

# Survival outcomes in myelofibrosis patients treated with ruxolitinib: A population-based cohort study in Sweden and Norway

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## Abstract

**Objective:** To estimate survival in Swedish and Norwegian myelofibrosis (MF) patients who received ruxolitinib.

**Methods:** Swedish and Norwegian patients with MF diagnosis in the National Cancer Registries (Sweden: 2001-2015; Norway: 2002-2016) and  $\geq 1$  record of ruxolitinib in the Prescribed Drug Registries (2013-2017) were included. Patients were followed from ruxolitinib initiation until death or end of follow-up; those who discontinued ruxolitinib were followed from ruxolitinib discontinuation. Relative survival (RS) and excess mortality rate ratios (EMRRs) were calculated vs a matched general population. Average loss in life expectancy (LEL) was predicted using flexible parametric models.

**Results:** Among patients who initiated ruxolitinib ( $n = 190$ ), 1- and 4-year RS were 0.80 (95% confidence interval [CI]: 0.74, 0.86) and 0.52 (95% CI: 0.42, 0.64), respectively, and LEL was 11 years. EMRR was greater in patients aged  $>70$  vs  $<60$  years (3.16; 95% CI: 1.34-7.40). Among patients who discontinued ruxolitinib ( $n = 71$ ), median RS was 16.0 months (95% CI: 6.3, NE), and LEL was 12 years. After ruxolitinib treatment discontinuation, Swedish patients ( $n = 37$ ) received glucocorticoids, hydroxyurea, busulfan, danazol and lenalidomide.

**Conclusion:** Swedish and Norwegian MF patients who discontinued ruxolitinib had dismal survival outcomes and limited subsequent treatment options, highlighting the need for improved therapies.

## KEYWORDS

hematopoiesis and hematopathology, myeloproliferative neoplasms

## 1 | INTRODUCTION

Myelofibrosis (MF) is a clonal malignancy of hematopoietic cells characterised by progressive bone marrow fibrosis, splenomegaly, inefficient haematopoiesis, constitutional symptoms

and bone pain. MF can either develop de novo (primary MF) or secondary to polycythaemia vera (PV) or essential thrombocythemia (ET).<sup>1</sup> Survival in patients with myeloproliferative neoplasms (MPNs) is shorter compared with the general population and particularly pronounced for MF.<sup>2</sup> Furthermore, MF is often

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associated with a profound negative effect on quality of life.<sup>3</sup> Approximately 8%-20% of patients with MF eventually transform into acute myeloid leukaemia and consequently have an even shorter survival.<sup>4-6</sup>

Historically, available treatment options for MF have been symptomatic with limited or no disease modifying potential. In a Swedish population-based study, Hultkrantz et al<sup>2</sup> described improved survival outcomes in MPN patients over the last decades; however, the improvement was less pronounced after the calendar year 2000 and confined to patients with PV and ET, suggesting dismal outcomes with current treatment options for MF in clinical practice. Recent evidence suggests that the Janus kinase (JAK) signalling pathway may play a central role in the pathogenesis of MF. Results from clinical studies suggest that the JAK-1/2 inhibitor ruxolitinib is effective in reducing symptoms of MF, which also has translated into improved quality of life.<sup>1</sup> Ruxolitinib was approved based on the results of two phase-III studies that compared ruxolitinib with placebo or best available care. The US Food and Drug Administration approved ruxolitinib for intermediate and high-risk MF,<sup>7,8</sup> while the European Medicines Agency approved ruxolitinib for treatment of splenomegaly and/or constitutional symptoms of MF, irrespective of risk group.<sup>1</sup> There is limited evidence to show that ruxolitinib improves survival outcomes by modifying the disease course, although its effect on metabolic and nutritional variables may translate into survival benefits.<sup>9</sup> Eventually, most patients discontinue treatment due to adverse events or lack of efficacy.<sup>9</sup> In recent phase-III studies, about 50% of patients discontinued ruxolitinib within 3 years of treatment.<sup>7</sup> Salvage therapy options remain scarce<sup>10</sup> and mostly include allogeneic stem cell transplantation (allo-SCT) followed by immunomodulators; however, prognosis is unfavourable.<sup>9</sup> Although allo-SCT is the only curative treatment, it is rarely used in Sweden and Norway in this patient population due to the significant risk of morbidity and mortality.<sup>11</sup>

Randomised controlled clinical trials are critical tools when assessing benefits of novel agents compared to standard of care. However, longitudinal observational studies can be an invaluable complement to these studies in the evaluation of patient outcomes in clinical practice. The present study is the first national population-based study to describe survival outcomes in MF patients receiving ruxolitinib outside clinical trial settings in Sweden and Norway.

