualization; Writing - review & editing; Resources; and Data curation. **Eloise Beggiato**: Investigation; Writing - review & editing; and Resources. **Massimiliano Bonifacio**: Investigation; Writing - review & editing; and Resources. **Mirko Farina**: Investigation; Writing - review & editing; and Resources. **Bruno Martino**: Investigation; Writing - review & editing; and Resources. **Giovanni Caocci**: Investigation; Writing - review & editing; and Resources. **Novella Pugliese**: Investigation; Writing - review & editing; and Resources. **Alessia Tieghi**: Investigation; Writing - review & editing; and Resources. **Monica Crugnola**: Investigation; Writing - review & editing; and Resources. **Gianni Binotto**: Investigation; Writing - review & editing; and Resources. **Francesco Cavazzini**: Investigation; Writing - review & editing; and Resources. **Elisabetta Abruzzese**: Investigation; Writing - review & editing; and Resources. **Alessandra Iurlo**: Investigation; Writing - review & editing; and Resources. **Alessandro Isidori**: Investigation; Writing - review & editing; and Resources. **Costanza Bosi**: Investigation; Writing - review & editing; and Resources. **Veronica Guglielmana**: Investigation; Writing - review & editing; and Resources. **Marta Venturi**: Investigation; Writing - review & editing; and Resources. **Alessandra Dedola**: Investigation; Writing - review & editing; and Resources. **Michele Loffredo**: Investigation; Writing - review & editing; and Resources. **Gabriele Fontana**: Investigation; Writing - review & editing; and Resources. **Andrea Duminuco**: Investigation; Writing - review & editing; and Resources. **Alessia Moioli**: Investigation; Writing - review & editing; and Resources. **Luca Tosoni**: Investigation; Writing - review & editing; and Resources. **Emilia Scalzulli**: Investigation; Writing - review & editing; and Resources. **Daniele Cattaneo**: Investigation; Writing - review & editing; and Resources. **Roberto M. Lemoli**: Investigation; Writing - review & editing; and Resources. **Daniela Cilloni**: Investigation; Writing - review & editing; and Resources. **Monica Bocchia**: Investigation; Writing - review & editing; and Resources. **Fabrizio Pane**: Investigation; Writing - review & editing; and Resources. **Florian H. Heidel**: Writing - review & editing. **Nicola Vianelli**: Investigation; Writing - review & editing; and Resources. **Michele Cavo**: Investigation; Writing - review & editing; and Resources. **Giuseppe A. Palumbo**: Investigation; Conceptualization; Writing - original draft; Writing - review & editing; Visualization; Resources; and Data curation. **Filippo Branzanti**: Writing - original draft; Writing - review & editing; Data curation; Formal analysis; and Visualization. **Massimo Breccia**: Conceptualization; Writing - original draft; Writing - review & editing; Visualization; Data curation; and Resources.

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CONFLICT OF INTEREST STATEMENT

Francesca Palandri reports consultancy and honoraria from Novartis, Celgene, AOP, Sierra Oncology, and CTI. Giulia Benevolo reports honoraria from Novartis, Janssen, Amgen, Takeda, and BMS. Alessandra Iurlo reports honoraria from Novartis, BMS, Pfizer, and Incyte. Massimo Breccia reports honoraria from Novartis, BMS, Pfizer, Incyte. Massimiliano Bonifacio reports honoraria from Novartis, BMS, Pfizer, and Incyte. Monica Crugnola reports honoraria from Novartis and Amgen. Gianni Binotto reports honoraria from Novartis, Incyte, BMS-Celgene, and Pfizer. Roberto M. Lemoli reports honoraria from Jazz, Pfizer, AbbVie, BMS, Sanofi, and StemLine. Fabrizio Pane reports honoraria from Incyte, Novartis, Jazz, BMS-Celgene, Amgen, and Gilead. Michele Cavo acted as consultant and received honoraria from Jannsen, BMS Celgene, SanoFI, GlaxoSmithKline, Takeda, Amgen, Oncopeptides, AbbVie, Karyopharm, and Adaptive. Giuseppe A. Palumbo reports consultancy and honoraria from Abbvie, AOP, AstraZeneca, BMS, Incyte, GSK, Morphosys, and Novartis. Michele Cavo acted as consultant and received honoraria from Jannsen, BMS Celgene, SanoFI, GlaxoSmithKline, Takeda, Amgen, Oncopeptides, AbbVie, Karyopharm, and Adaptive.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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