


## ORIGINAL RESEARCH ARTICLE

# Efficacy and safety of ruxolitinib in intermediate-1 IPSS risk myelofibrosis patients: Results from an independent study

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## Abstract

Patients with myelofibrosis at intermediate-1 risk according to the International Prognostic Score System are projected to a relatively long survival; nonetheless, they may carry significant splenomegaly and/or systemic constitutional symptoms that hamper quality of life and require treatment. Since registrative COMFORT studies included only patients at intermediate-2/high International Prognostic Score System risk, safety and efficacy data in intermediate-1 patients are limited. We report on 70 intermediate-1 patients treated with ruxolitinib according to standard clinical practice that were evaluated for response using the 2013 IWG-MRT criteria. At 6 months, rates of spleen and symptoms response were 54.7% and 80% in 64 and 65 evaluable patients, respectively. At 3 months, ruxolitinib-induced grade 3 anemia and thrombocytopenia occurred in

40.6% and 2.9% of evaluable patients, respectively. Notably, 11 (15.9%) patients experienced at least one infectious event  $\geq$  grade 2. Most (82.6%) patients were still on therapy after a median follow-up of 27 months. These data support the need for standardized guidelines that may guide the decision to initiate ruxolitinib therapy in this risk category, balancing benefit expectations and potential adverse effects.

#### KEYWORDS

intermediate-1 risk, IPSS, MF, myelofibrosis, ruxolitinib

## 1 | INTRODUCTION

Myelofibrosis (MF) is a progressive disease that is burdened by symptomatic splenomegaly, debilitating systemic symptoms, worsening cytopenias, and overall reduced survival.<sup>1</sup> Prognosis is currently assessed by the International Prognostic Scoring System (IPSS) at diagnosis,<sup>2</sup> by the dynamic-IPSS (DIPSS) over the follow-up,<sup>3</sup> and by the DIPSS-plus that includes also transfusion requirement, thrombocytopenia, and cytogenetic abnormalities.<sup>4</sup> Molecular abnormalities including driver ( $JAK2^{V617F}$ /CALR/MPL) and subclonal (ASXL1/SRSF2) mutations have been recently integrated in the mutation-enhanced IPSS (MIPSS) score.<sup>5</sup> Balancing life expectancy (ranging between 6.5 and 14.2 y) and the risk of severe complications, intermediate-1 IPSS risk patients are not candidates for allogeneic hematopoietic stem cell transplantation (alloSCT) in clinical routine, which is the only potentially curative treatment option so far. Nonetheless, these patients may carry severe splenomegaly and/or symptoms that are not taken into consideration by commonly used prognostic scores but that hamper quality of life and may urge treatment.

Ruxolitinib is the first-in-class  $JAK1/JAK2$  inhibitor currently available for the treatment of MF-related splenomegaly and/or symptoms.<sup>6,7</sup> The registrative COMFORT studies randomized intermediate-2/high IPSS risk patients to receive either ruxolitinib or placebo (COMFORT-1)<sup>8</sup> or best available therapy (COMFORT-2).<sup>9</sup> In this setting, ruxolitinib proved clear superiority in spleen and symptoms responses over control arms. The subsequent expanded access JUMP trial enrolled also 163 patients at intermediate-1 IPSS risk with a palpable spleen length  $\geq 5$  cm below left costal margin (LCM) that were treated for a median time of 14.4 months. Results from this subanalysis were consistent with findings for the total population, with similar response and toxicity rates.<sup>10</sup> However, only a few independent data are available on this particular patients' population.<sup>11,12</sup> Here, we evaluated the outcome of 70 intermediate-1 IPSS risk MF patients that were treated with ruxolitinib in 16 Italian or German Hematology Centers. Patients were homogeneously evaluated for responses according to the 2013 International Working Group–Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria,<sup>13</sup> with the aim to provide independent and standardized data on safety and efficacy of ruxolitinib therapy in this risk category.

## 2 | METHODS

### 2.1 | Patients and treatment

Between August 2011 and January 2014, a total of 70 intermediate-1 IPSS risk MF patients were treated with ruxolitinib in 15 Italian and 1

German Hematology Centers. Patients received ruxolitinib after inclusion in the JUMP trial ( $n = 51$ ) or within a compassionate use program ( $n = 19$ ) and were evaluated for responses according to the 2013 IWG-MRT criteria.<sup>13</sup> The decision to start ruxolitinib treatment was based on physician's discretion. Baseline clinical/laboratory features, outcome measures (evolution into acute leukemia, death, and spleen/symptoms responses), and toxicities were retrospectively recorded. Primary myelofibrosis (PMF) and post-Essential Thrombocythemia/post-Polycythemia Vera myelofibrosis (PET-MF/PPV-MF) were diagnosed according to the WHO2008<sup>14</sup> or the IWG-MRT criteria,<sup>15</sup> respectively. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v4. Comorbidities were evaluated according to the Charlson Comorbidity Index (CCI).<sup>16</sup> Body mass index (BMI) was evaluated according to standard criteria; specifically, BMI  $\geq 25$  identified patients overweight.<sup>17</sup> The study was approved by the Institutional Review Board of each Institution and was conducted according to the Helsinki declaration.

