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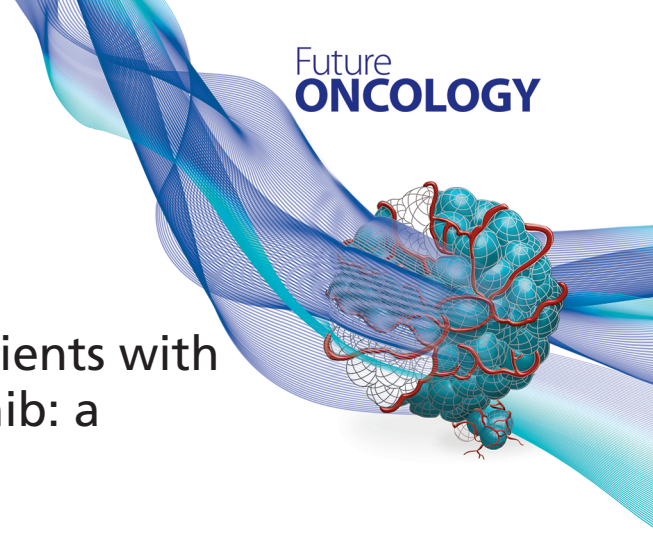

Real-world clinical outcomes of patients with myelofibrosis treated with ruxolitinib: a medical record review

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Aim: To assess real-world ruxolitinib treatment patterns and outcomes in patients diagnosed with primary or secondary myelofibrosis. **Materials & methods:** Patient medical records were reviewed in six countries. **Results:** Eligible patients (n = 469) had a mean age of 63.5 years, and most were male (66.5%) with primary myelofibrosis (78.5%). Median duration of ruxolitinib treatment was 13.1 months; 40% of patients initiated treatment at the recommended dose. The Kaplan–Meier estimate of median survival from ruxolitinib initiation was 44.4 months (95% CI, 38.8–50.2 months). Approximately one quarter (23%) of patients continued ruxolitinib after progression. **Conclusion:** These results suggest an unmet need for more effective treatments for patients with myelofibrosis who failed ruxolitinib.

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Keywords: medical record review • myelofibrosis • real-world data • ruxolitinib • survival analysis

Myeloproliferative neoplasms (MPNs) are a group of rare hematological diseases that are caused by an overproduction of blood cells or platelets [1,2]. The three main types of MPNs include primary myelofibrosis (PMF), polycythemia vera (PV) and essential thrombocythemia (ET). Patients with MPNs can present with diverse symptoms, and PV and ET can progress into postpolycythemia vera (PPV) and post-essential thrombocythemia (PET) MF [3,4]. Myelofibrosis is characterized by cytopenias, splenomegaly and often debilitating constitutional symptoms such as fatigue, early satiety, weight loss, night sweats, fever, bone pain and pruritus. The most commonly observed gene mutations in patients with MF are *JAK2 V617F* (*JAK2*; 45–68% of patients), calreticulin (*CALR*; 25–35% of patients) and myeloproliferative leukemia virus (*MPL*; 5–10% of patients) [5].

Allogeneic hematopoietic stem-cell transplant (HSCT) is the only available treatment with the potential to cure MF, but it is associated with substantial morbidity and mortality and is considered an option for patients with MF without significant comorbidities who have high-risk molecular features and an available donor [6]. Therefore, the main objectives of non-HSCT treatments for MF are symptom control and prolonged survival [1]. The development of JAK inhibitors in the last decade has transformed the treatment prospects of patients with MF, but only two JAK inhibitors are approved for MF treatment so far: ruxolitinib and fedratinib. JAK inhibition has become a recommended induction therapy for MF treatment due to significantly improved patient prognosis in JAK inhibitor clinical trials [6–12]. Ruxolitinib was the first approved JAK inhibitor for the treatment of MF and has been associated with significant symptom improvement, including reducing spleen volume by approximately 35% over the duration of therapy, and improvements in quality-of-life [11,13,14]. Splenomegaly is a potentially painful symptom of MF and is associated with delayed treatment and poor prognosis, so the advent of JAK inhibitors to manage this characteristic in some patients with MF has had a high clinical impact [15]. Although ruxolitinib is a valuable treatment option for patients with MF, long-term evaluation in clinical trials has shown that up to

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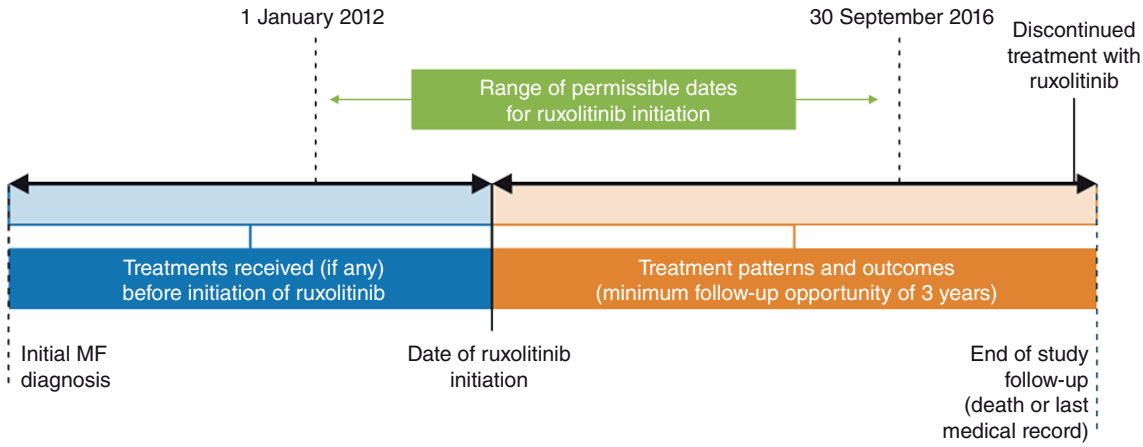

Figure 1. Study design.
MF: Myelofibrosis.

89% of patients discontinue ruxolitinib within 3 years, with common reasons for discontinuation being adverse events, disease progression and death [12,16–18]. Management of ruxolitinib-related adverse events (e.g., cytopenias) may require close monitoring and subsequent ruxolitinib dose adjustment while not compromising treatment efficacy [19]. Until the recent approval of fedratinib, dose modification and ruxolitinib rechallenge were potential approaches to managing MF in patients whose disease progressed while on ruxolitinib treatment [20].

An unmet need for additional therapeutic options remains for patients with MF who experience disease progression while being treated with ruxolitinib. However, there is limited real-world evidence on the treatment patterns and clinical outcomes associated with ruxolitinib treatment. This study examined the treatment patterns and clinical outcomes of ruxolitinib in a real-world multinational cohort of patients diagnosed with MF.