## 2 | PATIENTS AND METHODS

### 2.1 | Data sources and patient selection

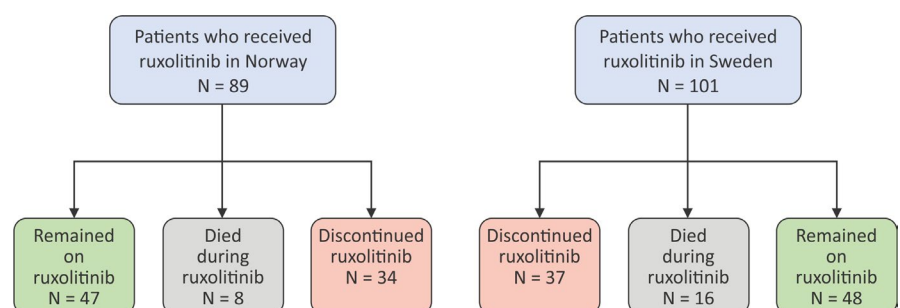
All residents of Sweden ( $\approx 10$  million) and Norway ( $\approx 5$  million) receive health care through one universal national system, and a unique personal identification number is assigned to each resident at birth which enables linkage between registers. All malignant disorders have been registered in the nationwide Swedish Cancer Register since 1958, and since 1984, there has been a double reporting routine where clinicians and pathologists/cytologists are obliged by law to report all new cases of cancer. Similarly, in Norway, registration of new malignant cases has been compulsory since 1951.

For the present study, inclusion criteria were age  $\geq 18$  years at MF diagnosis (identified by ICD7: 209 [Sweden]; ICD-O/3:9975/3, 9960/3, 9961/3 [Norway]) in the national cancer registries (Sweden: 2001-2015; Norway: 2002-2016) and at least one record of ruxolitinib (ATC: L01XE18) in the Prescribed Drug Registries (2013-2017) (Figure 1). The total observation time for the Prescribed Drug Registry in Sweden was from June 2005 to September 2017. The completeness and diagnostic accuracy of the national Cancer Registers have been demonstrated to be about 96% in Sweden<sup>12</sup> and 98% in Norway.<sup>13</sup> Although the Cancer Register has a high overall coverage, there has been a certain degree of under-reporting of indolent malignancies such as MPNs and Waldenström Macroglobulinemia.<sup>14,15</sup> Mortality data were collected from the Cause of Death Registries (Sweden: January, 2014 to November, 2017; Norway: January, 2014 to September 2017).

The study was approved by the Regional Ethical Review Board in Stockholm and the SOR-OST Regional Ethics Committee in Norway. The study was also approved by the National Board of Health and Welfare in Sweden, and the National Agency of Data Protection in Norway, for patient integrity and data handling. Informed consent was waived since there was no contact with study objectives.

### 2.2 | Study design and data collection

This was a retrospective cohort study. All patients who received ruxolitinib ( $n = 190$ ) were followed from treatment initiation until death, censoring or end of follow-up ([Sweden] November 2017; [Norway] October, 2017). Patients who discontinued ruxolitinib treatment were followed from ruxolitinib discontinuation until death, censoring



**FIGURE 1** Patient selection [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 1** Baseline characteristics of myelofibrosis patients receiving ruxolitinib

	Sweden (n = 101)	Norway (n = 89)	Merged (n = 190)
Number of patients with primary myelofibrosis (n, %)	100 (99%)	89 (100%)	189 (99.5%)
Age (years) at diagnosis, median (IQR)	63 (54, 71)	65 (56, 70)	64 (55, 71)
Sex, male (n, %)	50 (49.5)	51 (56.0)	101 (53.2)
Median time (years) from diagnosis to start of ruxolitinib treatment (IQR)	3.2 (1.1, 6.2)	3.3 (1.0, 4.9)	3.2 (1.1, 5.9)
Median ruxolitinib treatment duration (months) (IQR)	11.9 (6.0, 21.0)	10.8 (4.8, 24.7)	11.5 (5.2, 22.0)

Abbreviation: IQR, interquartile range.

or end of follow-up. Ruxolitinib treatment duration was defined as the time between the date of the first dispensation to the date of the last dispensation plus the number of days of assumed drug supply for the last dispensation (28 days for one package (56 tablets) and 56 days if  $\geq 2$  packages were dispensed) in the Prescribed Drug Register.

