REGULAR ARTICLE

blood advances

Real-world treatment patterns and health care resource use for patients with myelofibrosis: results from the METER study

Vikas Gupta,[1] Ciprian Tomuleasa,[2-4] Gilberto Israel Barranco Lampón,[5] Hsin-An Hou,[6,7] Grzegorz Helbig,[8] Pankit Vachhani,[9] Argiris Symeonidis,[10] Ibrahim Haznedaroglu,[11] Kenny Galvez,[12] Fernando Tatsch,[13] Avijeet S. Chopra,[14] Meng Zhang,[15] Tamas Vizkelety,[13] Bryan Murray,[16] and David M. Ross[17]

[1]Clinical Cancer Research Unit, Princess Margaret Cancer Centre, Toronto, ON, Canada; [2]Medfuture Research Center for Advanced Medicine and [3]Department of Hematology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [4]Department of Hematology, Ion Chiricuta Clinical Cancer Center, Cluj-Napoca, Romania; [5]Hematology, Hospital General De México, Mexico City, Mexico; [6]Division of Hematology and [7]Division of General Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [8]Department of Haematology and Bone Marrow Transplantation, Medical University of Silesia, Katowice, Poland; [9]Division of Hematology and Oncology, University of Alabama at Birmingham School of Medicine, Birmingham, AL; [10]Hematology Division, Department of Internal Medicine, University of Patras, Patras, Greece; [11]Department of Hematology, Faculty of Medicine, Hacettepe University, Ankara, Turkey; [12]Cancer Unit, Hospital Pablo Tobón Uribe, Medellín, Colombia; [13]Global Medical Affairs, AbbVie Inc, North Chicago, IL; [14]HEOR, AbbVie Inc, North Chicago, IL; [15]Medical Affairs & Health Technology Assessment Statistics, AbbVie, Inc, North Chicago, IL; [16]AbbVie Inc, North Chicago, IL; and [17]Haematology, Royal Adelaide Hospital and Flinders Medical Centre, Adelaide, SA, Australia

Key Points

- In the JAK inhibitor era, RUX is the most used therapy as first (1L), second, or subsequent lines of therapy for myelofibrosis.
- In patients ≤70 years, the use of transplant as 1L therapy is uncommon with a cumulative incidence increasing from 2.2% at week 24 to 11.0% at week 156.

Myelofibrosis (MF), a myeloproliferative neoplasm, was most commonly treated with hydroxyurea (HU) before approval of ruxolitinib (RUX), now the standard of care. Factors that influence real-world MF treatment patterns are not well understood. The METER study was a multi-country, retrospective chart review of MF treatment patterns, treatment effectiveness, and health care resource utilization. Of 997 eligible patients, 65.9% had primary MF, and 11.7% were transfusion dependent. Median time from diagnosis to the start of initial treatment (index date) was 29 days (interquartile range [IQR], 1-140). RUX was the most common first-line (1L) therapy (49.0%), followed by HU (40.2%); 48.5% of patients remained on 1L therapy through week 156. Seventy-seven patients underwent allogeneic stem cell transplantation; transplantation was uncommon at 1L, increasing from 2.2% at week 24 to 11.0% at week 156 in patients ≤70 years of age. Median overall survival was 79.1 months (95% confidence interval [95% CI], 70.8 to not estimable [NE]) in all patients, 142.3 months (95% CI, 74.1 to NE) for non-RUX patients, 77.6 months (95% CI, 64.2-85.9) for patients on RUX 1L therapy, and 72.6 months (95% CI, 62.0 to NE) for RUX 2L+ patients. Of patients who experienced ≥1 corresponding event, the median hospital length of stay (LoS; n = 520), intensive care unit LoS (n = 71), and number of transfusions (n = 375) were 16 days (IQR, 7-37), 5 days (IQR, 2-13), and 12 (IQR, 4-26), respectively. Despite improvements, there were numerous hospitalization and transfusion events among these patients in routine practice. This trial was registered at www.ClinicalTrials.gov as #NCT05444972.

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The full-text version of this article contains a data supplement.

Introduction

Myelofibrosis (MF) is a rare myeloproliferative neoplasm associated with significant morbidity and mortality.[1-3] MF signs and symptoms typically include severe fatigue, splenomegaly, weight loss, low-grade fever, bone pain, and night sweats.[4] MF may present as primary or secondary MF, which develops from other myeloproliferative neoplasms (eg, polycythemia vera or essential thrombocythemia).

MF treatment approaches are based on symptom presence and disease risk stratification[5-8] Asymptomatic patients are often monitored by active surveillance, a period of close monitoring with no received treatment. If treatment is indicated because of risk stratification or disease progression, potential therapy goals include symptom control, improving anemia, and reducing spleen size, among others.[9]

Hydroxyurea (HU) was the most frequent first-line (1L) treatment in patients with MF before ruxolitinib (RUX) approval, a first-in-class Janus kinase 1/2 inhibitor (JAKi).[10,11] Clinical trials have shown that, despite significant initial clinical activity in many cases, patients with MF may lose response to RUX with 50% to 70% discontinuing therapy within 3 to 5 years.[12,13] Outside clinical trial settings, the duration of RUX treatment is shorter, although real-world data are limited.[14-16] In a recent US-based, real-world study of 104 patients with MF treated with RUX, 64.4% discontinued treatment after a median duration of treatment of 11.0 months.[15] In a separate study that reviewed the medical records of patients with MF from 6 countries, the median duration of RUX treatment was 13.1 months, and 44% of patients experienced inadequate response or disease progression; ~54% of these patients discontinued RUX.[16] In addition to RUX, 3 further JAKis were approved by the US Food and Drug Administration, including fedratinib, pacritinib, and more recently, momelotinib.[17-19] Other agents commonly used, but not approved, to treat MF include interferons, erythropoiesis-stimulating agents, danazol, and immunomodulators.[10,20-22] How the approval of RUX and other JAKis have affected the use of various therapies is unclear. In addition, allogeneic stem cell transplantation (SCT) is the only treatment with potential of cure. Although data from the Center for International Blood and Marrow Transplant Research registry indicate a gradual, sustained increase in the use of transplantation in the last decade, the optimal timing of transplants is unclear.[23]

