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ORIGINAL ARTICLE

Dosing and clinical outcomes of ruxolitinib in patients with myelofibrosis in a real-world setting: Interim results of the Italian observational study (ROMEI)

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Abstract

Background: Myelofibrosis (MF) significantly impacts patients' overall survival (OS) and quality of life (QOL). This prospective study analyzed ruxolitinib dosing patterns and associated clinical outcomes in patients with MF over 12 months.

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Massimo Breccia, Francesca Palandri, Paola Guglielmelli and Francesco Passamonti share equal contribution.

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Methods: ROMEI, a multicenter, observational, ongoing study, enrolled 508 adult patients with MF treated with ruxolitinib. For the current interim analysis, eligible patients with baseline platelet values were categorized into two groups based on ruxolitinib starting dosage: as expected (AsEx, $n = 174$) and lower than expected (LtEx, $n = 132$); ruxolitinib dose changes, interruptions and time to permanent discontinuation were analyzed, along with symptoms response, health-related QOL scores, spleen response, OS, and safety.

Results: Forty-three percent of patients started at a lower-than-expected dose. Both groups showed reduction in average daily ruxolitinib doses over 12 months. Symptoms response rate was similar in both groups at week 48 (40.8% AsEx vs 40.9% LtEx). The AsEx group demonstrated higher spleen response rates at both 24 weeks (50.0% vs 30.2%) and 48 weeks (57.7% vs 45.8%) with a shorter median time to first response (3.3 vs 11.1 months, $p = .019$) when compared to the LtEx group. Both groups showed upward trends in health-related QOL values. Estimated median OS was not reached for the AsEx group versus 4.7 years in the LtEx group ($p = .014$). Adverse events were reported in 87.4% and 84.9% of patients in the AsEx and LtEx groups, respectively.

Conclusions: The ROMEI study demonstrated the importance of optimal ruxolitinib dosage in patients with MF for maximum effectiveness and improved OS, with manageable safety.

KEYWORDS
dosing patterns, lower recommended dose, myelofibrosis, ruxolitinib, ROMEI study, spleen response

INTRODUCTION

Myelofibrosis (MF), a chronic myeloproliferative neoplasm, occurs because of constitutive activation of the JAK/STAT pathway, resulting in ineffective clonal hematopoiesis, bone marrow fibrosis, extramedullary hematopoiesis, splenomegaly, and has a considerable symptom burden.[1–3] The therapeutic goals for MF primarily focus on alleviating the clinical manifestations of MF, thereby increasing the quality of life (QOL) and extending overall survival (OS).[4–6]

Ruxolitinib is the first oral JAK1/JAK2 inhibitor approved for MF treatment with a well-consolidated efficacy and manageable safety profile.[7,8] In the more than 10 years since JAK1/JAK2 approval, controlled clinical studies, pooled analyses, and real-world data have demonstrated the efficacy of ruxolitinib in spleen volume reduction, and symptom resolution, ultimately improving OS when compared with best available therapy or controls.[7,8] The expected optimal starting dose for ruxolitinib is based on the baseline platelet count, with further dose titration (up to 25 mg twice daily) aiming to maximize efficacy, which has been shown to be dose dependent in clinical studies.[8,9]

The ongoing Ruxolitinib Observational study in Myelofibrosis Treated patiEnts in Italy (ROMEI) study (CINC424AIT04) is an observational study of ruxolitinib-treated patients with MF in Italy.[10,11] The study confirmed in its 24-week findings, the beneficial effect of ruxolitinib in improving symptoms and QOL (primary endpoints) and reducing spleen size. A favorable safety profile was observed, consistent with results from clinical studies.[7,10] The interim results in the ROMEI study indicated high adherence (60%–75%) to oral ruxolitinib at 24 weeks.[12] However, one third (25%–40%) of the patients receiving ruxolitinib may be undertreated owing to suboptimal adherence,[12] potentially undermining disease control and survival outcomes.[13]

This interim analysis (IA) investigated ruxolitinib dosing patterns and correlations with clinical outcomes in patients who completed the first 12 months of follow-up or prematurely discontinued the ROMEI study.

METHODS

Study design and definition of subgroup and endpoints

ROMEI is an ongoing national, multicentric, observational prospective study conducted across 51 centers in Italy.[14] The study enrolled 508 adult patients (between April 2017 and May 2022), who were diagnosed with primary or secondary MF, naive to ruxolitinib, and starting ruxolitinib as per clinical practice and according to the approved label.[9,12] Patient follow-up was conducted for up to 5 years. At the time of enrollment, ruxolitinib was the only JAK inhibitor approved.

Eligible patients who had baseline platelets counts available were stratified into two groups according to the assigned ruxolitinib starting dose versus expected dose as per the approved label: (1) as expected (AsEx) group and (2) lower than expected (LtEx) group (Table 1). Details of dosing based on platelet count class are presented in supplementary Table S1.

The current IA focuses on the ruxolitinib dosing pattern and its impact on clinical outcomes. Ruxolitinib starting dosages, changes (number and reasons), temporary interruptions, and permanent discontinuation were analyzed. The primary aim was to assess the patient subgroups for changes in both symptoms and health-related QOL (HRQOL) during ruxolitinib treatment evaluated using Myeloproliferative Neoplasm 10 total symptom score (MPN-10 TSS) and EuroQol5-Dimension 5-Level (EQ-5D-5L) score. Secondary efficacy endpoints included changes in spleen length and OS. Safety analyses evaluated adverse events (AEs; hematologic and nonhematologic).

This study followed the principles of the Declaration of Helsinki and Good Clinical Practice standards of the International Council for Harmonization. The study plan was approved by an independent ethics committee or institutional review board at each site. All study participants provided informed consent before data collection.

Statistical analysis

The eligible population comprised all enrolled patients considered for the IA who did not have missing MPN-10 TSS and EQ-5D-5L scores at baseline visits and received at least one dose of the study medication. Eligible patients with available baseline platelet counts were grouped by ruxolitinib's expected starting dose group.

The proportion of patients with symptoms response was evaluated and summarized at each visit until visit 7, focusing mainly at 24 (visit 5) and 48 (visit 7) weeks. HRQOL was analyzed in terms of percentages for each answer level of each EQ-5D-5L dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at baseline, weeks 24 and 48 and in terms of EQ visual analogue scale (VAS) values at each visit until visit 7. The Last Observation Carried Forward method was used to impute missing values for the MPN-10 TSS, EQ-5D-5L dimensions, and EQ VAS value. The proportion of patients with spleen response was evaluated and summarized at each visit focusing on weeks 24 (visit 5) and 48 (visit 7).

Data on ruxolitinib intake were analyzed within 12 months (i.e., focusing on dosage reported within visit 7 date or ruxolitinib start date plus 336 days, corresponding to 7 days $\times$ 4 weeks $\times$ 12 months), covering mean daily dose, dose adjustment, temporary interruption, and permanent discontinuation.

The Kaplan–Meier product-limit method was used to estimate time-to-event outcomes.

Further definitions and details are available in the supplementary file.

RESULTS

Patient disposition

At the data cutoff date (December 31, 2022), 359 patients with MF were eligible for inclusion in the analysis. Most (43.7%) patients started on ruxolitinib 20 mg twice daily, 20.6% on 15 mg twice daily, 22.3% on 10 mg twice daily, and only 12.0% on 5 mg twice daily; the remaining 1.4% of patients started on a different dosage (e.g., 5 mg/day, 11.3 mg/day, 15 mg/day). Forty-three percent of patients initiated the treatment at a lower starting dose that expected. Patient disposition is presented in Figure 1.