Materials & methods

Study design

This retrospective study of real-world ruxolitinib treatment patterns used data collected from a review of medical records for patients diagnosed with primary or secondary MF in the USA, Canada, the UK, Germany, Spain and France (Figure 1). A convenience sample of physicians practicing in various care settings representing various geographic regions of the respective countries were recruited for the study. Physician directories in respective countries were the primary source of recruitment. A total of 155 physicians, primarily hematologist-oncologists, abstracted data from qualifying patients' electronic medical records for this study. Forty-one physicians abstracted data in the USA, 22 in the UK, 28 in Germany, 30 in Spain, 5 in Canada and 24 in France. RTI Health Solutions received funding under a research contract with Bristol Myers Squibb to conduct this study. Data abstraction was conducted between April 2020 and June 2020 and included all relevant data from the time of the patient's diagnosis with MF through at least 3 years of follow-up after discontinuation of treatment. Physicians specializing in hematology and/or oncology were recruited from both academic and community practices in the six study countries to identify eligible patients and perform data abstraction. Eligible physician participants treated at least five patients with MF in the 12 months prior to data abstraction, acted as the main decision maker for MF treatment and follow-up, and had access to the medical records of both living and deceased patients. All patient data were deidentified, and RTI International's institutional review board (IRB) reviewed the study protocol and deemed the research exempt from full IRB review. The study was also subjected to and approved by applicable country-specific ethics review committees. Additional information on the ethics committees approving this study is available upon request.

Patient selection

Eligible patients were adults (aged ≥18 years) with a confirmed diagnosis of PMF, PPV or PET MF and intermediate 1 risk with constitutional symptoms, intermediate 2 risk or higher-risk MF at initial diagnosis. Eligible patients were also required to have initiated treatment with ruxolitinib between 1 January 2012 and 30 September 2016 for a period of at least 14 days and to have a palpable spleen at ruxolitinib initiation. Patients included in the study

could have either been living or deceased at the time of data abstraction. Patients were required to have discontinued treatment with ruxolitinib before the start of data abstraction in 2020; previous studies have indicated that 89% of patients discontinue ruxolitinib therapy within 3 years, which aligns with the minimum time between ruxolitinib initiation and discontinuation (i.e., from 30 September 2016 to 1 April 2020) in this study [18].

Patients were excluded from the study if they had evidence of other malignant neoplasms prior to their MF diagnosis, except for PV, ET, adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or another cancer from which they had been disease free for at least 5 years at the time of ruxolitinib initiation. Patients were also excluded if they participated in a clinical trial involving JAK2 inhibitors for the treatment of MF prior to discontinuing ruxolitinib treatment and if they received allogeneic hematopoietic cell transplantation after their initial MF diagnosis.

Study variables

Patient characteristics

Patients' country of residence, age at ruxolitinib initiation, sex and race/ethnicity (except in France) were abstracted from patient medical records. Clinical characteristics abstracted from patients' medical records included disease type (i.e., primary or secondary MF), risk status at initial MF diagnosis and ruxolitinib initiation (assessed using the international prognostic scoring system [IPSS] or myelofibrosis secondary to polycythemia and essential thrombocythemia-prognostic model [MYSEC-PM]), presence of constitutional symptoms, platelet count at ruxolitinib initiation and spleen size measured via palpation at ruxolitinib initiation [21]. Performance status, assessed via the Eastern Cooperative Oncology Group (ECOG) scale or Karnofsky score, and comorbidity, assessed via the Charlson Comorbidity Index, were also ascertained from patients' medical records.

Treatment characteristics

Treatments and/or procedures that patients received prior to ruxolitinib initiation and immediately after discontinuing ruxolitinib were abstracted from their medical records. Patients who received hydroxyurea, busulfan, cytarabine, melphalan, azacitidine and decitabine before initiating ruxolitinib were considered to have received ruxolitinib as a subsequent line of treatment, and the remaining patients were considered to have received ruxolitinib as the first line of treatment. Ruxolitinib treatment characteristics were also abstracted, including start and end dates, initial dose, dose changes (if any), concomitant treatments (if any) and reasons for initiating or stopping treatment. Patient receipt of recommended ruxolitinib dose at treatment initiation was determined when baseline platelet counts were available. The recommended starting dose was determined based on platelet count following US FDA and EMA labels [22,23]. The recommended ruxolitinib starting doses are as follows: 10 mg daily if platelet count at treatment initiation was $<100\ 10^9$/l; 30 mg daily if platelet count at treatment initiation was 100–200 10^9/l; or 40 mg daily if platelet count at treatment initiation was $>200\ 10^9$/l. An atypical dose was defined as any nonrecommended ruxolitinib dose.

Clinical outcomes

Progression-free survival (PFS) was defined as the time from initiation of ruxolitinib treatment until disease progression, inadequate response or death, and overall survival (OS) was defined as the time from initiation of ruxolitinib treatment until death. Disease progression was characterized by the treating physician following the criteria used at the time of patient treatment. Because of the retrospective nature of the study, clinicians were not asked to define progression based on predefined criteria; however, the most commonly used criteria for evaluating disease progression by treating physicians were constitutional symptoms, spleen volume, blood tests, Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)/MPN-10 and International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT). Progression-free survival time was censored at ruxolitinib discontinuation, and OS time was censored at the end of available follow-up for patients who were still alive at the time of data abstraction.

Statistical analysis

Demographic and clinical characteristics were described for all patients. Patient ruxolitinib treatment characteristics (e.g., duration of treatment) were described for the overall cohort and by platelet count as well as by receipt of recommended ruxolitinib dose at treatment initiation. The Kaplan–Meier method was used to estimate PFS and OS from ruxolitinib initiation, and Cox regression models were used to estimate hazard ratios (HRs) and 95%

CIs to identify factors associated with patients' risk of survival. A time-varying Cox regression model was also computed to account for variable time of subsequent treatment initiation after ruxolitinib discontinuation and the associated immortal time bias.