In routine clinical practice, there is neither a standard definition of treatment failure, nor an understanding of factors that influence a health-care provider (HCP) to modify or change therapy. Real-world treatment patterns and the impact of currently available JAKis on patients with MF are not well understood. As the treatment landscape evolves, with several novel agents under investigation (eg, pelabresib, imetelstat, and selinexor),[24-27] a better understanding of the treatment patterns and outcomes in clinical settings will assist in treatment decision-making and novel treatment positioning. The METER study, a multinational chart review, is aimed at understanding the treatment patterns, clinical outcomes, and health care resource utilization (HCRU) at the patient level among patients treated for primary or secondary MF.

Methods

Study design and patient population

The METER study (ClinicalTrials.gov identifier: NCT05444972) was a multi-country, noninterventional, retrospective chart review that assessed treatment patterns, effectiveness, and HCRU in patients diagnosed with MF. Existing patient-level data on the baseline characteristics, diagnosis, disease, treatment patterns, clinical outcomes, hospitalizations, and transfusion use were collected. Risk assessment results at the time of diagnosis were captured, along with the assessment method (eg, International Prognostic Scoring System [IPSS], dynamic IPSS [DIPSS], etc).

A total of 66 sites participated in the study across a total of 14 countries. Data were collected between 23 August 2022 and 14 November 2023, and data from patients ≥18 years of age with primary or secondary MF, irrespective of baseline risk, who were first treated on or after the local date of RUX approval and no later than 31 December 2021, were assessed. Patients who received treatment for MF in a clinical trial were excluded. RUX and other agents were prescribed by HCPs according to routine clinical practice. Because this was a single-arm, observational study, no comparison groups were involved to make statistical inferences about the differences between groups.

Moreover, because treated patients were the target population and the time from diagnosis to treatment initiation can vary, the start date of the first documented treatment was used as the index date. The index date was therefore defined as the start of initial treatment, either the initial MF drug treatment, or SCT or splenectomy (collectively referred to as procedure), whichever occurred first. Patients were followed until the last recorded contact or death, whichever came first.

Outcomes

The primary objective was to describe real-world MF treatment patterns, including patient characteristics, the time from MF diagnosis to 1L therapy, choice, duration, and reason for change or discontinuation of the initial and subsequent treatments, and treatment procedures. Secondary objectives included assessments of all-cause HCRU (hospital length of stay [LoS], intensive care unit [ICU] LoS, and number of transfusion events). Exploratory objectives included multivariable analyses of the factors potentially associated with the duration of MF treatments; assessments of the overall MF treatment effectiveness in improving clinical outcomes (ie, overall survival [OS] in patients with 1 line of therapy [LoT] and ≥2 LoTs, and OS among patients who received no RUX, RUX at 1L, and RUX at 2L+); and multivariable analyses of factors potentially associated with OS. Survival time-to-event analyses included time from initial treatment (index date) to death (any cause).

Statistical methods

All data analyses were conducted using SAS, version 9.4 (SAS Institute Inc, Cary, NC) and/or R package. Because of the descriptive nature of the study, no statistical power calculations were conducted. Analysis of the primary objective was descriptive. Continuous variables were described by the number of observations (n), mean, standard deviation, median, interquartile range (IQR), minimum, and maximum. Categorical values were described as the total number and percentage per category. The 2-sided

Table 1. Demographics and clinical characteristics

Characteristic	All patients (N = 997)
Sex at index*	
Female	424 (42.5)
Male	545 (54.7)
Undifferentiated	28 (2.8)
Age at index, median (Q1-Q3)†, y	66.0 (58.0-74.0)
Race at index	
White	655 (88.2)
Black	26 (3.5)
Asian	61 (8.2)
Multiple	1 (0.1)
Unknown	254
Geographic region at index	
North America	186 (18.7)
Latin America	216 (21.7)
Asia	50 (5.0)
Oceania	53 (5.3)
Europe	492 (49.3)
Type of cancer at diagnosis	
Primary MF	657 (65.9)
Secondary MF	340 (34.1)
Platelets ($\times 10^9$/L) at index, median (IQR)	345.0 (182.0-571.0)
Hemoglobin (g/L) at index, median (IQR)	112.0 (98.0-134.0)
Transfusion dependency at index	
Yes	108 (11.7)
No	815 (88.3)
Unknown‡	74
Time from MF diagnosis to first treatment (mean, median), d	263, 29
Risk classification method at diagnosis	
IPSS	194 (32.2)
DIPSS	251 (41.7)
DIPSS+	139 (23.1)
MIPSS	10 (1.7)
Other	8 (1.3)
Unknown‡	2
Missing§	393
Risk classification at diagnosis‖	
Low	75 (12.5)
Intermediate-1	192 (32.1)
Intermediate-2	222 (37.1)
High	109 (18.2)
Unknown‡	6
Missing§	393
HMR mutation at diagnosis	
Yes	89 (50.6)
No	87 (49.4)
Unknown‡	8
Missing§	813

The data are presented as n (%) unless stated otherwise. Percentages were calculated on known information. Patients with data in an "unknown" category or missing data were excluded.