Demographic and baseline characteristics

Demographic and baseline characteristics are presented in Table 2. Median patient age and the proportion of patients aged >65 years were higher in the LtEx group than in the AsEx group ($p = .001$ and $p = .003$, respectively). The proportion of patients with a primary MF diagnosis was 51.2% and 62.1% in the AsEx and LtEx groups, respectively. In both AsEx and LtEx groups, most patients started ruxolitinib

TABLE 1 Distribution of patients according to the expected starting dose group (baseline platelet count).

Ruxolitinib expected starting dose group	Platelets at baseline (10^9/L) class	Starting dose	*N* (%)
As expected (AsEx, *N* = 174)	50–<75	5 mg bid (10 mg/day)	8 (4.6)
	75–<100	10 mg bid (20 mg/day)	5 (2.9)
	100–200	15 mg bid (30 mg/day)	24 (13.8)
	>200	20 mg bid (40 mg/day)	137 (78.7)
Lower than expected (LtEx; *N* = 132)	50–<75	<5 mg bid (<10 mg/day)	0
	75–<100	<10 mg bid (<20 mg/day)	10 (7.6)
	100–200	<15 mg bid (<30 mg/day)	29 (22.0)
	>200	<20 mg bid (<40 mg/day)	93 (70.5)

bid, twice daily.

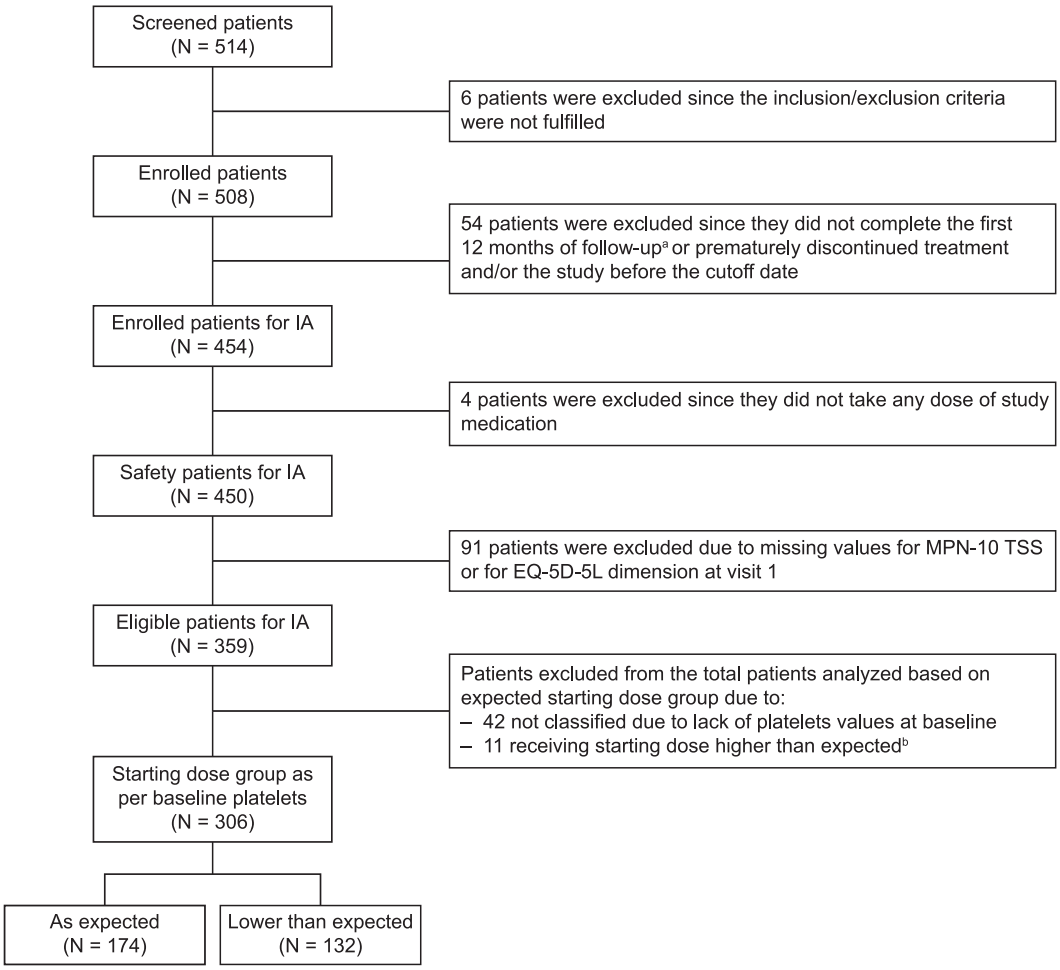

FIGURE 1 Patient disposition in the ROMEI study [a]patients who performed week 48 or later within the cutoff date). [b]Eleven patients receiving starting dose higher than expected. They were excluded because very few patients belong to this group according to the ruxolitinib dose and platelets value at baseline. Note: This interim analysis was performed considering enrolled patients who completed the first 12 months of follow -up (i.e., patients who performed week 48 [visit 7] or later or patients who discontinued ruxolitinib treatment before but still under observation) or prematurely discontinued the study by December 31, 2022 (i.e., cutoff date of the present interim analysis). EQ-5D-5L indicates EuroQol 5 Dimension 5 Level; IA, interim analysis; MPN-10, myeloproliferative neoplasm-10; TSS, total symptom score.

within 12 months of MF diagnosis (62.1% and 56.1%, respectively), whereas 30.5% and 35.6% of patients started ruxolitinib treatment ≥24 months after diagnosis, respectively. Both groups also had a similar proportion of patients with a spleen length ≥10 cm (AsEx group 35.2% vs LtEx group 37.7%; $p = .672$). Median hemoglobin (Hb) and platelet counts were significantly lower in the LtEx group than in the AsEx group (10.8 g/dL vs 11.4 g/dL, $p = .009$ and 290 $\times$ 10^9/L vs 354 $\times$ 10^9/L, respectively, $p = .021$). Concomitant conditions in medical history did not substantially differ between the two groups (Table S2 in supplementary).

Ruxolitinib treatment characteristics–dosing patterns

In the AsEx group, the mean daily dose during month 1 was slightly higher (i.e., 36.0 mg/day), which then decreased and stabilized with only small fluctuations from month 2 (i.e., 31.0 mg/day) to month 12 (25.3 mg/day). In the LtEx group, the mean daily dose slightly decreased from month 1 (i.e., 20.7 mg/day) to month 12 (i.e., 17.6 mg/day; Figure 2).

On average, both platelet counts and Hb levels at baseline were slightly higher in the AsEx group than in the LtEx group (Figure S1 in supplementary). A Sankey diagram was developed to understand the flow between the expected dose groups during the first 12 months (Figure S2 in supplementary).

Within the first 12 months, ruxolitinib dose adjustments were similar between the groups: in the AsEx group, the mean number of dose adjustments was 2.2 ± 2.3 (range, 0.0–12.0); 131 patients (75.3%) had at least one dose adjustment and 72 patients (41.4%) had a dose increment, whereas 125 patients (71.8%) had a dose reduction. In the LtEx group, the mean number of dose adjustments was 2.0 ± 2.0 (range, 0.0–9.0); 101 patients (76.5%) had at least one dose adjustment and 73 patients (55.3%) had a dose increment, whereas 77 patients (58.3%) had a dose reduction.

TABLE 2 Demographic and clinical baseline characteristics by ruxolitinib expected starting dose group in the eligible population.