### 2.2 | Statistical analysis

Continuous variables were expressed as median and ranges and categorical variables were presented as frequencies and percentages. Regression logistic analysis was performed to correlate spleen/symptoms responses with several baseline features, namely, sex, primary/secondary MF, age  $> 65$  years, transfusion dependency, leukocytosis ( $> 25 \times 10^9/L$ ), presence of constitutional symptoms and blast cells, palpable hepatomegaly,  $JAK2^{V617F}$  mutation and mutation load, severe (grade 3) marrow fibrosis, Charlson Comorbidity Index  $\geq 2$ , overweight, large splenomegaly (spleen length palpable  $\geq 10$  and  $\geq 15$  cm below LCM), Total Symptom Score (TSS) higher than the median value ( $\geq 20$ ) and severely increased ( $\geq 44$ ). Survival analysis was calculated from the date of ruxolitinib start to the time of death or last follow-up, whichever came first, and was performed by means of Kaplan-Meier curve. All tests were 2-sided, and a  $P$  value less than .05 was considered statistically significant. Analyses were performed with IBM SPSS Statistics 22 (IBM Analytics) and GraphPad Prism 6 (GraphPad Software).

## 3 | RESULTS

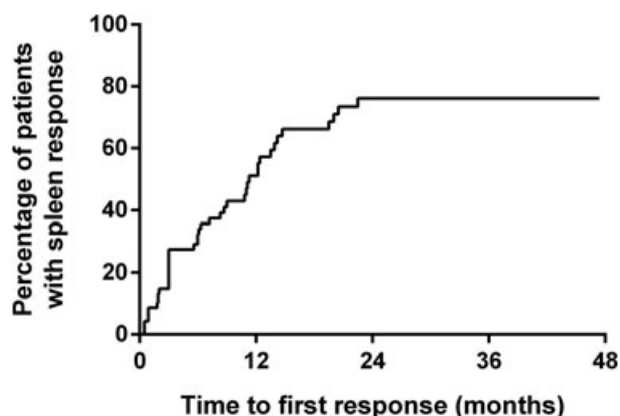
### 3.1 | Study population

Between June 2011 and July 2016, 70 patients with intermediate-1 risk MF were treated with ruxolitinib. Table 1 summarizes main baseline clinical and laboratory data of the cohort at ruxolitinib start. Twenty-three (32.8%) patients were  $> 65$  year old, 6 (8.6%) had hemoglobin  $< 10$  g/dL, 6 (8.6%) had leukocyte  $> 25 \times 10^9/L$ , and 30 (42.8%)

**TABLE 1** Patients' characteristics at ruxolitinib start

Characteristics	Patients (no. = 70)
Male sex, no. (%)	44 (62.8%)
Primary myelofibrosis, no. (%)	39 (55.7%)
Post-essential Thrombocythemia MF, no. (%)	8 (11.4%)
Post-polycythemia Vera MF, no. (%)	23 (32.9%)
JAK2 <sup>V617F</sup> mutation, no. (%) on 65 evaluable	55 (84.6%)
Median age, years (range)	60 (26.5-78.1)
Age > 65 years, no. (%)	23 (32.8%)
Median hemoglobin, g/dl (range)	12.7 (8.1-16.7)
Hemoglobin <10 g/dl, no. (%)	6 (8.6%)
Transfusion dependent, no. (%)	2 (2.9%)
Median leukocyte, $\times 10^9/l$ (range)	11.1 (2.7-46.6)
WBC >25 $\times 10^9/l$ , no. (%)	6 (8.6%)
Median platelet, $\times 10^9/l$ (range)	290 (101-1200)
PLT <200 $\times 10^9/l$ , no. (%)	20 (28.6%)
Constitutional symptoms, no. (%)	31 (44.3%)
Palpable spleen, no. (%)	69 (98.6%)
Median cm below LCM (range)	10 (5-30)
Spleen $\geq 10$ cm below LCM, no. (%)	40 (57.1%)
Spleen $\geq 15$ cm below LCM, no. (%)	26 (37.1%)
Palpable liver no. (%)	26 (37.1%)
Median Total symptom score (range)	20 (0-90)
TSS >44, no. (%)	7 (10%)
Abnormal karyotype, no. (%) on 32 evaluable	8 (25.0%)
Unfavorable karyotype, no. (%) on 32 evaluable	2 (6.3%)
Grade 3 marrow fibrosis, no. (%)	15 (21.4%)
Median Charlson comorbidity index (range)	0 (0-8)
CCI $\geq 2$ , no. (%) on 59 evaluable	19 (32.2%)
BMI > 25, no. (%) on 59 evaluable	30 (50.9%)
Median time MF-RUX start, months (range)	19.2 (0.1-203.3)
Time from MF-RUX start >2 years, no. (%)	31 (44.3%)
RUX starting dose, no. (%)	
10 mg BID	4 (5.7%)
15 mg BID	18 (25.7%)
20 mg BID	48 (68.6%)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; LCM, left costal margin; MF, myelofibrosis; RUX, ruxolitinib; WBC, white blood cells; PLT, platelets; BID, twice a day; TSS, Total Symptom Score.