DIPSS, Dynamic International Prognostic Scoring System; HMR, high molecular risk; MF, myelofibrosis; MIPSS, Mutation-Enhanced International Prognostic Scoring System.

*Index defined as first date of the initial treatment in either drug or procedure.

†Patients who were >89 years of age were not included in the calculation.

‡Unknown category was available in the electronic case form for sites to select in case there was no corresponding information available in the patient chart.

§Missing category may include patients who did not complete the respective testing or classifications or who had missing information for the respective question.

‖Pooled from the risk classification methods, namely IPSS, DIPSS, DIPSS+, MIPSS, and other.

95% confidence interval (95% CI) for means, medians, and percentages, when appropriate, are presented.

The time-to-event parameters (ie, treatment discontinuation/change, death, loss to follow-up, or end of study) were analyzed using the Kaplan-Meier method to determine the median time and the associated 95% CI. For the time from initial treatment (index date) to death, patients who did not die within the study observation period were censored at the study end date or the last contact data available, whichever occurred first.

Multivariable analyses of the factors associated with MF treatment duration and factors associated with OS were performed using a Cox regression model. Variables included age, sex, risk classification at diagnosis, bone marrow fibrosis (BMF) grade at diagnosis, high molecular risk at diagnosis, transfusion dependency at diagnosis, treatment type, type of cancer, SCT status, and splenectomy status. The multivariable analyses data are reported as hazard ratios (HRs) with associated 95% CIs. Competing risk analyses of SCT in the presence of death by any cause for patients ≤70 years of age and splenectomy in the presence of death by any cause were also performed using the cumulative incidence function; the data are reported as cumulative incidence and associated 95% CI.

The hospital LoS, the ICU LoS, and the number of transfusion events were not calculated for all patients but, instead, were calculated for patients who experienced a corresponding event of hospitalization, ICU admission, or transfusion, respectively. The total observational time in person-years was calculated for patients with or without an HCRU event to estimate the duration of drug exposure; this calculation was performed separately for all patients and patients who received RUX or non-RUX based therapies. Reporting observational time in person-years allows for a standardized comparison of hospitalization rates by adjusting for the total time each patient was at risk for hospitalization.

Results

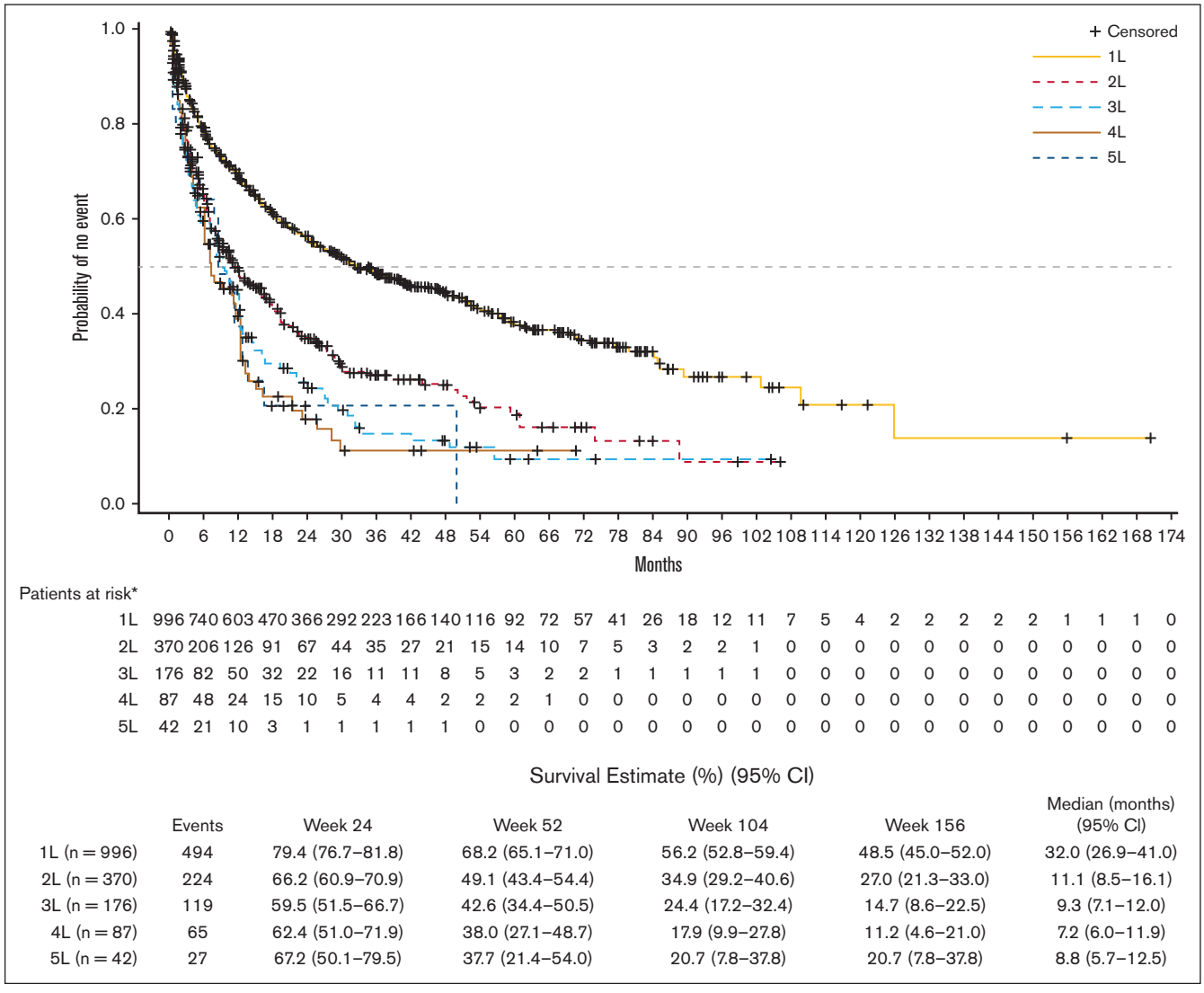
Baseline demographics and clinical characteristics