Demographic	AsEx group (n = 174)	LtEx group (n = 132)	p value
Age (years)			
Median (Q1; Q3)	68.0 (59.0; 74.0)	71.0 (65.0; 77.0)	.001
Age group, *n* (%)			
≤65 years	75 (43.1)	35 (26.5)	.003
>65 years	99 (56.9)	97 (73.5)	
Sex, *n* (%)			
Male	100 (57.5)	71 (53.8)	.520
Female	74 (42.5)	61 (46.2)	
MF diagnosis, *n* (%)			
Primary MF	89 (51.2)	82 (62.1)	.056
Secondary MF	85 (48.9)	50 (37.9)	
Time from MF diagnosis to ruxolitinib start (months)			
Median (Q1; Q3)	4.3 (1.7; 42.4)	6.5 (1.8; 45.7)	.356
Time from MF diagnosis to ruxolitinib start (months) classes, *n* (%)			
<12 months	108 (62.1)	74 (56.1)	.567
≥12 to <24 months	13 (7.5)	11 (8.3)	
≥24 months	53 (30.5)	47 (35.6)	
Bone marrow biopsy available, *n* (%)	164 (94.3)	125 (94.7)	
Grade of bone marrow fibrosis, *n* (%)[a]			
0	8 (4.9)	11 (8.8)	.545
1	39 (23.8)	25 (20.0)	
2	70 (42.7)	54 (43.2)	
3	47 (28.7)	35 (28.0)	
Prior transfusions performed (PRBC), *n* (%)			
No	159 (91.4)	100 (75.8)	<.001
Yes	15 (8.6)	32 (24.2)	
International Prognostic Scoring System (IPSS) available, *n* (%)	170 (97.7)	122 (92.4)	
Low risk[a]	5 (2.9)	1 (0.8)	.587*
Intermediate-1 risk[a]	56 (32.9)	36 (29.5)	
Intermediate-2 risk[a]	66 (38.8)	51 (41.8)	
High risk[a]	43 (25.3)	34 (27.9)	
Manual palpation of the spleen performed, *n* (%)	159 (91.4)	114 (86.4)	
Spleen length (cm)			
Median (Q1; Q3)	7.0 (5.0; 12.0)	7.0 (5.0; 11.0)	.843
Spleen length class, *n* (%)[a]			
<10 cm	103 (64.8)	71 (62.3)	.672
≥10 cm	56 (35.2)	43 (37.7)	
Hemoglobin at baseline available, *n* (%)	174 (100.0)	130 (98.5)	
Hemoglobin at baseline (g/dL)			
Median (Q1; Q3)	11.4 (10.1; 13.2)	10.8 (8.9; 12.9)	.009

(Continues)

TABLE 2 (Continued)

Demographic	AsEx group (n = 174)	LtEx group (n = 132)	p value
Hemoglobin at baseline (g/dL) class 1, n (%)[a]			
<8 g/dL	7 (4.0)	7 (5.4)	.019
≥ 8 to <10 g/dL	32 (18.4)	43 (33.1)	
≥ 10 to ≤ 12 g/dL	58 (33.3)	38 (29.2)	
>12 g/dL	77 (44.3)	42 (32.3)	
Hemoglobin at baseline (g/dL) class 2, n (%)[a]			
<10 g/dL	39 (22.4)	50 (38.5)	.002
≥10 g/dL	135 (77.6)	80 (61.5)	
Platelets at baseline (10^9/L), n (%)	174 (100.0)	132 (100.0)	
Median (Q1; Q3)	354.0 (213.0; 512.0)	290.0 (171.5; 430.5)	.021
Platelets at baseline (10^9/L) class[a], n (%)			
50–<75	8 (4.6)	0 (0.0)	.003*
75–<100	5 (2.9)	10 (7.6)	
100–200	24 (13.8)	29 (22.0)	
>200	137 (78.7)	93 (70.5)	

Note: p value for continuous variables were derived from Wilcoxon rank-sum test and for categorical variables were derived from chi-squared test. Percentages were computed within each group.

Abbreviations: AsEx, as expected; LtEx, lower than expected; MF, myelofibrosis; PRBC, packed red blood cells; Q1, first quartile; Q3, third quartile.

[a]Percentages were computed within each group considering patients with bone marrow biopsy available, with IPSS available, with manual palpation performed, with hemoglobin available and with platelets available, respectively.

*p value derived from Fisher exact test.

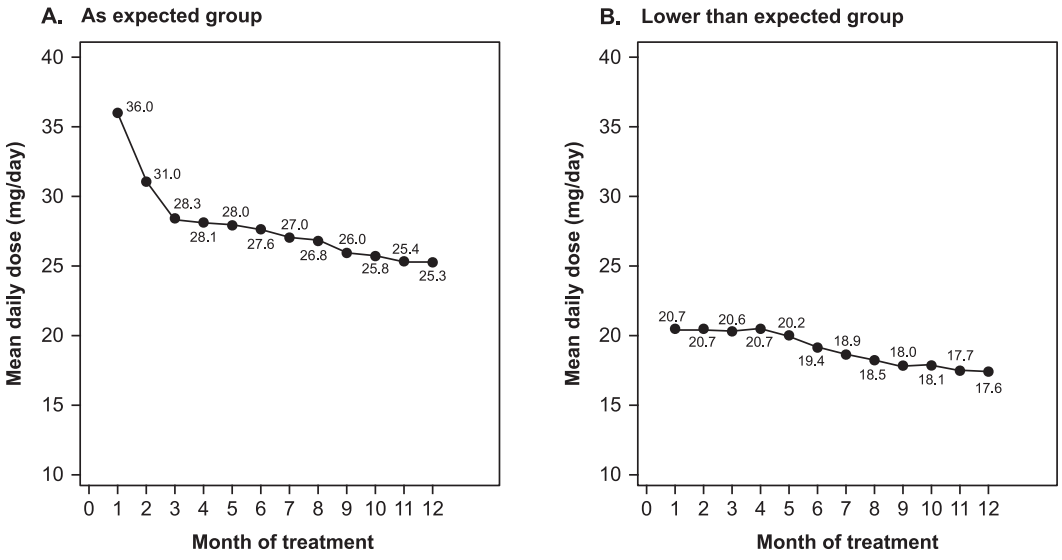

FIGURE 2 Plot of the mean daily dose of ruxolitinib by month by ruxolitinib expected starting dose group in the eligible population. The mean daily dose was computed dividing the cumulative total dose of ruxolitinib by the number of days in each month (i.e., 4 weeks). If patient discontinued treatment (temporarily or permanently), both treated and not treated days were considered for the mean daily dose computation.

Within the first 12 months, the AsEx and LtEx groups had similar temporary interruptions, but the LtEx group had more permanent discontinuation (Table 3). Median treatment duration was significantly longer in the AsEx group than in the LtEx group. Median (95% CI) treatment duration was 51.2 months (37.4, not evaluable [NE]) in the AsEx group and 33.3 months (25.2, 45.2) in the LtEx group (P = 0.009; Figure 3).

TABLE 3 Frequency and causes of temporary interruptions and permanent discontinuations by ruxolitinib expected starting dose group in the eligible population.

