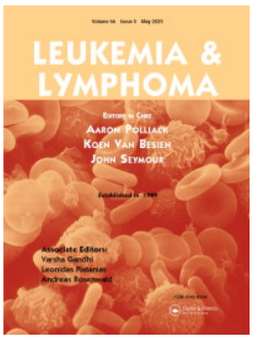


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LETTER TO THE EDITOR

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# Early intervention with ruxolitinib improves spleen response in patients with myelofibrosis

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Splenomegaly is a common clinical manifestation of myelofibrosis (MF), often associated with debilitating symptoms including early satiety, abdominal pain or discomfort, and inactivity, which negatively affect health-related quality of life (HRQoL) [1]. Splenomegaly is also associated with other complications including worsening cytopenias due to splenic sequestration, vascular issues, and poor outcomes following hematopoietic cell transplantation [2,3].

In the phase 3 COMFORT (Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment) trials, ruxolitinib improved spleen size, symptoms, and overall survival (OS) versus placebo or best available treatment in patients with MF [4]. Based on these findings, ruxolitinib was approved by the US Food and Drug Administration and the European Commission for treatment of intermediate- (Int) or high-risk MF. The phase 3b, single-arm, expanded-access JAK Inhibitor ruxolitinib in Myelofibrosis Patients (JUMP) study assessed efficacy and safety of ruxolitinib treatment for MF in a setting similar to routine clinical practice [5]. With 2233 patients enrolled, JUMP is the largest and most expansive clinical trial in patients with MF treated with ruxolitinib to date [5]. In the primary analysis, ruxolitinib demonstrated clinically meaningful reductions in spleen size and symptom improvement [4,6]. A subset analysis of patients with primary MF and baseline data on bone marrow (BM) fibrosis severity grade ($n = 1120$) found that those who initiated ruxolitinib ≤2 years after MF diagnosis had increased spleen response rates versus >2 years after diagnosis [5]. To verify effects of early versus delayed initiation of ruxolitinib on clinical outcomes, a *post hoc* analysis of the entire JUMP population is reported here.

Study details of the single-arm, open-label, phase 3b, expanded-access global JUMP trial have been published previously and are described in the supplementary methods [5]. This *post hoc* analysis evaluated spleen response (defined as percentage of patients who achieved ≥50% reduction from baseline in palpable spleen length) and change from baseline in spleen length at Weeks 12, 24, and 48. At Week 24, HRQoL was assessed by the percentage of patients achieving Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) response (≥6.5-point increase from baseline in FACT-Lym total score, the lower limit of the minimum clinically important difference [7]) and change from baseline in FACT-Lym total score. Time from first study dose to date of death was used to assess OS.

Patients were stratified into subgroups based on time between MF diagnosis and ruxolitinib initiation (≤12 vs. >12 months; ≤24 vs. >24 months). The percentage of patients who achieved spleen response and percentage change in spleen length were compared between subgroups using chi-square tests and least squares means from a mixed model procedure using pairwise differences, respectively. Analyses of spleen response and symptom response were conducted in the full study population, including patients with missing data. Other spleen and symptom analyses only included patients with data available at each time point. The Kaplan–Meier method was used to assess OS.

Demographics and baseline clinical characteristics were generally similar across subgroups, other than mean (SD) time since initial MF diagnosis [≤12 months, 4.2 (3.5) months ($n = 818$); >12 months, 79.3 (66.9; $n = 1415$); ≤24 months, 7.7 (7.2; $n = 1081$); >24 months, 93.2 (66.8; $n = 1152$); Table 1]. In all subgroups, >90% of patients had a palpable spleen. The most common prior therapies in the ≤12 versus >12 months subgroups were hydroxyurea [41.9% (343/818) vs. 67.8% (959/1415)], anagrelide [1.7% (14/818) vs. 4.0% (57/1415)], and interferon [1.2% (10/818) vs. 2.8% (39/1415)]. Mean (SD) ruxolitinib starting dose was similar in the ≤12 versus >12 months subgroups [35.6 (7.7) mg vs. 34.1 (8.6) mg daily], as were dose modifications (Supplementary Table 1). Mean daily doses of ruxolitinib (averaged over 4 weeks) were highest over the first 4 weeks of treatment (>30 mg) and from Week 8 onward remained >25 mg for all subgroups (Supplementary Figure 1).