Results

Patient demographic & clinical characteristics

A total of 469 patients treated with ruxolitinib were included in the study. Data were abstracted by 155 physicians, primarily hematologist-oncologists (73.6%), across the USA and Europe. Physician characteristics are presented in Supplementary Table 1. The largest proportion of patients was from the USA (n = 111, 23.7%), followed by Germany (n = 93, 19.8%), Spain (n = 90, 19.2%), the UK (n = 89, 19%), France (n = 64, 13.7%) and Canada (n = 22, 4.7%). Overall, the median age of patients was 64.9 years (range: 57.6–70.7), and most identified as male (66.5%) and white (76.8%). Most patients (78.5%) had primary MF and were in the intermediate 1 with constitutional symptoms (35.2%) or intermediate 2 (43.9%) IPSS or MYSEC-PM risk category at MF diagnosis (Table 1). Median (interquartile range [IQR]) follow-up from date of ruxolitinib initiation to the end of patient record (date of death or data extraction) for the overall cohort was 34.4 months (range: 14–52).

Ruxolitinib treatment characteristics

Hydroxyurea was the most common treatment (39.2% of all patients) received prior to ruxolitinib initiation, followed by prednisone (6.6%) and epoetin alpha (5.7%). Ruxolitinib was the first-line MF treatment in 37.5% of patients. The most common daily doses at ruxolitinib initiation were 30 mg (37.5%), 40 mg (22.4%) and 20 mg (19%), and the median (IQR) duration of ruxolitinib treatment was 13.1 months (range, 6.3–26.4). Supportive care with red blood cell transfusions were received by 17.4% of patients prior to ruxolitinib initiation. Hydroxyurea was the most common treatment (39.2% of all patients) received prior to ruxolitinib initiation, followed by red blood cell transfusions (17.4%), prednisone (6.6%) and epoetin alpha (5.7%). Ruxolitinib was the first-line MF treatment in 37.5% of patients. The most common daily doses at ruxolitinib initiation were 30 mg (37.5%), 40 mg (22.4%) and 20 mg (19%), and the median (IQR) duration of ruxolitinib treatment was 13.1 months (range, 6.3–26.4).

MF-related symptoms at ruxolitinib initiation are presented in Supplementary Table 2. Platelet counts at ruxolitinib initiation were reported in 422 patients. Of these patients, 157 (37.2%) had a platelet count below 100×10^9/l, 163 (38.6%) had a platelet count between 100×10^9/l and 200×10^9/l and 102 (24.2%) had a platelet count over 200×10^9/l. Overall, the recommended ruxolitinib dose was initiated in 169 (36%) patients. Just over half (n = 253, 53.9%) of patients started ruxolitinib treatment with a dose that differed from label recommendations. Patients with a platelet count below 100×10^9/l who received an atypical dose were more likely to receive a higher (vs lower) dose of ruxolitinib than that recommended at treatment initiation (n = 115, 99.1%), and patients with a platelet count above 200×10^9/l who received an atypical dose were more likely to receive a lower (vs higher) dose of ruxolitinib than recommended at treatment initiation (n = 50, 84.8%; Table 2).

The median (IQR) duration of ruxolitinib treatment among the 169 patients who received a recommended dose at treatment initiation was 12.1 months (6.3–23.8) and the median (IQR) duration of treatment among the 253 patients who received an atypical dose at treatment initiation was 16 months (7.9–29.4). Reason for first ruxolitinib dose modification was reported for 186 (44.1%) patients who had platelet counts at their initial MF diagnosis. Among these patients, the three most frequent reasons for first dose modification were change in platelet/absolute neutrophil count (38.2%), inadequate response to ruxolitinib (26.9%), and hematologic toxicity/adverse reaction (22.6%; Table 3).

In the overall cohort of 469 patients, 172 (36.7%) received red blood cell transfusions while being treated with ruxolitinib, and most patients (n = 106, 61.6%) received two units per month. Of the 410 patients who were alive and not lost to follow-up, 147 (35.9%) received red blood cell transfusions after discontinuing ruxolitinib.

Ruxolitinib discontinuation

During the study follow-up period, extending from discontinuation of treatment until data abstraction in 2020, 206 (43.9%) patients experienced an inadequate response or disease progression while being treated with ruxolitinib. Of the patients who experienced an inadequate response or disease progression (n = 206), more than half of these patients (54.4%) discontinued ruxolitinib, nearly a quarter (23.3%) continued ruxolitinib due to a lack of other effective treatments, 11.2% of patients continue ruxolitinib with additional treatments and no specific

Table 1. Patient demographic and clinical characteristics.

Characteristic	All patients (n = 469)
Demographic characteristics	
Country, n (%)	
USA	111 (23.7)
UK	89 (19)
Germany	93 (19.8)
Spain	90 (19.2)
Canada	22 (4.7)
France	64 (13.7)
Age (y)	
Median (IQR)	64.9 (57.6–70.7)
Sex, n (%)	
Male	312 (66.5)
Race/ethnicity, n (%)†	
White	360 (76.8)
Black/African American (US only), Black/African (UK, Canada, Spain, and Germany)	26 (5.5)
Asian, Native Hawaiian or other Pacific Islander	15 (3.2)
Other	3 (0.6)
Unknown	1 (0.2)
Ethnic origin (USA only), n (%)	
Hispanic	8 (7.2)
Not Hispanic	102 (91.9)
Unknown	1 (0.9)
Duration of follow-up, mo‡	
Median (IQR)	34.39 (14–52)
Clinical characteristics	
Primary or secondary MF, n (%)	
Primary MF	368 (78.5)
Post-polycythemia vera MF	66 (14.1)
Post-essential thrombocytopenia MF	35 (7.5)
IPSS or MYSEC-PM risk status at initial MF diagnosis, n (%)	
Intermediate 1 risk with constitutional symptoms	165 (35.2)
Intermediate 2 risk	206 (43.9)
High risk	98 (20.9)
Risk status at ruxolitinib initiation, n (%)	438 (93.9)
Low risk	2 (0.5)
Intermediate 1 risk	79 (18)
Intermediate 2 risk	222 (50.7)
Intermediate risk	11 (2.5)
High risk	120 (27.4)
Unknown	4 (0.9)
Evaluation of spleen at ruxolitinib initiation, n (%)	
Physical evaluation	417 (88.9)
Very mild or mild splenomegaly (5–10 cm can be palpated)	107 (25.7)
Moderate splenomegaly (10–20 cm can be palpated)	223 (53.5)
Severe splenomegaly (>20 cm can be palpated)	87 (20.9)

†Race/ethnicity not reported for France.
‡Length of follow-up is duration of time between the date of ruxolitinib initiation and death or end of patient record.
§Performance statuses: 0 = normal activity; 1 = symptoms demonstrated, but patient remains ambulatory and able to perform self-care; 2 = ambulatory >50% of the time and requires occasional assistance; 3 = ambulatory <50% of the time and requires nursing care; 4 = bedridden.
IPSS: International prognostic scoring system; IQR: Interquartile range; MF: Myelofibrosis; MPN-SAF: Myeloproliferative neoplasm symptom assessment form; MYSEC-PM: Myelofibrosis secondary to polycythemia and essential thrombocythemia-prognostic model; SD: Standard deviation.