Parameter	AsEx group (*n* = 174)	LtEx group (*n* = 132)
Temporary interruptions (within 12 months)		
Number of temporary interruptions	20	18
Number of patients with at least one interruption, *n* (%)	18 (10.3)	14 (10.6)
Due to AE/laboratory/test abnormality, *n* (%)	16/20 (80.0)	17/18 (94.4)
Restarted with the same dosage, *n* (%)	11/20 (55.0)	11/18 (61.1)
Restarted with a reduced dose, *n* (%)	7/20 (35.0)	6/18 (33.3)
Median duration of interruptions, days (Q1; Q3)	10.5 (6.0; 20.5)	10.5 (7.0; 14)
Median time to first interruption, days (Q1; Q3)	76.0 (57.0; 138.0)	116.5 (32.0; 149.0)
Permanent discontinuations (within 12 months)		
Number of patients, *n* (%)	26 (14.9)	34 (25.8)
Main reasons for discontinuation (>10% patients)[a], *n* (%)	-	-
Death	5 (19.2)	8 (23.5)
HSCT	5 (19.2)	4 (11.8)
Acute leukemia transformation	4 (15.4)	4 (11.8)
Physician decision	4 (15.4)	3 (5.9)
Lost to follow-up	4 (15.4)	2 (5.9)
AEs	1 (3.9)	7 (20.6)
Permanent discontinuations (by cutoff)		
Total permanent discontinuations, *n* (%)	64 (36.8)	61 (46.2)
Number of patients permanently discontinued due to AEs[a], *n* (%)	10 (15.6)	16 (26.2)
Treatment duration		
Median (95% CI) treatment duration, months	51.2 (37.4–NE)	33.3 (25.2–45.2)
Permanent discontinuation rate at 6 months, %	8.7 (95% CI, 5.4–14.1)	15.6 (95% CI, 10.3–23.1)
Permanent discontinuation rate at 12 months, %	17.3 (95% CI, 12.3–23.9)	27.6 (95% CI, 20.7–36.3)

Abbreviations: AEs, adverse events; AsEx, as expected; HSCT, hematopoietic stem cell transplantation; LtEx, lower than expected; NE, not estimable.
[a]Percentages were computed on patients with permanent discontinuation.

EFFECTIVENESS

MPN-10 TSS

The MPN-10 TSS improved at 24 and 48 weeks when compared with the baseline score in all dose categories of ruxolitinib (Table 4).

The proportion of patients with symptom response was higher in the AsEx group than in the LtEx group at 4 weeks (38.5% vs 27.3%) until 24 weeks (40.8% vs 39.4%), whereas at 48 weeks, the proportion of responders was similar between the groups (AsEx group, 40.8%; LtEx group, 40.9%). In sensitivity analysis without missing imputation, the proportion of patients with symptom response was higher in the AsEx group than in the LtEx group at week 48 (50.4% or 57/113 patients vs 43.6% or 34/78 patients). However, at week 24, the proportion of responders was similar between the groups (AsEx group, 44.8% [56/125]; LtEx group, 44.6% [41/192], respectively).

Patients in the AsEx group showed a trend toward a shorter median time to first symptom response versus patients in the LtEx group (2.3 months [95% CI, 1.8–3.3] vs 3.8 months [95% CI, 2.6–6.0]; $p = .207$) even though the difference was not statistically significant, whereas the proportion of patients reaching first symptom response (anytime) was higher in the AsEx group than in the LtEx group (65.5% [114/174 patients] vs 60.6% [80/132 patients]).

HRQOL analysis

In both groups, a slight improvement in all EQ-5D-5L dimensions was observed at 24 and 48 weeks compared with the baseline (Figure S3 in supplementary). Mean EQ-VAS scores, representing patients' health status from worst (0) to best (100), showed an upward trend at each visit compared with the baseline for both AsEx and LtEx groups, indicating health improvements. For the AsEx group, mean

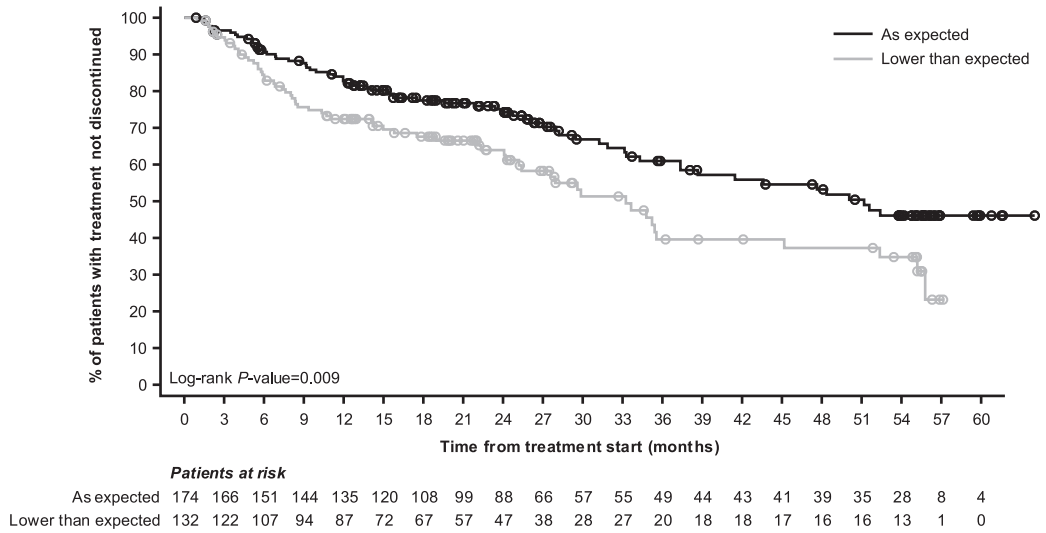

FIGURE 3 Kaplan–Meier plot showing time to permanent discontinuation by ruxolitinib expected starting dose group in the eligible population. Dots represent censors. Patients at risk are patients who had no censored observation and did not yet permanently discontinue the treatment at the considered timepoint.

TABLE 4 Mean myeloproliferative neoplasm-10 total symptom score (MPN-10 TSS) and absolute change from baseline by ruxolitinib expected starting dose groups in the eligible population.

Variable	AsEx group (n = 174)	LtEx group (n = 132)
MPN-10 TSS, mean ± SD		
Baseline	30.3 ± 18.9	31.8 ± 18.3
At week 24	19.3 ± 16.1	20.3 ± 14.5
Absolute change at 24 weeks	−10.9 ± 15.4	−11.6 ± 18.1
At week 48	19.7 ± 16.9	21.1 ± 15.4
Absolute change at 48 weeks	−10.6 ± 16.1	−10.8 ± 18.5

Abbreviations: AsEx, as expected; LtEx, lower than expected; MPN, myeloproliferative neoplasm.

EQ-VAS score at baseline was 62.9 ± 20.1, which increased to 67.7 ± 19.4 at 24 weeks and 65.3 ± 21.9 at 48 weeks (Figure S4A in supplementary). Similarly, for the LtEx group, mean EQ-VAS score at baseline was 59.5 ± 18.9, which increased to 67.1 ± 16.1 at 24 weeks and 64.4 ± 19.1 at 48 weeks (Figure S4B in supplementary).

Spleen response

Based on the International Working Group Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria, 86 and 78 patients in the AsEx group and 63 and 48 patients in the LtEx group were eligible for spleen response at 24 and 48 weeks, respectively. The spleen response rates at 24 and 48 weeks in the AsEx group were 50.0% (95% CI, 39.0–61.0) and 57.7% (95% CI, 46.0–68.8) versus 30.2% (95% CI, 19.2–43.0) and 45.8% (95% CI, 31.4–60.8) in the LtEx group, respectively.

Overall, 127 patients (73.0%) in the AsEx group and 86 patients (65.2%) in the LtEx group were eligible for the first spleen response. Of these, 62.2% (n = 79) in the AsEx group and 52.3% (n = 45) in the LtEx group reached the first spleen response and the median time to first spleen response was lower in the AsEx group than in the LtEx group: 3.3 months (95% CI, 1.9–6.6) vs 11.1 months (95% CI, 7.8–19.3; p = .019; Figure 4).