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**Table 1.** Patient demographics and baseline clinical characteristics.

| Variable | Time between MF diagnosis and RUX initiation | | | |
|---|---|---|---|---|
| | ≤12 months ($n$ = 818) | >12 months ($n$ = 1415) | ≤24 months ($n$ = 1081) | >24 months ($n$ = 1152) |
| Age, mean (SD), years | 65.9 (10.6) | 65.3 (10.5) | 65.9 (10.7) | 65.3 (10.4) |
| Age category, $n$ (%) | | | | |
| <65 years | 322 (39.4) | 577 (40.8) | 428 (39.6) | 471 (40.9) |
| ≥65 years | 496 (60.6) | 838 (59.2) | 653 (60.4) | 681 (59.1) |
| Male sex, $n$ (%) | 483 (59.0) | 734 (51.9)** | 625 (57.8) | 592 (51.4)** |
| Race, $n$ (%) | | | | |
| White | 755 (92.3) | 1332 (94.1) | 998 (92.3) | 1089 (94.5) |
| Black | 7 (0.9) | 13 (0.9) | 10 (0.9) | 10 (0.9) |
| Asian | 9 (1.1) | 14 (1.0) | 11 (1.0) | 12 (1.0) |
| Other | 47 (5.7) | 56 (4.0) | 62 (5.7) | 41 (3.6) |
| Ethnicity, $n$ (%) | | | | |
| Hispanic/Latino | 190 (23.2) | 319 (22.5) | 249 (23.0) | 260 (22.6) |
| Other | 628 (76.8) | 1096 (77.5) | 832 (77.0) | 892 (77.4) |
| BMI, mean (SD), kg/m$^2$ | 24.6 (3.8) | 24.2 (3.8) | 24.6 (3.8) | 24.2 (3.7) |
| Duration on study, median (range), months | 14.8 (0.4–59.3) | 13.7 (0.1–60.9) | 14.9 (0.4–59.3) | 13.2 (0.1–60.9) |
| DIPSS risk level, $n$ (%) | | | | |
| High | 68 (8.3) | 126 (8.9) | 93 (8.6) | 101 (8.8) |
| Intermediate 2 | 257 (31.4) | 498 (35.2) | 356 (32.9) | 399 (34.6) |
| Intermediate 1 | 328 (40.1) | 507 (35.8) | 424 (39.2) | 411 (35.7) |
| Low | 17 (2.1) | 43 (3.0) | 26 (2.4) | 34 (3.0) |
| Missing | 148 (18.1) | 241 (17.0) | 182 (16.8) | 207 (18.0) |
| Time since initial diagnosis, mean (SD), months | 4.2 (3.5) | 79.3 (66.9)*** | 7.7 (7.2) | 93.2 (66.8)*** |
| Hb level <100 g/L, $n$ (%) | 294 (35.9) | 562 (39.7) | 389 (36.0) | 467 (40.5)* |
| PLT level <100 × 10$^9$/L, $n$ (%) | 39 (4.8) | 99 (7.0)*** | 56 (5.2) | 82 (7.1)** |
| Palpable spleen, $n$ (%) | 749 (91.6) | 1338 (94.6)** | 1001 (92.6) | 1086 (94.3)** |
| Palpable spleen length below costal margin, mean (SD), cm | 12.0 (6.4) | 14.1 (6.8)*** | 12.3 (6.5) | 14.3 (6.9)*** |
| FACT-Lym total score, mean (SD) | 114.5 (23.2) | 113.6 (24.5) | 113.6 (23.5) | 114.2 (24.5) |

BMI, body mass index; DIPSS, Dynamic International Prognostic Scoring System; FACT-Lym, Functional Assessment of Cancer Therapy–Lymphoma; Hb, hemoglobin; MF, myelofibrosis; PLT, platelet; RUX, ruxolitinib.
*$p$ < 0.05; **$p$ < 0.01; ***$p$ < 0.0001 (≤12 vs. >12 months or ≤24 vs. >24 months).