A total of 998 patients from 66 sites across 14 countries were enrolled in the study; 997 (99.9%) patients met the eligibility criteria and had initial treatment information available (Table 1). Overall, 545 of 997

patients (54.7%) were male, 655 of 743 (88.2%) were White, and the median age for patients aged ≤89 years at the index date (n = 980) was 66 years. Most patients had primary MF (n = 657/997 [65.9%]) and were not transfusion dependent at the index date (n = 815/923 with known status [88.3%]). Among patients with available data, 50.6% (n = 89/176) had a high molecular risk mutation, 81.3% (n = 578/711) had grade ≥2 BMF at diagnosis, and 55.4% (n = 331/598) were classified as intermediate 2 to high risk at diagnosis. The median time from MF diagnosis to the start of initial treatment (index date) was 29 days (IQR, 1-140). Of the patients with available data, treatment was started within 1 year after diagnosis for 83.6% of patients (n = 824/985). The demographics and clinical characteristics of patients who did not receive RUX, who received RUX at 1L, and who received RUX at 2L+ are displayed in supplemental Table 1; the characteristics were similar between subgroups.

Initial treatment details

RUX (n = 489/997 [49.0%]) and HU (n = 401/997 [40.2%]) were the most common treatments received as 1L therapy (supplemental Table 2). This trend was similar across geographic regions, except for Latin American and the Asian regions, in which HU was more commonly used than RUX. The most common supportive care medications for all patients and across geographic regions included nonsteroidal anti-inflammatory drugs, nutritional support, acetaminophen, and bisphosphonates. Of the 997 patients who started 1L therapy, 79.4% remained on that treatment through week 24 and 48.5% remained on 1L treatment through week 156 (Figure 1). The median duration of 1L treatment was 32.0 months (95% CI, 26.9-41.0). For different geographic regions, the median duration of 1L treatment was 28.3 months (95% CI, 18.5-47.7) for North America, 23.7 months (95% CI, 17.7-35.5) for Latin America, 39.8 months (95% CI, 6.0 to not estimable [NE]) for Oceania, 47.6 months (95% CI, 32.7-59.6) for Europe, and 18.7 months (95% CI, 3.1-40.3) for Asia. Approximately 50% of all patients experienced treatment discontinuation or change. The main reasons for discontinuation or change of 1L treatment were inadequate response (n = 135/495 [27.3%]), disease



Survival Estimate (%) (95% CI)

	Events	Week 24	Week 52	Week 104	Week 156	Median (months) (95% CI)
1L (n = 996)	494	79.4 (76.7–81.8)	68.2 (65.1–71.0)	56.2 (52.8–59.4)	48.5 (45.0–52.0)	32.0 (26.9–41.0)
2L (n = 370)	224	66.2 (60.9–70.9)	49.1 (43.4–54.4)	34.9 (29.2–40.6)	27.0 (21.3–33.0)	11.1 (8.5–16.1)
3L (n = 176)	119	59.5 (51.5–66.7)	42.6 (34.4–50.5)	24.4 (17.2–32.4)	14.7 (8.6–22.5)	9.3 (7.1–12.0)
4L (n = 87)	65	62.4 (51.0–71.9)	38.0 (27.1–48.7)	17.9 (9.9–27.8)	11.2 (4.6–21.0)	7.2 (6.0–11.9)
5L (n = 42)	27	67.2 (50.1–79.5)	37.7 (21.4–54.0)	20.7 (7.8–37.8)	20.7 (7.8–37.8)	8.8 (5.7–12.5)

Figure 1. Duration of MF treatments by treatment lines. Only patients with no missing survival time were included.

Table 2. Treatment discontinuation/change by treatment lines

	Initial treatment (n = 997)	Treatment 2 (n = 370)	Treatment 3 (n = 176)	Treatment 4 (n = 87)	Treatment 5 (n = 42)
Main treatment ongoing	502 (50.4)	146 (39.5)	57 (32.4)	22 (25.3)	15 (35.7)
Main treatment discontinued or changed	495 (49.6)	224 (60.5)	119 (67.6)	65 (74.7)	27 (64.3)
Reason for discontinuation or change					
Inadequate response	135 (27.3)	80 (35.7)	39 (32.8)	19 (29.2)	8 (29.6)
Disease progression	88 (17.8)	21 (9.4)	9 (7.6)	8 (12.3)	5 (18.5)
Toxicity	57 (11.5)	20 (8.9)	15 (12.6)	6 (9.2)	1 (3.7)
Financial/insurance	4 (0.8)	0	0	2 (3.1)	0
Completed planned treatment	25 (5.1)	14 (6.3)	9 (7.6)	1 (1.5)	3 (11.1)
Decline in performance status	4 (0.8)	5 (2.2)	3 (2.5)	2 (3.1)	1 (3.7)
Dead	30 (6.1)	11 (4.9)	12 (10.1)	6 (9.2)	4 (14.8)
Patient preference	7 (1.4)	7 (3.1)	0	0	0
Physician preference	60 (12.1)	30 (13.4)	15 (12.6)	3 (4.6)	1 (3.7)
Other	67 (13.5)	26 (11.6)	13 (10.9)	15 (23.1)	3 (11.1)
Not documented	18 (3.6)	10 (4.5)	4 (3.4)	3 (4.6)	1 (3.7)

The full analysis set includes all patients who received at least 1 dose of the first treatment. Calculated based on the number of patients in the full analysis set. For a patient with multiple treatment lines, the reason for each drug discontinuation or change was counted. One treatment line per patient has only 1 discontinuation reason. All treatment lines for a patient will be displayed from 1L to 5L, if applicable.

progression (n = 88/495 [17.8%]), and toxicity (n = 57/495 [11.5%]; Table 2); results were similar across geographic regions (supplemental Table 3).