### 2.3 | Statistical analysis

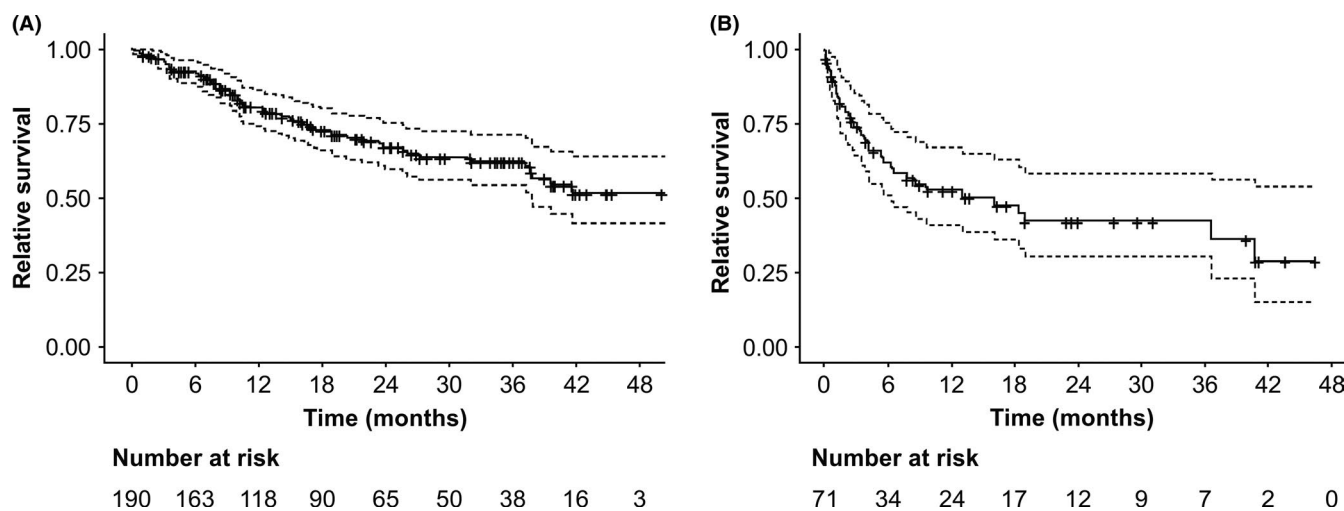
Overall survival (OS) and relative survival (RS) were estimated. For the RS analyses, excess mortality of MF patients compared with a general population matched on age, gender, calendar year at diagnosis and country, was calculated. Excess mortality rate ratios (EMRRs) were also estimated to assess the effect of age, sex and time from MF diagnosis to start of ruxolitinib on excess mortality. Mortality data of the general population used for RS and EMRR estimates were obtained from the Human Mortality Database.<sup>16</sup> In addition, we investigated the loss in life expectancy (LEL) from ruxolitinib initiation and discontinuation using flexible parametric models adjusted for age, sex, calendar year and country.<sup>17</sup> LEL was calculated as the difference in life expectancy of MF patients from their index dates and that of the matched population. For the Swedish cohort, the number of patients receiving other MF-specific treatments as defined in the Nordic MPN recommendations<sup>18</sup> before, during and

after ruxolitinib were summarised descriptively. Drugs dispensed before or on the date of the first ruxolitinib dispensation were considered treatment before ruxolitinib, and drugs dispensed after or on the date of the last ruxolitinib dispensation were considered treatment after ruxolitinib. Drugs dispensed between the first and the last ruxolitinib dispensation dates were considered dispensed during ruxolitinib treatment. RS and EMRRs were estimated using the *relsurv* package in R. LEL analyses were conducted using *stpm2* package in STATA.

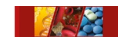
## 3 | RESULTS

Among the 190 patients who received ruxolitinib, 101 were Swedish and 89 were Norwegian. Twenty-four patients died during the observation period, and 95 remained on treatment at the end of follow-up. Most patients had primary MF, median age at MF diagnosis was 64 years (inter quartile range [IQR]: 55,71) and 53.2% were male. Median time from MF diagnosis to ruxolitinib treatment initiation was 3.2 years (IQR 1.1,5.9) and median ruxolitinib treatment duration was 11.5 months (IQR 5.2,22.0) (Table 1).