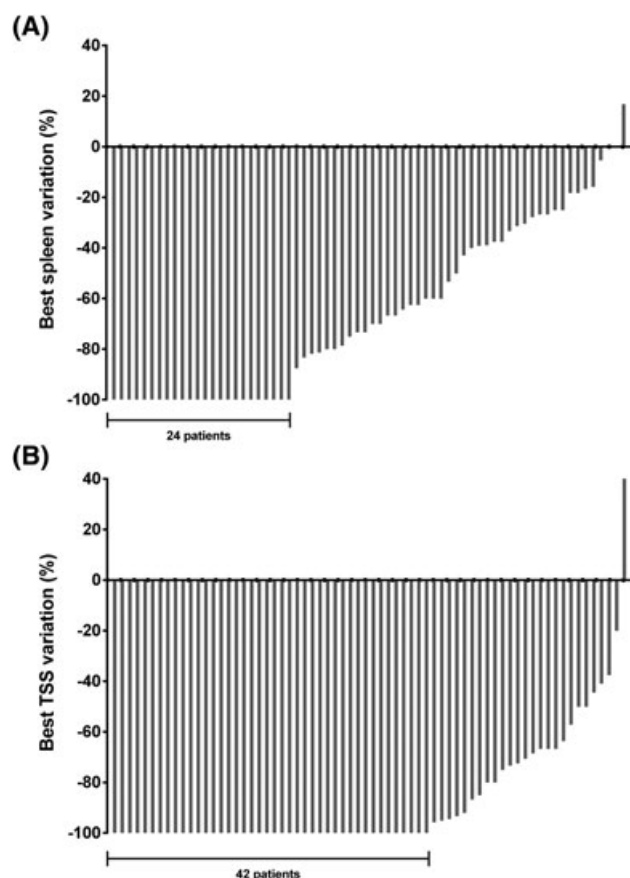
**FIGURE 1** Percentage of patients achieving a spleen response

reported on constitutional symptoms; 5 (7.2%) patients had circulating blasts in peripheral blood. Two patients were transfusion dependent according to 2013-IWG-MRT criteria. A total of 40 (57.1%) patients had a large splenomegaly (37.1% with spleen palpable  $\geq 15$  cm below LCM). One patient did not present palpable splenomegaly at ruxolitinib start and was therefore not evaluable for response; the remaining 69 patients had a baseline spleen length palpable of more than 5 cm below left costal margin. Seven (10%) were heavily symptomatic, with a baseline Total Symptom Score (TSS) >44. Charlson Comorbidity Index (CCI) was evaluated in 59 patients and was 0 in 27 (45.8%), one in 13 (22.0%), and  $\geq 2$  in 19 patients (32.2%). At 3 and 6 months, 69 and 65 patients were still on therapy, respectively.

### 3.2 | Spleen and symptom responses

Per intention-to-treat analysis, 42 (60%) patients achieved a spleen response or symptom reduction by 24 months (Figure 1). Sixty-three patients (90%) had a symptom response that occurred in most cases (73%) within the first 2 months of therapy. Median reductions in palpable spleen length and TSS were 71.7% and 100%, respectively. A complete resolution of palpable splenomegaly and of TSS was achieved in 24 (34.3%) and 42 (60.0%) patients (Figure 2A,B, respectively).