Table 1. Patient demographic and clinical characteristics (cont.).

Characteristic	All patients (n = 469)
Blood tests at ruxolitinib initiation	
Platelets (mm^3), n (%)	418 (89.1)
Mean (SD)	193,080.9 (227,146.6)
Charlson Comorbidity Index, n (%)	351 (74.8)
Mean (SD)	1.55 (1.55)
Performance status at ruxolitinib initiation, n (%)§	374 (79.7)
0 or 1	227 (60.7)
2, 3, or 4	147 (39.3)

†Race/ethnicity not reported for France.
‡Length of follow-up is duration of time between the date of ruxolitinib initiation and death or end of patient record.
§Performance statuses: 0 = normal activity; 1 = symptoms demonstrated, but patient remains ambulatory and able to perform self-care; 2 = ambulatory >50% of the time and requires occasional assistance; 3 = ambulatory <50% of the time and requires nursing care; 4 = bedridden.
IPSS: International prognostic scoring system; IQR: Interquartile range; MF: Myelofibrosis; MPN-SAF: Myeloproliferative neoplasm symptom assessment form; MYSEC-PM: Myelofibrosis secondary to polycythemia and essential thrombocythemia-prognostic model; SD: Standard deviation.

action/measure was taken for 10.2% of patients. Similar patterns were observed among both patients who received a recommended ruxolitinib starting dose and those who received atypical ruxolitinib starting doses (Table 3). Following ruxolitinib discontinuation, subsequent treatment was initiated in 91 patients. The most common subsequent treatments were hydroxyurea (n = 27, 29.7%), lenalidomide (n = 12, 17% [excluding the UK]) and interferon (n = 10, 11%).

Progression-free survival

In the overall cohort, approximately half of patients (n = 242, 51.6%) were determined to have progressive disease or died, and the estimated median (95% CI) real-world PFS from ruxolitinib treatment initiation was 23.7 months (20.9–26.5). The criteria used to assess progression included the presence of constitutional symptoms (69.4%), spleen size or volume increase (67.0%), blood tests abnormalities (51.5%), MPN-SAF/MPN-10 score worsening (9.2%) and IWG-MRT assessment (8.7%). Among the subgroups of patients who initiated recommended and atypical ruxolitinib starting doses, the estimated median (95% CI) real-world PFS from ruxolitinib treatment initiation was 23.0 months (19.9–28.0) and 23.7 months (17.0–27.5), respectively.

Overall survival

At the end of study follow-up in 2020, 250 (53.3%) patients in the overall cohort had died. The estimated median (95% CI) OS from ruxolitinib initiation was 44.4 months (38.8–50.2). Among the subgroups of patients who initiated recommended and atypical ruxolitinib starting doses, the estimated median (95% CI) OS from ruxolitinib initiation was 44.7 months (31.7–60.1) and 44.5 months (38.6–50.2), respectively (Figure 2). In patients with available platelet count data, estimated OS from ruxolitinib initiation was highest in patients with a platelet count greater than 200 $\times$ 10^9/l (median [95% CI]: 63.4 [54.9–not estimatable] months). Estimated median (95% CI) OS from ruxolitinib initiation among patients with a platelet count between 100 $\times$ 10^9/l and 200 10^9/l and patients with a platelet count less than 100 $\times$ 10^9/l was 42.9 months (31.8–50.2) and 32.9 months (25.6–44.7), respectively (Figure 3). Patients who took a 10-mg daily dose of ruxolitinib had a median survival of 42.8 months (31.7–74.3) from ruxolitinib initiation. Patients taking 20, 30, 40 or 50 mg daily had median (range) OS of 44.2 (34.4–62.6), 45.9 (29.6–59.5), 46.5 (31.8–60.1) and 40.7 months (30.1–not estimatable), respectively (Supplementary Figure 1). Dose modification played a significant role in OS; patients whose ruxolitinib dose was modified in the first 6 months had a median OS of 36.7 months (27.5–43.8) from ruxolitinib initiation, while patients who remained on a constant ruxolitinib dose had a longer OS of 47.8 months (42.8–59.2; Figure 4).

In the overall cohort, the patients who were younger than 65 years at their initial primary MF or secondary MF diagnosis had a 57% lower risk of death than patients who were aged 65 years or older (HR [95% CI]: 0.43 [0.32–0.57], $p < 0.0001$), and patients who had a platelet count greater than 200 10^9/l at ruxolitinib initiation had a 40% lower risk of death than patients who had a platelet count less than 100 10^9/l (HR [95% CI]: 0.60 [0.41–0.89], $p = 0.0109$). Risk of death was higher among patients who had a high or very high risk status (vs intermediate risk status) at ruxolitinib initiation (HR [95% CI]: 1.47 [1.10–1.96], $p = 0.0098$), patients who had severe splenomegaly (vs very mild or mild splenomegaly) at ruxolitinib initiation (HR [95% CI]: 2.29

Table 2. Ruxolitinib treatment patterns by platelet level at ruxolitinib initiation.