Median follow-up time from ruxolitinib initiation and discontinuation, respectively, were 16.6 (IQR: 8.5,32.2) and 5.4 (IQR: 1.6,16.9) months. For all survival analyses we only report RS since OS was



**FIGURE 2** A, Relative survival from ruxolitinib treatment initiation (n = 190), B, Relative survival from ruxolitinib treatment discontinuation (n = 71)



**TABLE 2** Excess mortality rate ratios (EMRRs) in myelofibrosis patients from ruxolitinib treatment initiation (n = 190) and discontinuation (n = 71)

Covariate	EMRR (95% CI)	P value	EMRR (95% CI)	P value
	From ruxolitinib initiation		From ruxolitinib discontinuation	
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.54 (0.86, 2.76)	0.15	1.93 (0.93, 4.02)	0.08
Age at diagnosis				
<60	1.00 (reference)		1.00 (reference)	
60-70	1.13 (0.43, 2.97)	0.8	1.10 (0.33, 3.65)	0.88
>70	3.16 (1.34, 7.40)	0.008	1.83 (0.59, 5.66)	0.29
Time from diagnosis to ruxolitinib initiation				
<1 y	1.00 (reference)		1.00 (reference)	
>1 y	0.71 (0.37, 1.36)	0.304	0.66 (0.30, 1.43)	0.29

Abbreviation: CI, Confidence interval.

**TABLE 3** Treatments used by Swedish myelofibrosis patients receiving ruxolitinib

Treatment	Before ruxolitinib (n = 101)	During ruxolitinib (n = 101)	After ruxolitinib (n = 37)
Busulfan	2	0	3
Hydroxyurea	73	12	12
Anagrelide	10	2	0
Danazol	3	1	2
Interferon alfa-2b	1	0	0
Peginterferon alfa-2a	17	4	2
Peginterferon alfa-2b	4	0	0
Thalidomide	8	0	2
Azathioprine	4	1	0
Methotrexate	2	0	0
Lenalidomide	0	1	0
Glucocorticoids	53	27	24

identical to RS. From ruxolitinib initiation, 1- and 4-year RS were 0.80 (95% confidence interval [CI]: 0.74, 0.86) and 0.52 (95% CI: 0.42, 0.64), respectively (Figure 2A). EMRR was greater in patients aged >70 vs <60 years (3.16; 95% CI: 1.34-7.40). Sex and time from MF diagnosis to ruxolitinib treatment initiation were not associated with risk of death (Table 2). Among patients who discontinued ruxolitinib (n = 71), median RS from treatment discontinuation was 16.0 months (95% CI: 6.3, NE) (Figure 2B). From ruxolitinib treatment, discontinuation none of the studied variables in the EMRR model were significantly associated with excess mortality (Table 2). The average MF-related LEL from ruxolitinib initiation was 11 years, and the corresponding LEL from ruxolitinib discontinuation was 12 years.

For the Swedish patients (n = 101), hydroxyurea (n = 73) was the most commonly used treatment before ruxolitinib initiation, followed by glucocorticoids (n = 53) and peginterferon alfa-2a (n = 17). During ruxolitinib treatment, glucocorticoids (n = 27) was frequently added and some patients also received hydroxyurea (n = 12). After ruxolitinib discontinuation (n = 37), a proportion of patients received glucocorticoids (n = 24), hydroxyurea (n = 12) and busulfan (n = 3) (Table 3).

## 4 | DISCUSSION

In the present study, Swedish and Norwegian registries were used to estimate survival in MF patients treated with ruxolitinib in clinical practice. The study demonstrates poor RS compared with a matched general population and emphasizes the lack of effective salvage treatment options after ruxolitinib discontinuation.