Secondary and subsequent treatment details

Treatment pattern changes by LoT are detailed in Figure 2. RUX (n = 229/370 [61.9%]) and HU (n = 105/370 [28.4%]) remained the most common 2L treatments, followed by erythropoiesis-stimulating agents (n = 86/370 [23.2%]; supplemental Table 2). Although this pattern continued for subsequent LoT, the use of steroids also increased with each subsequent line. Combination therapies (ie, ≥2 drugs) were used by approximately 15% of patients at 1L, 16% at 2L, and <8% at 3L+. The median duration of 2L treatment was 11.1 months (95% CI, 8.5-16.1; Figure 1). Most patients who received 2L treatment (n = 224 [60.5%]) experienced treatment discontinuation or change with the main reasons being

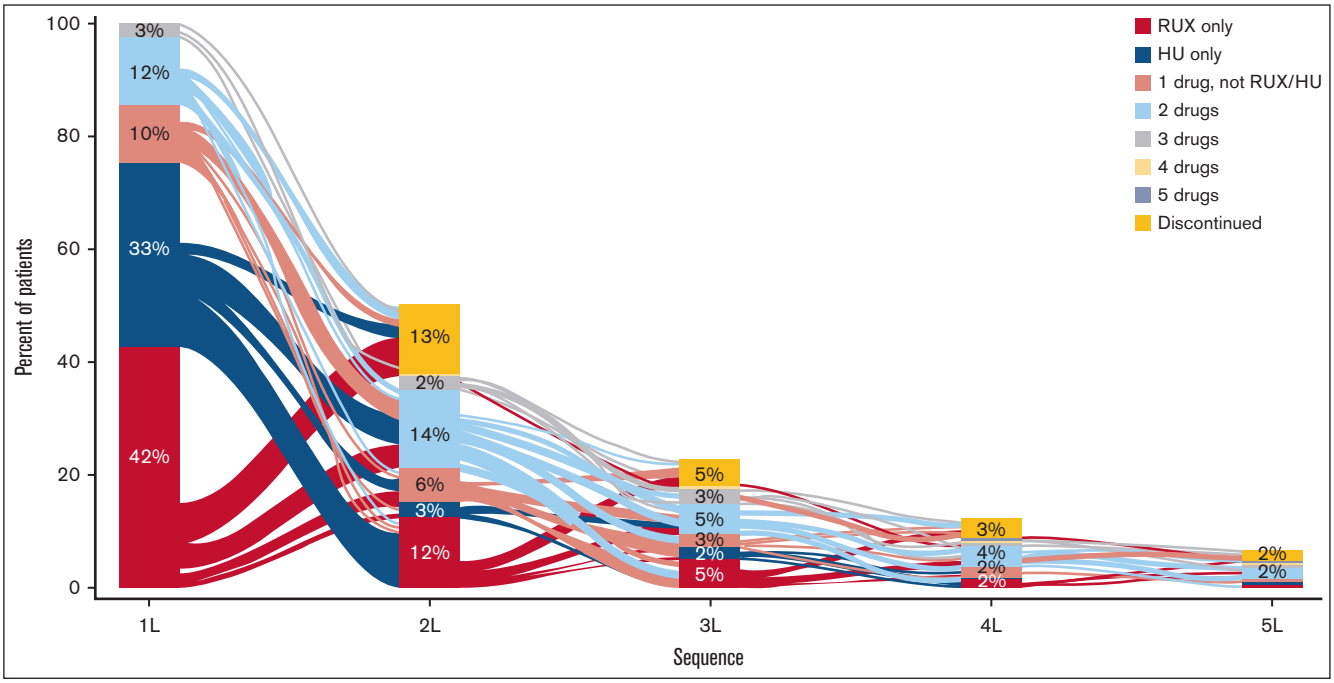
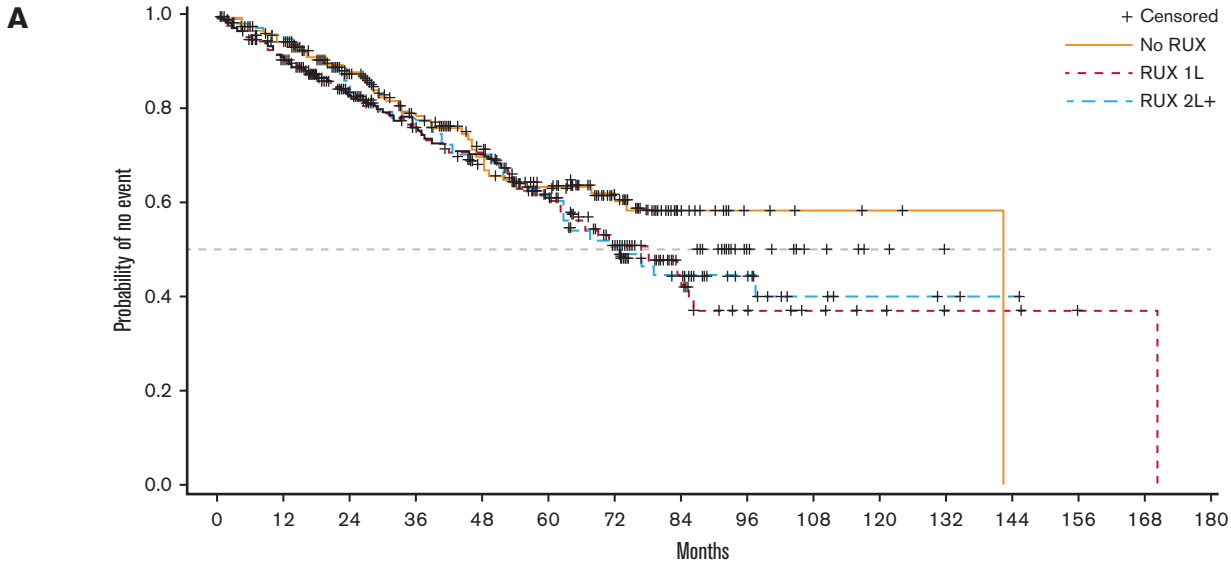