Treatment characteristic	Platelet count (unit 10^9/l)				
	Overall (n = 469)	<100 (n = 157)	100–200 (n = 163)	>200 (n = 102)	Unknown or not assessed (n = 47)
Year of ruxolitinib initiation, n (%)					
2012	53 (11.3)	18 (11.5)	18 (11)	10 (9.8)	7 (14.9)
2013	49 (10.5)	16 (10.2)	19 (11.7)	12 (11.8)	2 (4.3)
2014	84 (17.9)	30 (19.1)	36 (22.1)	10 (9.8)	8 (17)
2015	128 (27.3)	48 (30.6)	38 (23.3)	28 (27.5)	14 (29.8)
2016	155 (33.1)	45 (28.7)	52 (31.9)	42 (41.2)	16 (34)
Time from MF diagnosis to ruxolitinib initiation, mo					
Median (IQR)	2 (0.5–9.3)	2.6 (0.5–9.3)	1.9 (0.5–9.3)	2 (0.5–7.8)	1 (0.4–10)
Rationale for initiating ruxolitinib treatment, n (%)†					
Splenomegaly	327 (69.7)	124 (80)	118 (72.4)	71 (69.6)	14 (29.8)
Treatment efficacy	319 (68)	107 (68.2)	106 (65)	66 (64.7)	40 (85.1)
Lack of symptom control	174 (37.1)	64 (40.8)	55 (33.7)	44 (43.1)	11 (23.4)
Duration of ruxolitinib treatment, mo‡					
Median (IQR)	13.1 (6.3–26.4)	16 (7.2–25.9)	13.1 (7.2–26.8)	12.6 (4.6–29.1)	8 (3–19.4)
Recommended dose of ruxolitinib when treatment was initiated, n (%)	422 (90)	157 (100)	163 (100)	102 (100)	0 (0)
Yes	169 (36)	41 (26.1)	85 (52.2)	43 (42.2)	0 (0)
No	253 (53.9)	116 (73.9)	78 (47.9)	59 (57.8)	0 (0)
Lower dose	86 (34)	1 (0.9)	35 (44.9)	50 (84.8)	–
Higher dose	167 (66)	115 (99.1)	43 (55.1)	9 (15)	–
Total daily dose at ruxolitinib initiation, n (%)					
10 mg	66 (14.1)	41 (26.1)	13 (8)	3 (2.9)	9 (19.2)
20 mg	89 (19)	38 (24.2)	18 (11)	20 (19.6)	13 (28)
30 mg	176 (37.5)	47 (29.9)	85 (52.2)	27 (26.5)	17 (36.2)
40 mg	105 (22.4)	21 (13.4)	35 (21.5)	43 (42.2)	6 (12.8)
50 mg	24 (5.1)	7 (4.5)	8 (4.9)	8 (7.8)	1 (2.1)
Unclassified	9 (2)	3 (1.9)	4 (2.5)	1 (1)	1 (2.1)
Total daily dose at ruxolitinib discontinuation, n (%)					
10 mg	67 (14.3)	30 (19.1)	23 (14.1)	6 (5.9)	8 (17)
20 mg	104 (22.2)	39 (24.8)	34 (20.9)	17 (16.7)	14 (29.8)
30 mg	133 (28.4)	45 (28.7)	54 (33.1)	21 (20.6)	13 (27.7)
40 mg	108 (23)	29 (18.5)	32 (19.6)	42 (41.2)	5 (10.6)
50 mg	30 (6.4)	5 (3.2)	10 (6.1)	12 (11.8)	3 (6.4)
Unclassified	27 (5.8)	9 (5.7)	10 (6.1)	4 (3.9)	4 (8.5)
Times ruxolitinib dose or frequency was changed (n)					
Median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Reason for first dose change, n (%)†	204 (43.5)	70 (44.6)	73 (44.8)	43 (42.2)	18 (38.3)
Change in platelet/absolute neutrophil count	76 (37.3)	33 (47.1)	30 (41.1)	8 (18.6)	5 (27.8)
Hematologic toxicity/adverse reaction	47 (23)	15 (21.4)	18 (24.7)	9 (20.9)	5 (27.8)
Inadequate response	54 (26.5)	17 (24.3)	16 (21.9)	17 (39.5)	4 (22.2)
Reason for discontinuing ruxolitinib treatment, n (%)†					
Adverse event – anemia	41 (8.7)	18 (11.5)	8 (4.9)	14 (13.7)	1 (2.1)
Adverse event – thrombocytopenia	49 (10.5)	22 (14)	23 (14.1)	4 (3.9)	0 (0)
Adverse event – other	12 (2.6)	2 (1.3)	2 (1.2)	8 (7.8)	0 (0)
Patient decision	110 (23.5)	35 (22.3)	37 (22.7)	31 (30.4)	7 (14.9)

†Multiple responses were allowed; rows will add up to greater than 100%.
‡Time from ruxolitinib initiation to discontinuation does not include treatment interruption or treatment holiday.
AML: Acute myeloid leukemia; IQR: Interquartile range; mo: Month; SD: Standard deviation.

Table 2. Ruxolitinib treatment patterns by platelet level at ruxolitinib initiation (cont.).

Treatment characteristic	Platelet count (unit 10^9/l)				
	Overall (n = 469)	<100 (n = 157)	100–200 (n = 163)	>200 (n = 102)	Unknown or not assessed (n = 47)
Improvement in patients' condition, with no additional clinical benefit of continued treatment anticipated	85 (18.1)	23 (14.7)	36 (22.1)	13 (12.8)	13 (27.7)
Inadequate response	64 (13.7)	31 (19.8)	18 (11)	11 (10.8)	4 (8.5)
Progressive disease with regard to anemia (including transformation to AML)	84 (17.9)	38 (24.2)	30 (18.4)	12 (11.8)	4 (8.5)
Progressive disease with regard to splenomegaly	88 (18.8)	34 (21.7)	36 (22.1)	17 (16.7)	1 (2.1)
Loss of response	62 (13.2)	29 (18.5)	18 (11)	8 (7.8)	7 (14.9)
Lost to follow-up	19 (4.1)	4 (2.6)	5 (3.1)	3 (2.9)	7 (14.9)
Death	43 (9.2)	14 (8.9)	15 (9.2)	8 (7.8)	6 (12.8)
Other	26 (5.5)	13 (8.3)	7 (4.3)	5 (4.9)	1 (2.1)
Unknown	39 (8.3)	9 (5.7)	15 (9.2)	9 (8.8)	6 (12.8)

†Multiple responses were allowed; rows will add up to greater than 100%.
‡Time from ruxolitinib initiation to discontinuation does not include treatment interruption or treatment holiday.
AML: Acute myeloid leukemia; IQR: Interquartile range; mo: Month; SD: Standard deviation.

Table 3. Ruxolitinib treatment patterns by receipt of recommended dose at initiation.

Treatment characteristic	Received recommended ruxolitinib dose at initiation		
	Overall (n = 469)	Yes (n = 169)	No (n = 253)
Duration of ruxolitinib treatment, mo†			
Median (IQR)	13.1 (6.3–26.4)	12.1 (6.3–23.8)	16 (7.9–29.4)
Reason for first dose change of ruxolitinib, n (%)‡	204 (43.5)	73 (43.2)	113 (44.7)
Change in platelet/absolute neutrophil count	76 (37.3)	35 (48)	36 (31.9)
Hematologic toxicity/adverse reaction	47 (23.0)	7 (9.6)	36 (31.9)
Bleeding	4 (2.0)	2 (2.7)	1 (0.9)
Inadequate response	54 (26.5)	21 (28.8)	29 (25.7)
Loss of response	15 (7.4)	9 (12.3)	6 (5.3)
Re-escalation	26 (12.8)	12 (16.4)	13 (11.5)
Concomitant medication affecting ruxolitinib exposure	1 (0.5)	0 (0)	1 (0.9)
Other	10 (4.9)	3 (4.1)	7 (6.2)
Unknown	7 (3.4)	1 (1.4)	1 (0.9)
Inadequate response or disease progression while on treatment with ruxolitinib, n (%)			
Yes	206 (43.9)	69 (40.8)	127 (50.2)
No	236 (50.3)	92 (54.4)	117 (46.3)
Unknown	27 (5.8)	8 (4.7)	9 (3.6)
Patients who discontinued treatment after inadequate response/progression	112 (54.4)	36 (52.2)	72 (56.7)
Time from inadequate response/progression to ruxolitinib treatment discontinuation§			
Median (IQR), mo	3 (1.1–9.3)	2.5 (1.05–7.6)	4.2 (1.1–9.4)
Dose modification, n (%)			
Modified dose¶	98 (23.2)	40 (23.7)	58 (22.9)
Stable dose#	324 (76.8)	129 (76.3)	195 (77.1)