Follow-up studies of the COMFORT-I and COMFORT-II trials showed that half of the patients discontinued ruxolitinib within 3 years and another 25% discontinued within 5 years from ruxolitinib initiation. In controlled clinical trial settings, the most frequently reported causes of treatment discontinuation were disease progression, adverse events and lack of efficacy.<sup>7</sup> These findings were also supported by Kuykendall et al<sup>9</sup> in a retrospective, single-centre study in the US and by Palandri et al<sup>19</sup> in a retrospective database analysis including data from 23 European hematology centres. Data on reasons for ruxolitinib discontinuation were not available in the present study. In a clinical phase I/II study, Newberry et al<sup>20</sup> reported a median survival of 14 months from ruxolitinib



discontinuation and concluded that low platelet counts at initiation or discontinuation of ruxolitinib therapy as well as clonal evolution during therapy may predict a worse prognosis. However, generalizability of these findings may be limited due to a single-centre design.

Although not presented in the current study, crude OS estimates were identical to the RS estimates, which is in line with what one would expect given age distribution and short expected survival in the late stage disease of interest in the present study. Since there is a scarcity of similar studies reported in available literature, the possibility to compare our results with those of other studies is limited. In the US study, Kuykendall et al<sup>9</sup> reported a median OS from ruxolitinib discontinuation of 13 months in MF patients with low to high Dynamic International Prognostic Scoring System (DIPSS) scores. In the present study, median RS was 16 months after ruxolitinib discontinuation. However, these results should be interpreted with caution since few patients (n = 20) were alive at 16 months, resulting in a wide confidence interval (95% CI: 6.3-NE). Also, these results may not be comparable with the US study since the latter included healthier patients (low to high DIPSS scores). In the present study, although no information on DIPSS or International Prognostic Scoring System scores were available, it was assumed that most of the patients had intermediate-2 or high-risk MF, since ruxolitinib treatment is only reimbursed and recommended for patients within these risk groups in Sweden and Norway.<sup>18</sup> Furthermore, in another retrospective study in the US, Mehra et al<sup>21</sup> reported a median OS of 14 months in patients who discontinued ruxolitinib. However, Palandri et al<sup>19</sup> reported a median OS of 22.6 months (95% CI, 13.2-30.7), which is superior compared with what we report in the present study (16 months, 95% CI, 6.3-NE). Distribution of patient characteristics and differences in reasons for treatment discontinuation may be reasons for this rather small difference.

Previous studies have reported that allo-SCT, lenalidomide, thalidomide, interferon, danazol and hydroxyurea are frequently used after ruxolitinib discontinuation.<sup>9,17-19</sup> In the present study, the most commonly used drugs were glucocorticoids (65.9%) followed by hydroxyurea (32.4%). The lack of effective treatment options is likely to contribute to high mortality rates.

The main strength of this study was the quality of data, that is complete national coverage from two countries, population-based and longitudinal. Study limitations included small sample sizes, no information on risk scores and relatively short follow-up since ruxolitinib has only been available in clinical practice since 2013 in Sweden and Norway. In addition, we did not have access to information on allo-SCT or if patients received treatments within clinical trials. Furthermore, since we only included patients with MF who received ruxolitinib treatment, findings may not be generalizable to a broader MF population. Since patients that received a MF diagnosis early in the observation period per definition had to survive long enough to get access to ruxolitinib, we included time from MF diagnosis to ruxolitinib initiation as a covariate in the EMRR model. However, since index date is set to ruxolitinib initiation and discontinuation, and not MF diagnosis, the risk for immortal time bias is minimised. This assumption was also confirmed by the EMRR analyses since there

was no statistical association with death when comparing patients with MF diagnosis less or more than 1 year from ruxolitinib initiation. Results from the present study may be generalizable to corresponding patient populations in countries that have a healthcare system and treatment guidelines comparable to that in Sweden and Norway.

This is the first real-world study using nationwide population-based data to describe survival outcomes in MF patients who received ruxolitinib. The study results corroborate previous findings in similar patient populations and show that patients who discontinued ruxolitinib treatment had poor survival outcomes. Treatment options after ruxolitinib discontinuation were scarce and mostly limited to palliative care, highlighting the need for more effective therapeutic options.

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## CONFLICT OF INTEREST

CS, EV, JL, CL and JH are employees of Janssen. JL and CL hold stocks in the company. FS was an employee of Janssen at the time this study was conducted, and currently, she is an employee and owner of Schain Research AB and work as a consultant for Janssen. MB has previously received consultancy fees from Janssen.

## AUTHOR CONTRIBUTIONS

FS, JL, JH and MB contributed to the conception and design; FS and JL acquired the data; EV, CS, JL, CL, FS, JH and MB contributed to data analysis and interpretation. All authors were involved in drafting the manuscript and approval of the final manuscript for submission.

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