Figure 2. Treatment pattern change by treatment lines.

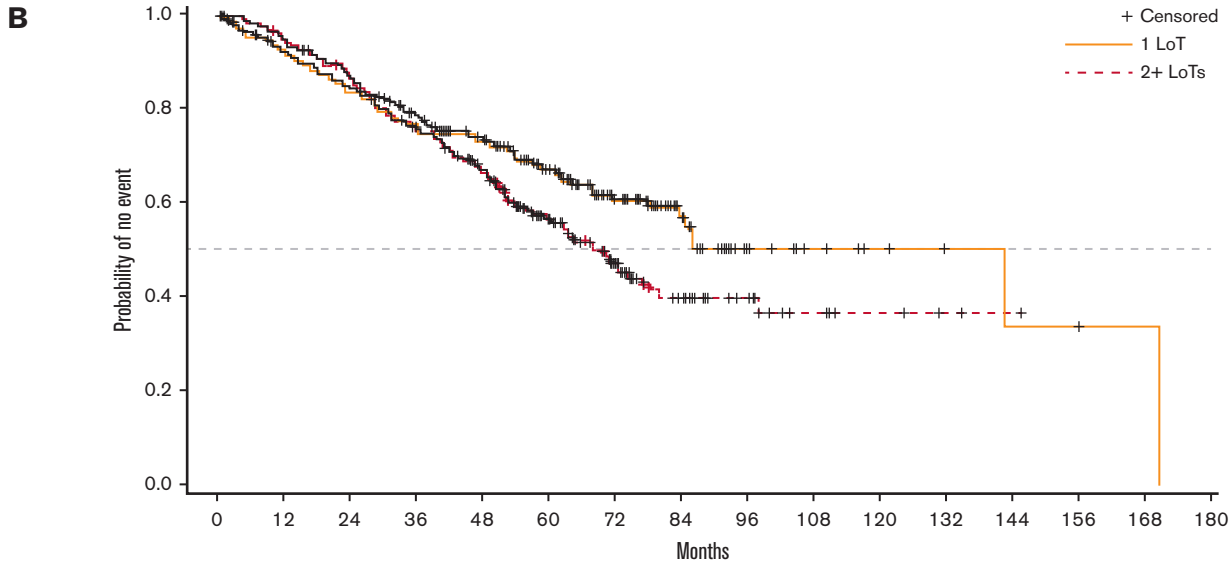


Patients at risk*

No RUX**	284	241	168	108	62	50	38	14	5	3	2	1	0	0	0	0
RUX 1L	489	409	280	181	118	73	40	18	9	7	4	2	2	1	1	0
RUX 2L+	223	206	162	114	73	48	30	21	12	5	3	2	1	0	0	0

Survival Estimate (%) (95% CI)

	Events	Week 24	Week 52	Week 104	Week 156	Median (months) (95% CI)
No RUX (n = 284)	62	98.2 (95.7–99.2)	95.5 (92.3–97.4)	88.2 (83.4–91.8)	79.3 (72.9–84.3)	142.3 (74.1–)
RUX 1L (n = 489)	135	95.4 (93.1–97.0)	91.3 (88.4–93.5)	83.1 (79.2–86.4)	76.1 (71.4–80.2)	77.6 (64.2–85.9)
RUX 2L+ (n = 223)	73	98.7 (95.9–99.6)	94.6 (90.6–96.9)	85.0 (79.3–89.2)	77.0 (70.4–82.4)	72.6 (62.0–)



Patients at risk*

1 LoT**	626	517	343	221	139	96	62	26	12	8	5	3	2	1	1	0
2+ LoTs	370	339	267	182	114	75	46	27	14	7	4	2	1	0	0	0

Survival Estimate (%) (95% CI)

	Events	Week 24	Week 52	Week 104	Week 156	Median (months) (95% CI)
1 LoT (n = 626)	141	95.9 (94.0–97.2)	92.6 (90.2–94.5)	84.4 (81.0–87.2)	78.5 (74.4–82.0)	142.3 (83.4–)
2+ LoTs (n = 370)	129	98.6 (96.8–99.4)	94.3 (91.3–96.2)	85.9 (81.7–89.2)	75.8 (70.6–80.2)	69.1 (59.4–77.7)

Figure 3.