Among those who reached at least one spleen response, 36 patients from the AsEx group and 17 patients from the LtEx group lost their first spleen response within the specified cutoff date, and the duration of the first spleen response was similar between the AsEx and LtEx groups (Table 5).

Overall survival

In total, 23 (13.2%) and 27 (20.5%) patients in the AsEx and LtEx groups, respectively, died within the cutoff date. The estimated median survival time was NE for the AsEx group and 4.7 years (95% CI, 3.8–NE) in the LtEx group (p = .014) (Figure 5). On average, the duration of follow-up was equal to 2.2 ± 1.5 years (min; max: 0.1; 5.1 years) and 1.8 ± 1.4 years (min; max: 0.1; 4.9 years) in the AsEx and LtEx groups, respectively.

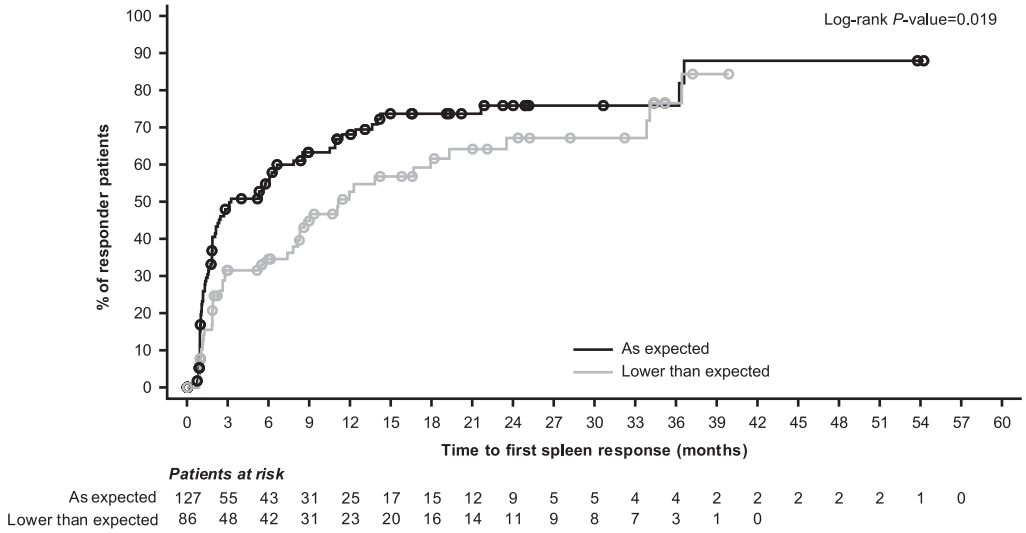

FIGURE 4 Reverse Kaplan–Meier plot of time to first spleen response based on IWG-MRT criteria by ruxolitinib expected starting dose group in the eligible population. Dots represent censors. Patients at risk are patients eligible for at least one spleen response evaluation (i.e., patients with manual palpation performed both at baseline and at least at one postbaseline visit and without baseline splenomegaly <5 cm) who had no censored observation and did not have spleen response at the considered timepoint yet. Patients with a baseline splenomegaly that is palpable at <5 cm were not eligible for spleen response. IWG-MRT indicates International Working Group-Myeloproliferative Neoplasms Research and Treatment.

TABLE 5 Duration of the first spleen response: events and Kaplan–Meier estimates by ruxolitinib expected starting dose group, eligible population with at least one spleen response based on the IWG-MRT criteria.

	AsEx group (n = 79)	LtEx group (n = 45)
Duration of first spleen response based on IWG-MRT criteria		
Number of events, n (%)[a]	36 (45.6)	17 (37.8)
Number of censored, n (%)[a]	43 (54.4)	28 (62.2)
Kaplan–Meier estimates (months)		
Median (95% CI)	17.7 (11.8, NE)	22.1 (7.2, NE)
p value	.578	

Abbreviations: AsEx, as expected; IWG-MRT, International Working Group Myeloproliferative Neoplasms Research and Treatment; LtEx, lower than expected; NE, not estimable.

[a]Percentages were computed on eligible population with spleen response based on IWG-MRT criteria. Events were defined as first spleen response observed and lost within the cutoff date. Patients with first spleen response observed that is maintained within the cutoff date were censored. Patients who lost the first spleen response were considered.

SAFETY

Within the cutoff date, 264 patients (152 [87.4%] vs 112 [84.9%]) reported at least one AE in the AsEx and LtEx groups, respectively (Table 6). Drug-related AEs, serious AEs, and severe AEs of grade 3/4 in both AsEx and LtEx groups are listed in supplementary Table S3 and AEs leading to permanent discontinuation are listed in supplementary Table S4. Treatment-related hematological AEs were commonly observed. Patients with grade 3 anemia requiring dose adjustment/temporary interruption/permanent discontinuation were 17 (9.8%) and 6 (4.6%) in the AsEx and LtEx group, respectively. Fifty-two patients (29.9%) and 34 patients (25.8%) in the AsEx and LtEx group, respectively, exhibited thrombocytopenia of any grade.

DISCUSSION

The dosing pattern of ruxolitinib emerging from the ROMEI study indicates the possibility for its suboptimal use in clinical practice for the approved indications at the time of data cutoff. This study revealed that 43% of patients were assigned a starting dose that was lower than that expected based solely on their baseline platelet count. A similar trend was reported in another real-world study in Italy (N = 3647), where 67% of patients with MF started at a reduced ruxolitinib dose.[15] Interestingly, most patients (70.5%) in the LtEx group had a higher baseline platelet count (>200 × 10^9/L), indicating that they could have potentially been started on the maximum dosage of 20 mg twice per day (40 mg/day). Indeed, patients in the LtEx starting dose group had a significantly lower median baseline Hb

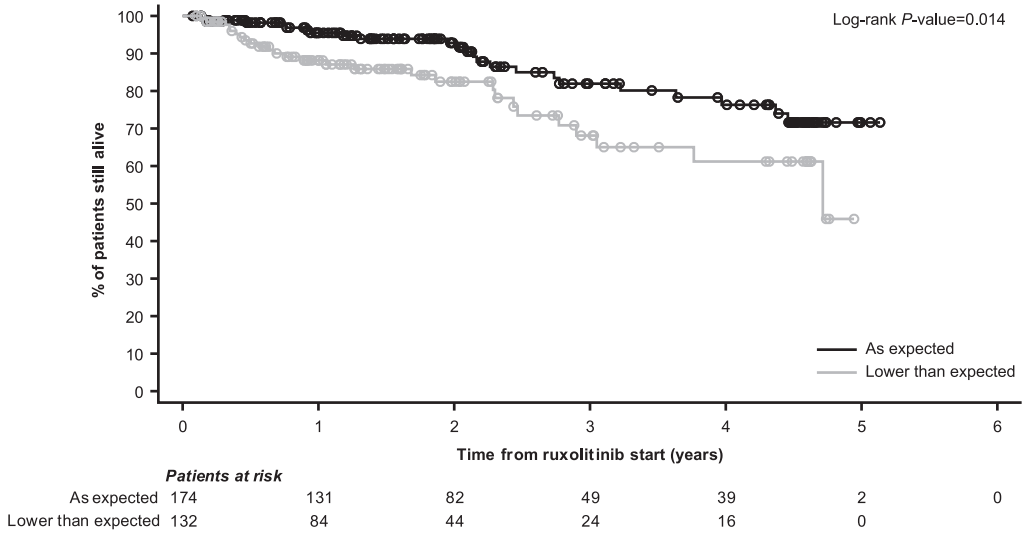

FIGURE 5 Kaplan–Meier plot of overall survival by the ruxolitinib expected starting dose group in the eligible population. Dots represent censors. Patients at risk are patients who have no censored observation and were alive at the considered timepoint yet.