†Time from ruxolitinib initiation to discontinuation does not include treatment interruption or treatment holiday.
‡Multiple responses were allowed; rows will add up to greater than 100%.
§Among patients who did not discontinue treatment after from inadequate response/progression.
¶Dose modification within 6 months of ruxolitinib initiation.
#No dose modification within 6 months of ruxolitinib initiation.
IQR: Interquartile range; mo: Month.

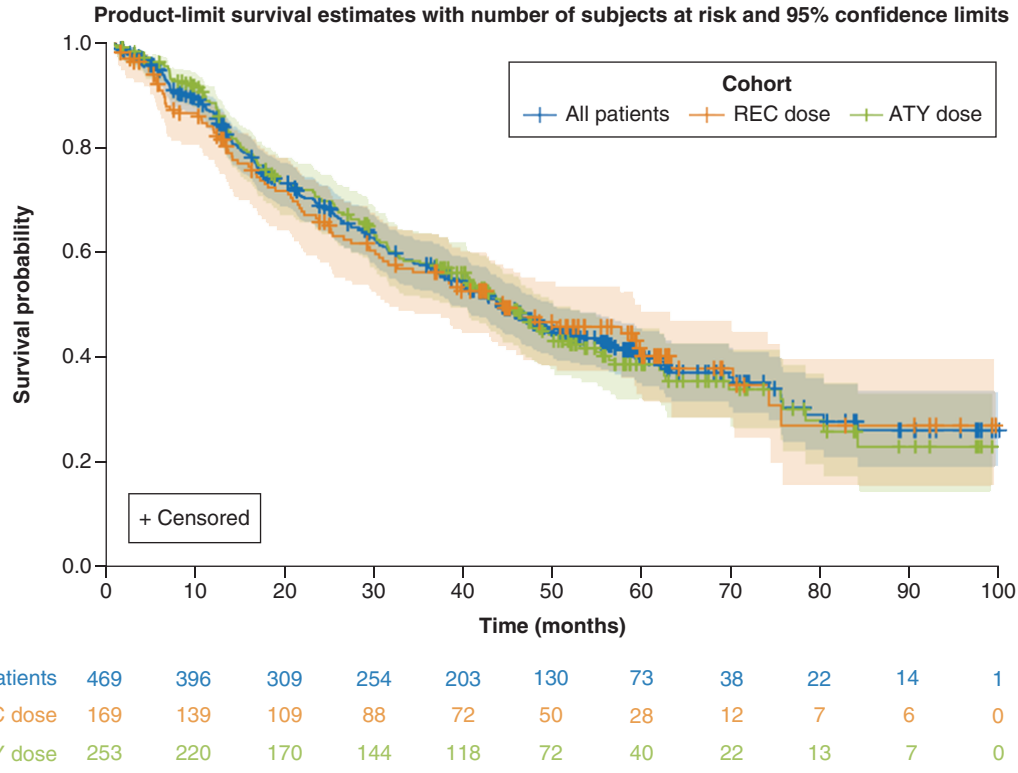

Figure 2. Median overall survival from ruxolitinib initiation based on ruxolitinib dose received at initiation.
ATY: Atypical; REC: Recommended.

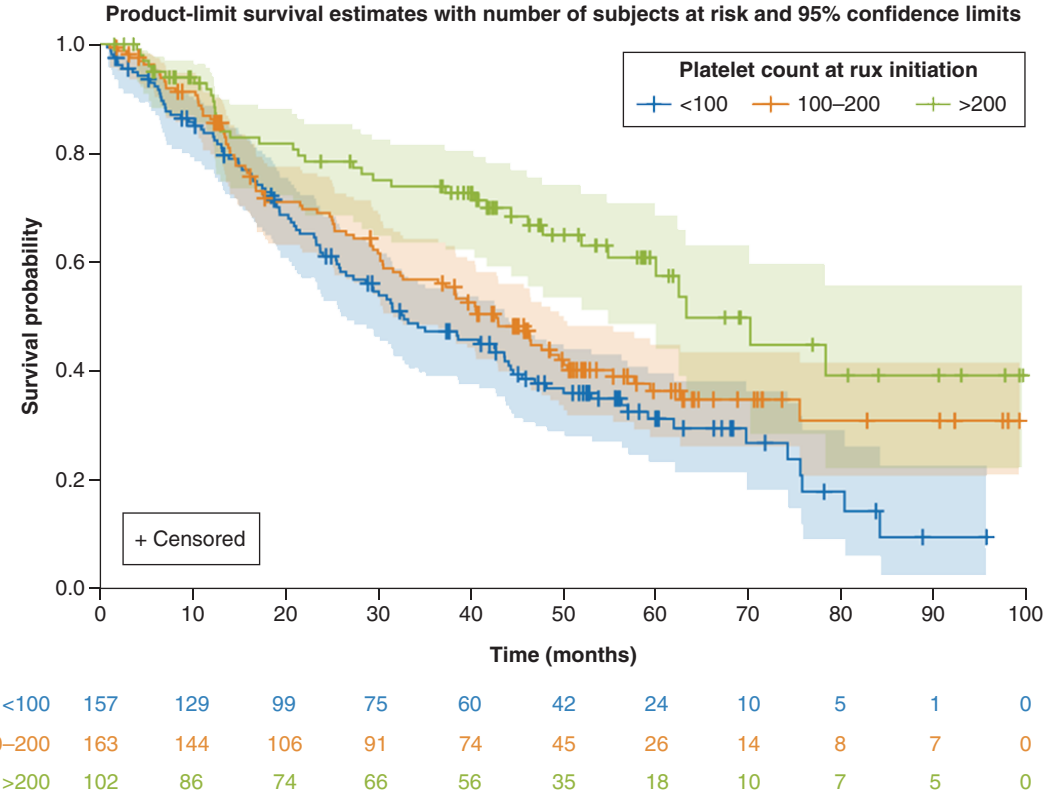

Figure 3. Median overall survival from ruxolitinib initiation based on platelet count at initiation.
Rux: Ruxolitinib.