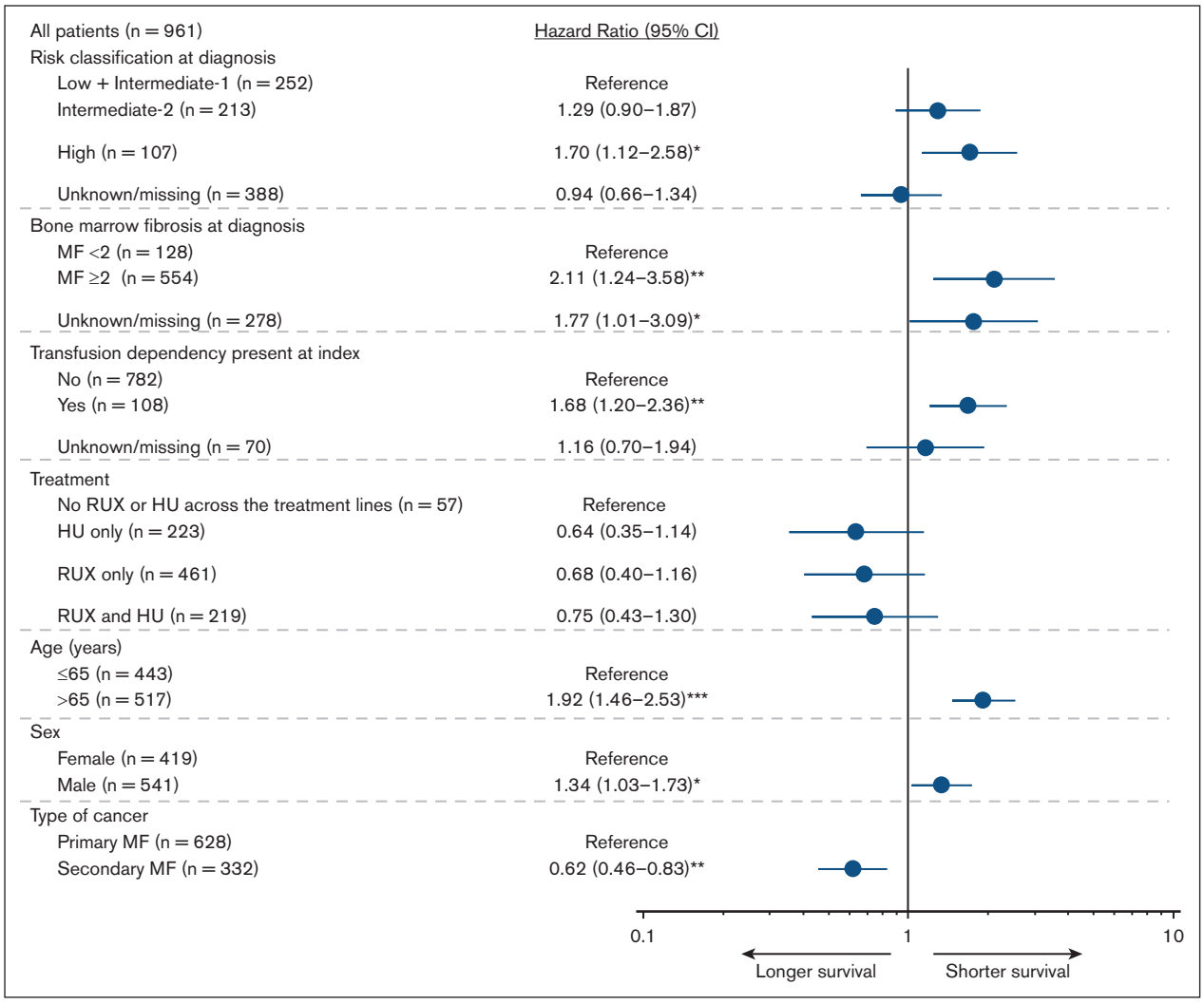


Figure 4. Multivariable analysis of factors that predict OS. For the variable treatment, the 4 categories were mutually exclusive. The Cox proportional survival analysis only displays the best model based on the following factors that were checked: treatment (this variable should be forced into this model), age group, sex, type of cancer, risk classification at diagnosis, BMF grade, high molecular risk mutation at diagnosis, transfusion dependent at index date, stem cell transplant (yes/no), and splenectomy (yes/no). The risk categories were pooled from multiple risk classification systems. Patients with missing data on age and undifferentiated sex were not included in the analysis because of low frequency. *$P < .05$; **$P < .01$; ***$P < .001$.

inadequate response (n = 80/224 [35.7%]), physician preference (n = 30/224 [13.4%]), and disease progression (n = 21/224 [9.4%]). The median duration of treatment decreased further to 9.3 months (95% CI, 7.1-12.0) for 3L therapy. More than half (n = 119/176 [67.6%]) of patients who received 3L treatment experienced treatment discontinuation or change.

The median duration of treatment was 24.5 months (95% CI, 21.1-31.1) for patients treated with HU as 1L, 59.6 months (95% CI, 52.2-73.0) for RUX as 1L, and 22.3 months (95% CI, 12.0-30.2) for RUX as 2L. The proportion of patients with treatment discontinuation or change was 57.9% (n = 232/401) for patients who received HU as 1L, 36.6% (n = 179/489) for patients who received RUX as 1L, and 50.0% (n = 86/172) for patients who received RUX as 2L (supplemental Table 4).

Procedural intervention

The median time from index date to procedural intervention was 12.0 months (IQR, 6.4-28.8), that is, 364 days (IQR, 196-877). The most common procedure(s) received was SCT (n = 77), followed by splenectomy (n = 21). A total of 23 patients (2.3%) received SCT as their 1L treatment; 16 (1.6%) patients with splenectomy had previous exposure to RUX. Based on the competing risk analysis for the time from index date to SCT or death for patients ≤70 years of age, it was estimated that the cumulative incidence of SCT gradually increased over time from week 24 (2.2% [95% CI,

Figure 3. OS for patients with no RUX vs RUX 1L vs RUX 2L+ and 1L vs 2L+ treatments. OS for patients with (A) no RUX vs RUX as 1L vs RUX as 2L+ and (B) 1L vs 2L+ treatments. There is not a statistical comparison being made between groups that are on the same plot.