TABLE 6 Number of patients with adverse events by system organ class and preferred term by ruxolitinib-expected starting dose group in the eligible population (>10% patients in any group).

Adverse events, *n* (%)	AsEx group (*n* = 174)	LtEx group (*n* = 132)	Total (N = 306)
Patients with adverse events within the cutoff date	152 (87.4)	112 (84.9)	264 (86.3)
Blood and lymphatic system disorders	111 (63.8)	68 (51.5)	179 (58.5)
Anemia	88 (50.6)	54 (40.9)	142 (46.4)
Thrombocytopenia	52 (29.9)	34 (25.8)	86 (28.1)
Gastrointestinal disorders	30 (17.2)	32 (24.2)	62 (20.3)
General disorders and administration site conditions	62 (35.6)	48 (36.4)	110 (36)
Asthenia	40 (23.0)	25 (18.9)	65 (21.2)
Pyrexia	16 (9.2)	15 (11.4)	31 (10.1)
Infections and infestations	50 (28.7)	43 (32.6)	93 (30.4)
Investigations	36 (20.7)	28 (21.2)	64 (20.9)
Musculoskeletal and connective tissue disorders	27 (15.5)	18 (13.6)	45 (14.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	15 (8.6)	14 (10.6)	29 (9.5)
Nervous system disorders	19 (10.9)	18 (13.6)	37 (12.1)
Respiratory, thoracic and mediastinal disorders	24 (13.8)	23 (17.4)	47 (15.4)
Skin and subcutaneous tissue disorders	19 (10.9)	20 (15.2)	39 (12.8)
Vascular disorders	16 (9.2)	23 (17.4)	39 (12.8)

Abbreviations: AsEx, as expected; LtEx, Lower than expected.

level (10.8 g/dL vs 11.4 g/dL in the AsEx group; $p = .009$), with more patients belonging to the moderate/severe anemia stratum (Hb < 10 g/dL: 38.5% vs 22.4% in the AsEx group; $p = .002$). However, among the remaining 61.5% of patients in the LtEx group, 42 patients (32.3% of overall population) had normal baseline Hb level >12 g/dL.

Throughout the observation period, a consistent decrease in the dose was observed, regardless of the starting dose group. A Sankey diagram revealed that a small percentage (2.9%) of patients were shifted to higher dosages, with the proportion decreasing from 40.2% at baseline to 37.3% at 48 weeks.

A significant difference in prior red blood cell transfusions at baseline was observed between the AsEx (8.6%) and LtEx (24.2%) groups ($p < .001$). This is also substantiated by the higher baseline Hb levels in the AsEx group. In the AsEx group, ruxolitinib mean daily dose and Hb level (11.0 g/dL) decreased with time and then stabilized by month 12 (10.5 g/dL). In the LtEx group, the mean daily dose

reduced from months 5 to12, but the Hb level was stable (from 10.7 g/dL at month 1 to 10.2 g/dL at month 12). Previous studies have shown that a decrease in Hb levels after ruxolitinib initiation did not seem to have an effect on OS.[16] Furthermore, in pooled analyses of COMFORT studies, OS in the ruxolitinib group was similar between patients who were transfusion dependent and transfusion independent at week 24 ($p = .455$).[17] Moreover, an analysis of 2233 patients in the JUMP study indicated that new/worsening anemia following ruxolitinib initiation did not reduce treatment benefits.[18] Ruxolitinib improved spleen size and reduced symptom burden regardless of anemia and transfusion status, with similar trends being observed at both 24 and 48 weeks, showing no significant differences between patients with and without anemia.[18]

Consistent with the other real-world studies,[16,19] cytopenic phenotype reported in the ROMEI study seems to explain the LtEx dosing approach only in the relatively limited proportion of patients. No specific differences were revealed between dosing patterns and type of center (academic or not; data not shown). Despite acknowledging that the ROMEI study was neither designed nor powered to detect differences among the two starting dose subgroups, the results highlighted older age, anemia, and prior transfusion history among the baseline parameters probably driving a reduced starting dose approach. In fact, the LtEx cohort was significantly older, in terms of both median age (71 years) and patients aged >65 years (73.5% of patients) than the AsEx cohort (median age, 68 years; $p = .001$; patients >65 years: 56.9%; $p = .003$). Elderly patients might indeed present a greater burden of comorbidities that deserve careful assessment before starting a new treatment. However, the analysis of data from medical histories in the ROMEI study did not reveal differences in comorbidities or clinical conditions (type and number) between the two groups, which could potentially explain the need for a different dosing approach. The recognition that older patients often represent a more vulnerable and fragile population may have influenced a cautious approach in determining their initial dosing.

Phase 3 studies have documented that a higher titrated dose of 20 mg/day (COMFORT I) is associated with greater spleen improvements.[20,21] Consistent with this finding, patients of the JUMP study, who received a titrated dose of >20 mg/day versus ≤20 mg/day at week 12 had higher spleen response rates, as observed in multivariate analysis (41.3% vs 30.4%; adjusted odds ratio, 0.47 [95% CI, 0.33–0.68]).[3] Likewise, in an independent study, patients titrated at doses ≥10 mg twice daily during the first 12 weeks of therapy had a higher rate of spleen response at 6 months (37.9% vs 22.2% in patients receiving lower doses; $p = .019$).[22] The results from the ROMEI study provide further confirmation of the dose-response relationship in patients who received recommended doses in the AsEx group showing a better trend in response versus the LtEx group.

Spleen response was achieved in a higher proportion of patients at both 24 weeks and 48 weeks in the AsEx group versus LtEx group (50.0% vs 30.2% and 57.7% vs 45.8%, respectively). Median time to first spleen response was significantly shorter in the AsEx group versus LtEx group (3.3 months and 11.1 months; $p = .019$). Among the patients eligible for spleen response evaluation, the first spleen response occurring anytime within the data cutoff was observed in 62.2% of patients in the AsEx group versus 52.3% in the LtEx group. Although the initial spleen response was less frequent and slower in the LtEx group, the median duration of response was similar to that in AsEx group (17.7 vs 22.1 months; $p = .578$).

Accumulating evidence supports the significant positive impact of ruxolitinib treatment on OS, both in controlled clinical studies and in real-world registries.[7,12] The ROMEI study showed that initiation at the recommended dose maximizes the OS, as observed in patients of the AsEx starting dose group in which patients had a better OS than those in the LtEx group (median not reached vs 4.7 years; $p = .014$). It should be taken into account however that other clinical features might influence OS such as older age, disease-related anemia, and cytopenic phenotype that indeed in our study were unbalanced between the two starting dose groups.

Additionally, in the pooled post hoc analysis of COMFORT studies, starting ruxolitinib within 12 months of MF diagnosis showed improved OS compared with starting later.[17] The group starting earlier (≤12 months) had a higher total daily dose, which may have contributed to better outcomes, possibly because of better tolerance of the higher dose.[17] Patients of the ROMEI study generally had timely start of ruxolitinib treatment regardless of starting dose subgroup. The median time from diagnosis to starting ruxolitinib was 4.3 and 6.5 months for the AsEx groups and LtEx groups, respectively. Most patients started ruxolitinib within 12 months of MF diagnosis. However, approximately >30% of patients started ruxolitinib treatment ≥24 months after diagnosis in both groups.