Comparison between early and delayed treatment subgroups (≤12 vs. >12 months; ≤24 vs. >24 months) found significantly more patients with earlier ruxolitinib initiation had a spleen response versus those with later initiation at each time point (Figure 1(A); $p$ < 0.05). Spleen length improvements were also significantly larger among patients with earlier ruxolitinib initiation (Figure 1(B); ≤12 vs. >12 months; ≤24 vs. >24 months; $p$ < 0.001). At Week 24, FACT-Lym response rates were similar in all subgroups [≤12 months, 25.7% (210/818); >12 months, 27.6% (391/1415); ≤24 months, 28.1% (304/1081); >24 months, 25.8% (297/1152)]. Corresponding mean (SD) percentage changes from baseline in FACT-Lym total score were 9.7% (20.1), 10.9% (22.9), 10.9% (22.9), and 10.0% (20.9), respectively. No differences in OS were observed across subgroups, and median OS was not reached in any subgroup [hazard ratio: ≤12 vs. >12 months, 1.08 (95% CI, 0.83–1.4); ≤24 vs. >24 months, 1.07 (0.83–1.4)].

In this *post hoc* analysis of patients from JUMP stratified by time between MF diagnosis and initiation of ruxolitinib, significantly more patients who initiated treatment earlier had a spleen response versus patients who initiated treatment later. Spleen length improvements were also significantly greater among patients with earlier versus later treatment initiation, with significant differences between subgroups observed by Week 12 and through Week 48 for both spleen outcomes. These results support early initiation of ruxolitinib to provide patients with the best opportunity to obtain a spleen response.

The findings of the present study are consistent with those from a prior subset analysis of patients from JUMP ($n$ = 1120, limited to patients with primary MF and a documented fibrosis grade) that stratified patients by baseline BM fibrosis [5]. Although no statistical analyses were performed, patients who initiated ruxolitinib within 12 or 24 months of MF diagnosis had increased spleen response rates versus those who initiated ruxolitinib more than 12 or 24 months after diagnosis, regardless of BM fibrosis severity at baseline [5]. Consistent with OS results in the present study, no differences in OS were reported based on timing of ruxolitinib treatment initiation. Another secondary analysis of data from JUMP, which aimed to identify predictive factors of spleen and symptom response with ruxolitinib treatment, demonstrated that earlier treatment (≤2 vs. >2 years) was associated with a higher spleen response rate in a univariate analysis [8]. Time since diagnosis was not identified as an independent predictor of spleen or symptom response in a multivariate analysis; however, alternative definitions of early treatment were identified as independent predictors for both [i.e. lower International Prognostic Scoring System (IPSS) risk status and first-line vs. second- or later-line ruxolitinib treatment]. Importantly, in low-risk and high-risk patients, OS was numerically longer among patients with versus without spleen response at 24 weeks of ruxolitinib treatment, albeit with small sample sizes and without statistical analysis. The results from JUMP presented here add to the previous analyses by extending the ≤12- versus >12-month treatment delay findings to the entire JUMP population, including patients with secondary MF, and by comparing subgroups with statistical analyses.

Also consistent with the present analysis, a pooled analysis of COMFORT data showed that more patients who initiated ruxolitinib ≤12 months after MF diagnosis achieved ≥35% reduction in spleen volume compared