At 3 months, 28 (41.2%) and 50 (72.5%) of 68 and 69 evaluable patients achieved a spleen or a symptom response, respectively. At 6 months, 35 (54.7%) and 52 (80%) of 64 and 65 evaluable patients

**FIGURE 2** A, Best percent change from baseline in palpable spleen length and, B, in Total Symptom Score by 2 years from RUX start at any time. Each bar represents data from an individual patient

achieved a spleen or a symptom response, respectively. Additionally, 25% and 15.6% of patients had 25% to <50% reductions in spleen lengths at weeks 12 and 24, respectively. After a median ruxolitinib exposure of 27.3 months (range, 1–56.2), 27 (39.1%) patients maintained their spleen response.

Among baseline features that were tested for correlation with subsequent spleen or symptoms response at 3 and 6 months, none was significantly associated with responses.

### 3.3 | Ruxolitinib dose and safety

Ruxolitinib starting dose was  $\geq 10$  mg BID in all patients. During the first 12 weeks of therapy, 32.8% of patients had a decrease in RUX dose, while only 2 patients were able to increase the dosage. The incidence of RUX dose reductions was slightly higher in patients starting with 20 mg BID (37.5% versus 19% in patients that started with <20 mg BID,  $P = .06$ ). Overall, 80.6% patients could maintain a RUX dose  $\geq 15$  mg BID, and only 7.5% of patients experience reduction to <10 mg BID. Most notably, starting and average ruxolitinib doses did not influence the rate of responses at all time points.

Overall, 32 (45.7%) patients experienced RUX-induced anemia at any time during RUX therapy, (29%, grade 2; 21.7%, grade 3). At 3 months and 6 months, anemia was observed in 28 (40.6%) and 20 (30.8%) evaluable patients. Fifteen patients required occasional transfusion support. At baseline, all these patients carried a large ( $>10$  cm) splenomegaly, with a median TSS of 20 (range, 10–90). At 3 and 6 months, a spleen and symptoms response was achieved by 21.4% and 50% of the patients, respectively. Three patients acquired an IWG-MRT defined transfusion dependency. Thrombocytopenia any grade occurred in 35 (50.7%) patients (4.4%, grade 2; 2.9%, grade 3). At 3 months and 6 months, grade  $\geq 2$  thrombocytopenia was observed in 2 and 4 patients; no grade 4 thrombocytopenia was recorded.

Five of 51 (9.8%) patients that were screened for HBV infection were found to be positive for the HBsAg and for the anti-HBc antibodies; in two of these patients, a lamivudine prophylaxis was started. No cases of HBV reactivation were observed. The screening for *Mycobacterium tuberculosis* (TBC) was performed with chest X-ray and Quantiferon test in 36 patients before ruxolitinib start; in all cases, no signs of TBC were detected, and no patient received isoniazid prophylaxis. In 2 patients with a previous study of zoster reactivations, acyclovir prophylaxis was initiated together with the start of ruxolitinib. A total of 17 infectious complications  $\geq$  grade 2 were experienced by 12 patients after a median time of 8 months from ruxolitinib start (range, 2.3–40.2). Specifically, infections were grade 2 bronchitis (7 cases), grade 2 herpes simplex mucosal infection (3 cases), grade 3 herpes zoster reactivation (2 cases), grade 2 fever of unknown origin, urinary tract infection, grade 2 influenza virus infection, grade 2 *Staphylococcus aureus* skin infection, and grade 3 bone TBC infection.

### 3.4 | Treatment discontinuation and overall survival

A total of 12 (17.1%) patients discontinued RUX after a median time of 9.3 months (1–28.8). Reasons for treatment discontinuation were acute renal failure (1 case), lung cancer (1), disease progression without

evolution into acute leukemia (2), infectious complication (bone TBC, 1 case), evolution into acute leukemia (1), and lack or loss of response (6). Both patients that experienced a disease progression during ruxolitinib therapy with enlarging splenomegaly and worsening symptoms were submitted to alloSCT soon after ruxolitinib discontinuation. Overall, 4 patients died because of lung cancer, acute renal failure, complication after allogeneic transplant, and disease progression without acute evolution. Death occurred after a mean RUX exposure of 6.6 months (standard deviation, 4.4); in no case the death was directly attributed to therapy. Survival at 2 years was 80.1% for a median survival of 56.7 months.