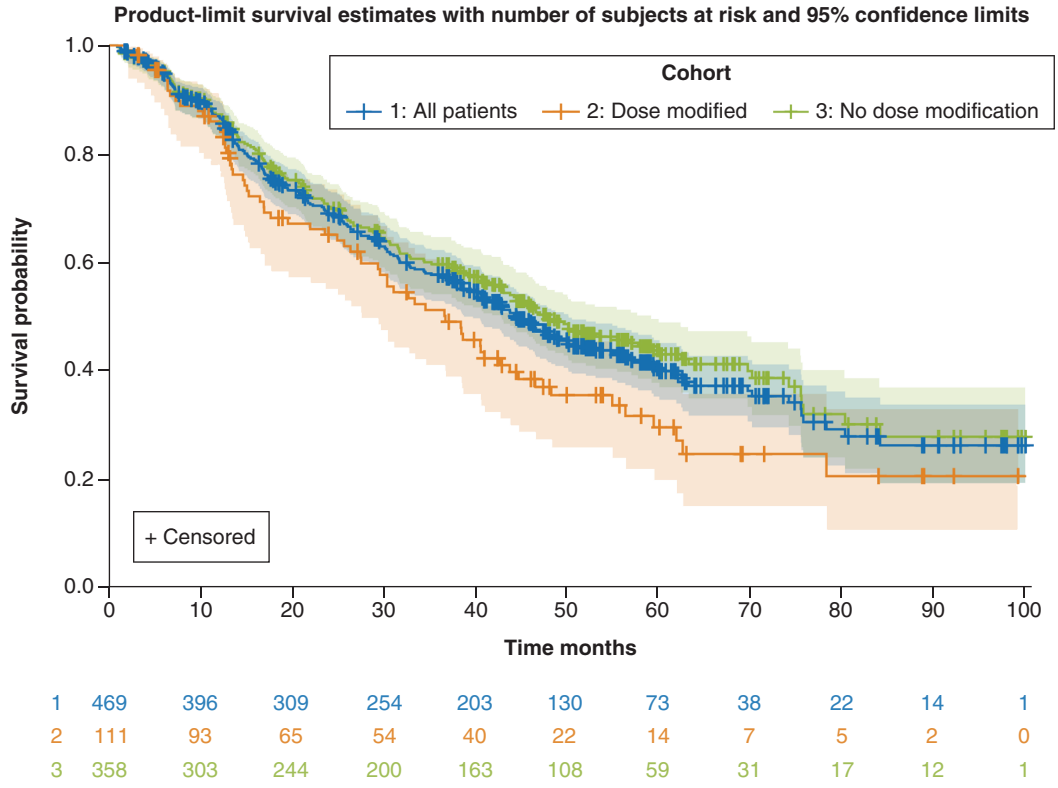

Figure 4. Median overall survival from ruxolitinib initiation based on dose modification.

[1.48–3.54], p = 0.0002) and patients who had greater comorbidity (e.g., Charlson Comorbidity Index score of 1 vs 0; HR [95% CI]: 1.94 [1.30–2.89], p = 0.0012). Patients who had an ECOG-PS of 2, 3, or 4 at ruxolitinib initiation were over twice as likely to experience death than patients who had an ECOG-PS of 0 or 1 (HR [95% CI]: 2.26 [1.67–3.06], p < 0.0001). The full model of factors associated with risk of survival is presented in Table 4. In a time-varying Cox regression analysis, patients' receipt of subsequent MF-related treatment following ruxolitinib treatment did not show a statistically significant beneficial effect on OS (Supplementary Table 3).

Discussion

This multinational, retrospective study of real-world treatment patterns and outcomes provided key insight into the unmet clinical need of adult patients with MF who were treated with ruxolitinib. In the overall cohort, the estimated median OS from ruxolitinib initiation was 44 months, which was similar in patients who initiated an atypical ruxolitinib dose (44.5 months) and to those who initiated a recommended ruxolitinib dose (44.7 months). Although the median duration of ruxolitinib treatment was 13 months for the overall cohort, it extended to 16 months for patients who started ruxolitinib treatment on an atypical dose. These data suggest that extended treatment with ruxolitinib may be possible with different dosing regimens. However, differential dosing with ruxolitinib remains controversial; while some evidence suggests that individualized dosing strategies can help manage adverse effects while maintaining efficacy, the effects of ruxolitinib have been clearly documented to be dose dependent [19,24,25]. Ruxolitinib doses are most commonly adjusted to manage cytopenias but are often increased stepwise following symptom management [19]. The JUMP trial, which analyzed the response to ruxolitinib, found that spleen response is dose dependent, but symptom improvements may not be [26]. Recent findings from the REALISE study indicate that patients experiencing adverse events, including anemia, would likely benefit from a lower starting dose of ruxolitinib (10 mg daily) with a dose escalation after 12 weeks [27,28]. Additional study is needed to fully determine whether atypical dosing of ruxolitinib can lead to the same desired response as the recommended dose and to determine the most effective dosing strategies.

Despite progression or inadequate response on treatment, 23% of patients continued treatment with ruxolitinib due to a lack of other effective treatments, and another 11% continued treatment with ruxolitinib by supple-

Table 4. Factors associated with risk of survival.

Covariate	HR (95% CI)	p-value
Age group at initial primary MF or secondary MF diagnosis, years		
≥65	1.00	
<65	0.43 (0.32–0.57)	<0.0001
Gender		
Male	1.00	
Female	0.89 (0.68–1.17)	0.3999
Receipt of MF-related treatment before ruxolitinib initiation[†]		
No	1.00	
Yes	1.11 (0.85–1.45)	0.4449
Risk status at ruxolitinib initiation		
Intermediate risk[‡]	1.00	
High/very high risk	1.47 (1.10–1.96)	0.0098
Physical evaluation at ruxolitinib Initiation		
Very mild or mild splenomegaly	1.00	
Moderate splenomegaly	1.31 (0.91–1.87)	0.1431
Severe splenomegaly	2.29 (1.48–3.54)	0.0002
Unknown/not assessed	1.34 (0.81–2.22)	0.2566
Platelet count at ruxolitinib initiation		
<100 10^9/l	1.00	
100–200 10^9/l	1.24 (0.89–1.72)	0.1968
>200 10^9/l	0.60 (0.41–0.89)	0.0109
Unknown or not assessed	2.15 (0.83–5.59)	0.1177
Charlson Comorbidity Index score		
0	1.00	
1	1.94 (1.30–2.89)	0.0012
2	2.36 (1.55–3.61)	<0.0001
≥3	2.91 (1.89–4.48)	<0.0001
Performance status at the start of ruxolitinib treatment[§]		
0,1	1.00	
2, 3, 4	2.26 (1.67–3.06)	<0.0001
Unknown/missing	1.82 (1.26–2.61)	0.0013
Received recommended dose at ruxolitinib initiation		
No	1.00	
Yes	0.92 (0.70–1.22)	0.5649
Unknown/missing	0.91 (0.41–2.01)	0.8194