A real-world study demonstrated that the simultaneous occurrence of AEs and poor response to ruxolitinib often led to a gradual reduction in the ruxolitinib dosage for many patients.[23] Therefore, by the time a final decision was made to discontinue drug use, many patients had already been prescribed low doses.[23] A similar trend was observed in the ROMEI study, where 35.0% ($n = 7$) and 33.3% ($n = 6$) of patients in the AsEx and LtEx groups, respectively, restarted treatment at a lower dose after temporary interruption, and most of the interruptions were due to AEs. Patients in the LtEx starting dose group showed a higher rate of permanent treatment discontinuation versus the AsEx group, and it was almost double at 6 months and still significantly higher at 12 months (27.6% vs 17.3%), suggesting that patients on lower doses are more likely to discontinue treatment earlier. In a real-world study, approximately 40% of patients discontinued ruxolitinib within 3 years of starting therapy.[24] The primary reason for discontinuation was AEs (28.6%).[23] The main reason for discontinuation in our study was AEs (15.6% and 26.2% of patients in the AsEx and LtEx groups, respectively). Ruxolitinib was well tolerated and had an AE profile similar to that reported previously (COMFORT and JUMP studies),[17,25] and no new safety concerns were identified.

The main limitation of this study is its observational design leading to selection bias, attrition bias, and lack of a control group. Given the observational nature of the study all the statistical analysis

had a descriptive purpose only, and no formal comparisons or hypothesis to be tested was planned. The two groups described were not sized nor was the analysis powered to detect significant differences. The two groups on which we performed the descriptive analysis had unbalanced baseline clinical characteristics that may have contributed in part to the observed/described differences.

Moreover, the classification of AsEx/LtEx on which comparisons and considerations are made is based on the patient's status at baseline and does not reflect any dynamic adjustments based on platelet count and the assigned dosage being studied. Therefore, a Sankey diagram has been included to visualize the flow of patients between different dose groups during the observation period.

CONCLUSIONS

To ensure optimal treatment with ruxolitinib, patients should be started on appropriate ruxolitinib doses and maintain the highest tolerated dose for maximum effectiveness. Patients who received the recommended doses showed a better trend in response. Dose titration and supportive care are important in managing treatment-associated cytopenias, which usually occur within the first 12 weeks of treatment. Some patients may require dose titrations for decreased platelet counts and supportive care for decreased Hb levels. Timely ruxolitinib treatment results in maximum patient benefits such as spleen size reduction, symptom relief, and improved OS.

AUTHOR CONTRIBUTIONS

Massimo Breccia: Conceptualization; Methodology; Formal analysis; Investigation; and Writing - review & editing. **Francesca Palandri**: Conceptualization; Methodology; Formal analysis; Writing - review & editing; and Investigation. **Maurizio Martelli**: Methodology; Investigation; and Writing - review & editing. **Francesco Mendicino**: Methodology; Investigation; and Writing - review & editing. **Alessandra Malato**: Methodology; Investigation; and Writing - review & editing. **Giuseppe A. Palumbo**: Methodology; Investigation; and Writing - review & editing. **Silvia Sibilla**: Methodology; Investigation; and Writing - review & editing. **Nicola Di Renzo**: Methodology; Investigation; and Writing - review & editing. **Elisabetta Abruzzese**: Methodology; Investigation; and Writing - review & editing. **Sergio Siragusa**: Methodology; Investigation; and Writing - review & editing. **Monica Crugnola**: Methodology; Investigation; and Writing - review & editing. **Carmine Selleri**: Methodology; Investigation; and Writing - review & editing. **Fabrizio Pane**: Methodology; Investigation; and Writing - review & editing. **Paolo Sportoletti**: Methodology; Investigation; and Writing - review & editing. **Bruno Martino**: Methodology; Investigation; and Writing - review & editing. **Stefana Impera**: Methodology; Investigation; and Writing - review & editing. **Alessandra Ricco**: Methodology; Investigation; and Writing - review & editing. **Maria Langella**: Methodology; Investigation; and Writing - review & editing. **Paolo Ditonno**: Methodology; Investigation; and Writing - review & editing. **Giuseppe Carli**: Investigation; Writing - review & editing; and Methodology. **Federico Itri**: Methodology; Investigation; and Writing - review & editing. **Anna Marina Liberati**: Methodology; Investigation; and Writing - review & editing. **Tiziana Urbano**: Methodology; Investigation; and Writing - review & editing. **Agostino Tafuri**: Methodology; Investigation; and Writing - review & editing. **Vita Polizzi**: Methodology; Investigation; and Writing - review & editing. **Domenico Pastore**: Methodology; Investigation; and Writing - review & editing. **Erika Morsia**: Methodology; Investigation; and Writing - review & editing. **Giulia Benevolo**: Methodology; Investigation; and Writing - review & editing. **Giorgia Micucci**: Methodology; Investigation; Writing - review & editing. **Gabriella Farina**: Methodology; Writing - review & editing; and Investigation. **Massimiliano Bonifacio**: Methodology; Investigation; and Writing - review & editing. **Elena Maria Elli**: Methodology; Investigation; and Writing - review & editing. **Angelo Gardellini**: Methodology; Investigation; and Writing - review & editing. **Valerio De Stefano**: Methodology; Investigation; and Writing - review & editing. **Giovanni Caocci**: Methodology; Investigation; and Writing - review & editing. **Antonietta Pia Falcone**: Methodology; Investigation; and Writing - review & editing. **Daniele Vallisa**: Methodology; Investigation; and Writing - review & editing. **Marco Brociner**: Methodology; Investigation; and Writing - review & editing. **Mario Tiribelli**: Methodology; Investigation; and Writing - review & editing. **Gianni Binotto**: Methodology; Investigation; and Writing - review & editing. **Barbara Pocali**: Investigation; Methodology; and Writing - review & editing. **Francesco Cavazzini**: Methodology; Writing - review & editing; and Investigation. **Simona Tomassetti**: Methodology; Investigation; and Writing - review & editing. **Francesca Lunghi**: Methodology; Investigation; and Writing - review & editing. **Mauro Di Ianni**: Methodology; Investigation; and Writing - review & editing. **Alessandro Allegra**: Methodology; Investigation; and Writing - review & editing. **Barbara Anaclerio**: Methodology; Investigation; and Writing - review & editing. **Serena Mazzotta**: Methodology; Investigation; and Writing - review & editing. **Nicola Orofino**: Investigation; Methodology; and Writing - review & editing. **Filippo Gherlinzoni**: Methodology; Investigation; and Writing - review & editing. **Chiara Castiglioni**: Project administration; Methodology; Conceptualization; Investigation; Formal analysis; and Writing - review & editing. **Marina Landoni**: Conceptualization; Methodology; Investigation; Formal analysis; and Writing - review & editing. **Diletta Valsecchi**: Conceptualization; Investigation; Writing - review & editing; Methodology; and Formal analysis. **Michela Magnoli**: Formal analysis; Data curation; Conceptualization; Investigation; and Writing - review & editing; Methodology. **Paola Guglielmelli**: Conceptualization; Methodology; Formal analysis; Investigation; and Writing - review & editing. **Francesco Passamonti**: Conceptualization; Methodology; Formal analysis; Investigation; and Writing - review & editing.