## 4 | DISCUSSION

In real-world clinical practice, a substantial proportion of patients with intermediate-1 risk MF may require ruxolitinib therapy. In the present report, at 6 months, we observed a rate of spleen responses (54.7%) that was comparable to that observed at week 24 in the 14 intermediate-1 risk patients enrolled in the UK ROBUST trial (57.1%).<sup>18</sup> Notably, similar (63.8%) spleen responses were also observed in the 169 patients enrolled in the JUMP trial demonstrating comparable efficacy in intermediate-2/high IPSS risk patients that achieved a spleen length reduction by  $\geq 50\%$  in 56.9% of the cases. Similarly with the results of the JUMP study, ruxolitinib starting and average doses did not correlate with subsequent responses. This may be related to the fact that almost all patients were titrated to a dose  $\geq 10$  mg BID that has been previously associated with better responses.<sup>19</sup>

Recently, an ELN-SIE panel suggested (weak recommendation) the use of ruxolitinib in intermediate-1 patients in case of severe ( $\geq 15$  cm below LCM) or symptomatic splenomegaly not responsive to hydroxy-urea/interferon and in case of severe and symptomatic splenomegaly front-line.<sup>20</sup> Additionally, a TSS  $>44$  was indicated as a good cutoff for selecting patients with relevant MF-related symptoms. Here, 45 (65.2%) patients received ruxolitinib because of severe/symptomatic splenomegaly front-line or after failure of conventional therapy. In the remaining cases, ruxolitinib was administered to less symptomatic patients. The probability to achieve a spleen response at 6 months was not influenced by baseline disease severity (51.2% in patients treated according to ELN-SIE recommendations versus 60.9% in patients treated with less advanced disease,  $P = .60$ ). The rate of symptom responses at 6 months was also comparable (78% versus 87%,  $P = .51$ ). Additionally, the incidence of drug-induced anemia at 3 months was comparable among the 2 cohorts (37.8% versus 25%,  $P = .24$ ). As a result, the selection of intermediate-1 patients with substantial clinical need that has been suggested by the ELN-SIE panel obviously neither jeopardize response to therapy nor increase toxicities.

Notably, the rate of responses to ruxolitinib was not influenced by comorbidities. Consequently, even if the number of patients with higher CCI was small, comorbidities per se should not be regarded as contraindication to RUX therapy. Previous studies have demonstrated that responses to tyrosine kinase inhibitors may be negatively affected by an increased BMI ( $>25$ –40) at diagnosis.<sup>21</sup> In patients with MF treated with ruxolitinib, no data has been available so far. In this cohort of selected intermediate-1 IPSS risk, BMI was above 25 in 50% of

patients, while only 3 patients presented a low BMI (<18). Notably, neither a high nor a low BMI influenced the probability to achieve spleen or symptom response to ruxolitinib.

Hematological toxicity was limited and never caused therapy discontinuation. Nonetheless, the issue of infections needs attention and thoughtful consideration, since 17.1% of patients experienced at least one infectious event. Particularly, uncommon infections (TBC and HZV reactivation) occurred in 3 patients that did not have a past medical history positive for this type of infections. Of note, while hepatitis B serology was performed in most cases (72.6%), the screening for TBC was assessed only in 51.4% of the cases, with one patient that was not investigated for TBC baseline that finally developed a life-threatening TBC infection. These data reinforce the need for an accurate infectious evaluation of MF patients before the start of ruxolitinib treatment.<sup>22,23</sup>

There is an ongoing debate on the use of ruxolitinib in intermediate-1 patients, a population of patients that were excluded from pivotal clinical trials so far. While early initiation of JAK-inhibitor therapy could potentially result in better therapeutic advantage,<sup>24,25</sup> the issue of short- and long-term complications need better clarification, especially because the duration of treatment in intermediate-1 patients may be much longer than for high-risk cases. Beyond the analysis of patients enrolled in the expanded access study JUMP (n = 163) and in the Robust trial (n = 14), this is one of the largest study reporting efficacy and safety of ruxolitinib in this setting. Here, rates of response in spleen length and symptoms favored efficacy on both endpoints, with overall good tolerance. Toxicities appeared as expected, manifesting as anemia (including some transfusion dependence), thrombocytopenia and notably 16% of patients experiencing infection. These data support the need for standardized guidelines that may guide the decision to initiate ruxolitinib therapy in this risk category, balancing benefit expectations and potential adverse effects.

## AUTHOR CONTRIBUTIONS

FP, MT, GBe, AT, FC, MBr, MBe, NS, NP, MCr, Al, GBi, FHH, FB, BM, RL, LK, GAP, EA, LS, and MBo designed the study and wrote the paper. MS performed the statistical analysis. All authors collected clinical, laboratory, molecular, and histology data. AC, MCa, and NV supervised the study. All authors gave final approval to the manuscript.

## CONFLICT OF INTERESTS

MT has acted as consultant and received honoraria from Novartis, BMS, and ARIAD. MBo declares research funding from Novartis. GAP and AC report personal fees and nonfinancial support from NOVARTIS, from null, outside the submitted work. The other authors declare no conflict of interests.

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