[†]MF-related treatments include hydroxyurea, busulfan, cytarabine, melphalan, azacytidine, decitabine.
[‡]Intermediate risk category contains two patients who were classified as low risk at ruxolitinib initiation, and patients with missing risk status at ruxolitinib initiation (n = 31) were assigned their risk status at time of myelofibrosis diagnosis.
[§]Karnofsky score converted to the Eastern Cooperative Oncology Group scale.
HR: Hazard ratio; MF: Myelofibrosis.

menting with other medications. Patients who continued ruxolitinib treatment after they experienced progression or inadequate response did so for a median of 3 months. Relatively few patients received subsequent treatment after discontinuing ruxolitinib, and results from the time-varying Cox regression analysis highlight that the subsequent treatments available to patients at the time of the study did not prolong their survival. Patients with severe splenomegaly and thrombocytopenia at initiation of ruxolitinib had shorter OS compared with other patients; severe thrombocytopenia and splenomegaly are known to negatively impact patient prognosis [29,30]. Overall, these findings underscore a significant unmet clinical need for newer and more effective treatments for some patients with MF post-ruxolitinib treatment, especially for those with high-risk factors.

In recent years, promising new JAK inhibitors have become available for patients who discontinue ruxolitinib (i.e., fedratinib), and a few others have reached late-stage clinical development (i.e., pacritinib and momelotinib) [20].

Findings from a recent analysis of data from the JAKARTA2 study indicate that fedratinib is an effective treatment in patients with MF post-ruxolitinib as well as JAK inhibitor-naive patients [10]. Pacritinib and momelotinib may also provide beneficial treatment options for specific MF patient populations post-ruxolitinib, including patients with severe thrombocytopenia (pacritinib) and patients with anemia (momelotinib) [31–33]. Momelotinib is also unique in that it inhibits not only JAK1 and JAK2 but activin A receptor type 1 [33]. However, neither pacritinib nor momelotinib have been approved by regulatory agencies like FDA and EMA for the treatment of MF to date, although momelotinib has been granted fast-track designation in USA [34]. Because many studies, including this one, have indicated that JAK inhibitors are powerful treatments for MF but do not work for a subset of patients, additional therapeutic avenues for MF are under investigation, including BET inhibitors (e.g., pelabresib, NCT04603495) [35,36], anti-Bcl-xl (e.g., navitoclax, NCT04468984) [37,38], MDM-2 inhibitors (e.g., navtemadlin, NCT03662126) [39], telomerase inhibitors (e.g., imetelstat, NCT01731951) [40], nucleic transport inhibitors (e.g., selinexor, NCT04562870) [41], interferon alpha (e.g. ropeginterferon alfa-2b, NCT04988815) [42] and anti-fibrotic agents (e.g., PRM-151, NCT01981850) [43,44]. These novel therapies have the potential to provide much needed treatment options for patients who experience disease progression on ruxolitinib. Many current trials, like the ADORE trial (NCT04097821), are evaluating therapeutics to use in combination with ruxolitinib in hopes of overcoming ruxolitinib resistance [45,46]. While the second-line therapies available at the time of this chart review did not prolong survival, recent advances in therapies tailored to patients who do not respond to ruxolitinib are providing new hope to patients and clinicians [47].

Our study has several limitations. As a retrospective analysis of patient medical records, the data collected represent a convenience sample that may not be generalizable to all patients treated with ruxolitinib and to all patients treated for MF. Additionally, the data submitted by physicians may be subject to recall bias, time constraints in completing the necessary forms and evaluations, or other unknown confounding variables. In order to gather sufficient follow-up data to calculate survival statistics, and to ensure we had a representative sample of ruxolitinib users, treatment needed to be initiated between 2012 and 2016 and be discontinued by data abstraction in 2020; however, because of the fast pace of new drug approvals, the rapidly evolving treatment landscape in myelofibrosis may not have been fully captured by this study.

Conclusion

In summary, our findings affirm that ruxolitinib is a valuable treatment option for patients with primary or secondary MF, but they also indicate that many patients continue treatment with ruxolitinib despite experiencing disease progression. This study also showed that the subsequent treatments available to patients after progression on ruxolitinib during the study period did not statistically significantly prolong their survival and trended toward increased risk for death. These results emphasize the need for newer and more effective therapies for certain patients with MF who progressed while being treated with ruxolitinib.

Summary points

- Ruxolitinib is a valuable treatment option for patients with primary or secondary myelofibrosis (MF).
- An unmet need for additional therapeutic options remains for patients with MF who experience disease progression while being treated with ruxolitinib.
- This study examined the treatment patterns and clinical outcomes of ruxolitinib in a real-world multinational cohort of patients diagnosed with MF.
- This multinational, retrospective study of real-world treatment patterns and outcomes in MF provided key insight into the unmet clinical need of adult patients with MF who were treated with ruxolitinib and experienced disease progression.
- The Kaplan–Meier estimate of median survival from ruxolitinib initiation was 44.4 months (95% CI, 38.8–50.2 months).
- Overall survival was not impacted by whether patients were treated with the recommended or an atypical dose.
- Modifications of ruxolitinib doses are associated with lower survival.
- At the time of conduct of this study, treatments available to patients after disease progression on ruxolitinib did not prolong patient survival.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-1358

Author contributions

All authors have contributed to this research by substantially contributing to the study concept or design, or data acquisition, analysis or interpretation; drafted the article or revised it critically for important intellectual content; approved the final version for submission; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethical conduct of research

The authors state that they have obtained institutional review board approval from the RTI Institutional Review Board for the research described.

Data sharing statement

Data are not publicly available but can be made available upon request on a case-by-case basis.

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- **Summarizes the key clinical studies involving JAK inhibitors for treating myeloproliferative neoplasms as well as studies involving various novel combinations and single agents that are currently underway.**