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CONFLICT OF INTEREST STATEMENT

Massimo Breccia: received honoraria from Novartis, Pfizer, Incyte, BMS/Celgene, AbbVie, AOP, and GSK; Francesca Palandri: consultant and received honoraria from AbbVie, Amgen, AOP, BMS Celgene, Novartis, CTI, GSK, Grifols, Karyopharm, Morphosis, Sierra Oncology, and Sobi; Maurizio Martelli: no conflicts of interest; Francesco Mendicino: no conflicts of interest; Alessandra Malato: no conflicts of interest; Giuseppe A. Palumbo: honoraria for Advisory Boards/Meetings as speaker from Abbvie, AOP Orphan, AstraZeneca, Beigene, Bristol-Myers Squibb, GSK, Incyte, Morphosys, and Novartis; support for attending meetings and travel from Abbvie, AOP Orphan, Beigene, Johnson & Johnson, Novartis, and Stemline Menarini; Silvia Sibilla: no conflicts of interest; Nicola Di Renzo: no conflicts of interest; Elisabetta Abruzzese: no conflicts of interest; Sergio Siragusa: no conflicts of interest; Monica Crugnola: no conflicts of interest; Carmine Selleri: no conflicts of interest; Fabrizio Pane: no conflicts of

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DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author after approval from the local ethical committee, according to the Novartis, Italian Data Protection Authority.

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REFERENCES

1. Schieber M, Crispino JD, Stein B. Myelofibrosis in 2019: moving beyond JAK2 inhibition. *Blood Cancer J*. 2019;9(9):74. doi:10.1038/s41408-019-0236-2
2. Mitra D, Kaye JA, Piecoro LT, et al. Symptom burden and splenomegaly in patients with myelofibrosis in the United States: a retrospective medical record review. *Cancer Med*. 2013;2(6):889-898. doi:10.1002/cam4.136
3. Gupta V, Griesshammer M, Martino B, et al. Analysis of predictors of response to ruxolitinib in patients with myelofibrosis in the phase 3b expanded-access JUMP study. *Leuk Lymphoma*. 2021;62(4):918-926. doi:10.1080/10428194.2020.1845334
4. Anderson LA, James G, Duncombe AS, et al. Myeloproliferative neoplasm patient symptom burden and quality of life: evidence of significant impairment compared to controls. *Am J Hematol*. 2015;90(10):864-870. doi:10.1002/ajh.24098
5. Mesa R, Miller CB, Thyne M, et al. Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey. *BMC Cancer*. 2016;16(1):167. doi:10.1186/s12885-016-2208-2
6. Asher S, McLornan DP, Harrison CN. Current and future therapies for myelofibrosis. *Blood Rev*. 2020;42:100715. doi:10.1016/j.blre.2020.100715
7. Verstovsek S, Mesa RA, Livingston RA, Hu W, Mascarenhas J. Ten years of treatment with ruxolitinib for myelofibrosis: a review of safety. *J Hematol Oncol*. 2023;16(1):82. doi:10.1186/s13045-023-01471-z
8. Pemmaraju N, Bose P, Rampal R, Gerds AT, Fleischman A, Verstovsek S. Ten years after ruxolitinib approval for myelofibrosis: a review of clinical efficacy. *Leuk Lymphoma*. 2023;64(6):1063-1081. doi:10.1080/10428194.2023.2196593
9. Summary of Product Characteristics - Jakavi. 2012. https://www.ema.europa.eu/en/documents/product-information/jakavi-epar-product-information_en.pdf
10. Breccia M, Guglielmelli P, Malato A, et al. Real-world management of myelofibrosis with ruxolitinib: initial analysis of an Italian Observational Study (ROMEI). *Blood*. 2018;132(Supplement 1):4312. doi:10.1182/blood-2018-99-110198
11. Breccia M, Guglielmelli P, Mendicino F, et al. Dosing pattern of ruxolitinib (RUX) in patients with myelofibrosis (MF) in Italy: results from a prospective observational study (ROMEI). *Blood*. 2022;140(Supplement 1):9688-9690. doi:10.1182/blood-2022-157914
12. Guglielmelli P, Palandri F, Selleri C, et al. Adherence to ruxolitinib, an oral JAK1/2 inhibitor, in patients with myelofibrosis: interim analysis from an Italian, prospective cohort study (ROMEI). *Leuk Lymphoma*. 2022;63(1):189-198. doi:10.1080/10428194.2021.1969388
13. Palandri F, Auteri G, Abruzzese E, et al. Ruxolitinib adherence in myelofibrosis and polycythemia vera: the "RAMP" Italian multicenter prospective study. *Ann Hematol*. 2024;103(6):1931-1940. doi:10.1007/s00277-024-05704-0
14. Breccia M, Guglielmelli P, Malato A, et al. Real world data on ruxolitinib (Rux) in myelofibrosis (Mf): 6 months (Mos) interim analysis of Italian Romei Study (Cinc424ait04). *Haematologica*. 2019;104:73-74.
15. Breccia M , Palandri F, Passamonti, et.al. Ruxolitinib starting dose reduction affect overall survival in myelofibrosis: AIFA monitoring registries analysis. Presented at: EHA2024; 2024; Session S1.
16. Maffioli M, Mora B, Ball S, et al. A prognostic model to predict survival after 6 months of ruxolitinib in patients with myelofibrosis. *Blood Adv*. 2022;6(6):1855-1864. doi:10.1182/bloodadvances.2021006889

17. Verstovsek S, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. *J Hematol Oncol*. 2017;10(1):156. doi:10.1186/s13045-017-0527-7
18. Al-Ali HKGP, Hamer-Maansson JE, Braunstein E, Gupta V. The impact of new or worsening anemia on clinical outcomes in 2233 patients with myelofibrosis treated with ruxolitinib: results from the expanded-access JUMP study; 2024. presented at: EHA 2024. https://library.ehaweb.org/eha/2024/eha2024-congress/419131/haifa.kathrin.al-ali.the.impact.of.new.or.worsening.anemia.on.clinical.html?f=menu%3D6%2Abrowseby%3D8%2Asortby%3D2%2Ace_id%3D2552%2Aot_id%3D29168%2Amarker%3D5101%2Afeaturedd%3D18498
19. Palandri F, Breccia M, Mazzoni C, et al. Ruxolitinib in cytopenic myelofibrosis: response, toxicity, drug discontinuation, and outcome. *Cancer*. 2023;129(11):1704-1713. doi:10.1002/cncr.34722
20. Verstovsek S, Gotlib J, Gupta V, et al. Management of cytopenias in patients with myelofibrosis treated with ruxolitinib and effect of dose modifications on efficacy outcomes. *OncoTargets Ther*. 2013;7:13-21. doi:10.2147/OTT.S53348
21. Mesa RA, Cortes J. Optimizing management of ruxolitinib in patients with myelofibrosis: the need for individualized dosing. *J Hematol Oncol*. 2013;6(1):79. doi:10.1186/1756-8722-6-79
22. Palandri F, Palumbo GA, Bonifacio M, et al. Baseline factors associated with response to ruxolitinib: an independent study on 408 patients with myelofibrosis. *Oncotarget*. 2017;8(45):79073-79086. doi:10.18632/oncotarget.18674
23. Palandri F, Palumbo GA, Elli EM, et al. Ruxolitinib discontinuation syndrome: incidence, risk factors, and management in 251 patients with myelofibrosis. *Blood Cancer J*. 2021;11(1):4. doi:10.1038/s41408-020-00392-1
24. Palandri F, Breccia M, Bonifacio M, et al. Life after ruxolitinib: reasons for discontinuation, impact of disease phase, and outcomes in 218 patients with myelofibrosis. *Cancer*. 2020;126(6):1243-1252. doi:10.1002/cncr.32664
25. Passamonti F, Gupta V, Martino B, et al. Comparing the safety and efficacy of ruxolitinib in patients with Dynamic International Prognostic Scoring System low-intermediate-1-intermediate-2-and high-risk myelofibrosis in JUMP, a phase 3b, expanded-access study. *Hematol Oncol*. 2021;39(4):558-566. doi:10.1002/hon.2898

SUPPORTING INFORMATION

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

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