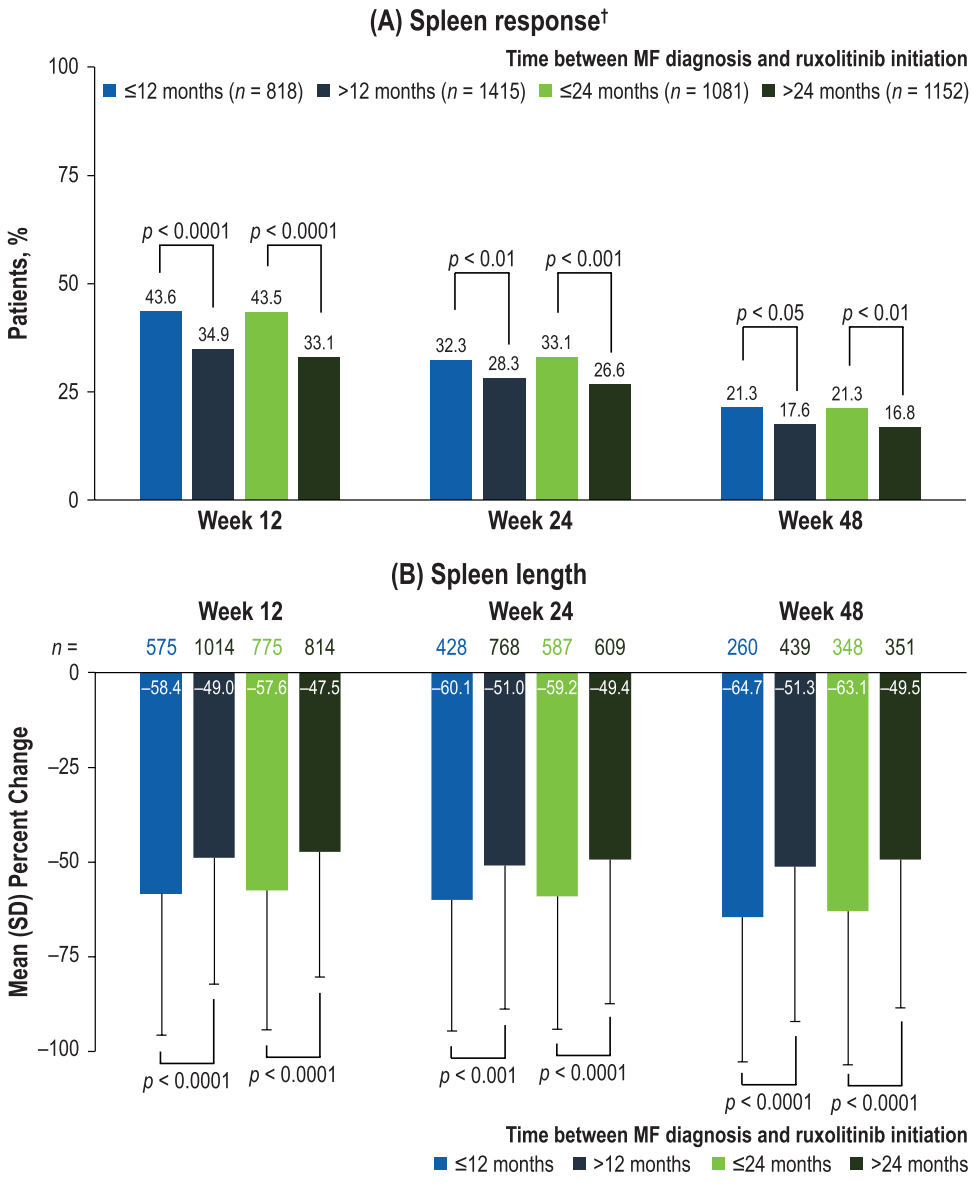


**Figure 1.** Spleen outcomes at Weeks 12, 24, and 48. †Spleen response was defined as ≥50% reduction in palpable spleen length from baseline. MF, myelofibrosis.

with those who initiated ruxolitinib >12 months after diagnosis [9]. However, in contrast to the current JUMP analysis, OS was significantly longer among patients who initiated ruxolitinib earlier versus later in the COMFORT analysis. One explanation for this discrepancy is that lower-risk patients were ineligible for inclusion in COMFORT but were included in JUMP, which may suggest that earlier initiation of ruxolitinib has survival benefits for high-risk MF. Alternatively, ruxolitinib dose and exposure may have differed between studies. Results from this JUMP analysis extend the spleen-related outcomes from the COMFORT analyses, which were observed in patients with Int-2 and high-risk MF, to a real-world population that includes patients with Int-1, Int-2, and high-risk MF. The main limitation of this analysis is that it was a *post hoc* investigation with no prespecified statistical testing.

Finally, an independent retrospective study of Italian patients with MF treated with ruxolitinib for 6 months ($n = 408$) investigated pretreatment factors negatively associated with spleen and symptom responses [10]. In agreement with the findings presented here, ruxolitinib initiation >2 years after MF diagnosis was significantly negatively correlated with spleen response in univariate and multivariate analyses. In univariate analysis, a longer time interval before ruxolitinib initiation was significantly associated with a lower probability of achieving a symptom response versus a shorter interval. However, the association was not significant in multivariable analysis [10].

In conclusion, in this *post hoc* analysis of data from JUMP, patients initiating ruxolitinib earlier after MF diagnosis had better spleen responses than those who initiated later. Improvements in symptom response and OS remained consistent, regardless of the timing of ruxolitinib initiation. These results are consistent with analyses from other trials supporting clinical benefit of earlier ruxolitinib

intervention in patients with MF, most notably for superior spleen response.

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## Data availability statement

Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except Phase 1 studies) for which the product and indication have been approved on or after 1 January 2020 in at least one major market (e.g. US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

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