1.3-3.6]) through week 156 (11.0% [95% CI, 8.6-13.8]). Likewise, a competing risk analysis for the time from index date to splenectomy or death estimated that the cumulative incidence also increased over time from week 24 (0.6% [95% CI, 0.3-1.3]) through week 156 (2.2% [95% CI, 1.3-3.4]).

Multivariable analyses of factors associated with duration of treatment

For patients treated with HU as 1L (n = 391), after controlling for potentially confounding factors, it was estimated that patients with high- or intermediate-2–risk classification at diagnosis had higher chances of discontinuation or change of 1L treatment than those with low-risk or intermediate-1 classification at diagnosis (HR, 2.57; 95% CI, 1.58-4.20 and HR, 1.88; 95% CI, 1.29-2.73, respectively; $P < .001$ for both; supplemental Figure 1). Patients treated with HU as 1L with MF ≥2 BMF at diagnosis had a higher chance of discontinuation or change of 1L treatment than patients with MF <2 BMF at diagnosis (HR, 1.81; 95% CI, 1.21-2.70; $P = .004$).

Among patients treated with RUX as 1L (n = 465), those aged >65 years had a higher chance of treatment discontinuation or change than patients ≤65 years (HR, 1.61; 95% CI, 1.14-2.28; $P = .007$). For patients treated with RUX as 2L (n = 166), those with primary MF had a higher chance of treatment discontinuation or change than patients with secondary MF (HR, 0.58; 95% CI, 0.36-0.94; $P = .026$). Patients treated with RUX as 1L or 2L who also received an SCT had a higher chance of RUX treatment discontinuation or change than patients who did not receive SCT (1L: HR, 6.01; 95% CI, 3.84-9.41; 2L: HR, 2.61; 95% CI, 1.40-4.89; $P < .01$).

OS

Of the 997 patients, 270 (27.1%) died. Among patients who died (n = 270), the most common reasons were disease progression (n = 89 [33.0%]), other reason (n = 83 [30.7%]), unknown reason (n = 59 [21.9%]), transformation to acute myeloid leukemia (n = 30 [11.1%]), and toxicity (n = 9 [3.3%]). For all patients, the median survival time from index date to death was 79.1 months (95% CI, 70.8 to NE). The median survival time from index date to death was 142.3 months (95% CI, 74.1 to NE) for patients who did not receive RUX, 77.6 months (95% CI, 64.2-85.9) for patients who received RUX as 1L, and 72.6 months (95% CI, 62.0 to NE) for patients who received 2L+ RUX (Figure 3A). The median survival time from index date to death was 142.3 months (95% CI, 83.4 to NE) for patients who received only 1 LoT, and 69.1 months (95% CI, 59.4-77.7) for patients who received 2+ LoT (Figure 3B). For different geographic regions, the median survival time from index date to death was 146.8 months (95% CI, 68.1 to NE) for North America, 95.3 months (95% CI, 63.2-119.6) for Latin America, 137.5 months (95% CI, 62.3 to NE) for Oceania, 130.6 months (95% CI, 80.3 to NE) for Europe, and not reached (NE months [95% CI, 42.4 to NE]) for Asia.

Multivariable analyses of factors associated with OS trends demonstrated a statistically significantly shorter survival in patients aged >65 years, male patients, patients with high-risk classification, patients with BMF ≥2, and patients who were transfusion dependent at index; patients with secondary MF had a statistically significantly prolonged survival when compared with patients with primary MF (Figure 4).

HCRU

Of the patients hospitalized (n = 520), the median hospital LoS after the index date was 16 days (IQR, 7-37; supplemental Table 5). The median ICU LoS after the index date for patients who required ICU admission (n = 71) was 5 days (IQR, 2-13). Of patients who received a transfusion(s) (n = 375), the median number of transfusion events was 12 (IQR, 4-26). Patients who received RUX had numerically shorter total hospital LoS and fewer transfusion events than patients who did not receive RUX. The follow-up time was 2158 patient-years for patients who received RUX (n = 712), 829 patient-years for patients who did not receive RUX (n = 285), and 2987 patient-years for all patients who received any treatment (n = 997).

Discussion

Studies that explore the characteristics of patients with MF and treatment outcomes in real-world settings are typically limited to individual countries. Results from a multi-country and ethnically diverse population remain an important data gap. This study provides a comprehensive analysis of data from a unique chart review of 998 patients with MF enrolled across 14 countries, representing various continents and diverse populations, to describe treatment patterns, effectiveness, and HCRU. Historically, HU was the most common 1L treatment in patients with MF before the approval of RUX, which is now a cornerstone MF treatment.[10] In this study, RUX was the most frequently used 1L therapy, followed by HU; RUX was also the most common therapy used in 2L+ settings. In addition, in patients ≤70 years, 1L transplant was uncommon and the cumulative incidence of receipt of SCT increased from 2.2% at week 24 to 11% at week 156, which is notable because SCT is the only potentially curative treatment. As the treatment landscape for MF continues to evolve,[17-19] real-world evidence on the current treatment patterns is needed.

Despite significant initial clinical activity in many cases, patients with MF can lose response to or become intolerant of RUX with 50% to 70% of these patients discontinuing therapy within 3 to 5 years.[12,13] In this study, the median duration of 1L therapy was 32.0 months (59.6 months for 1L RUX) and decreased in subsequent lines to 11.1 months in 2L and 9.3 months in 3L. When comparing patients who received HU or RUX, the proportion of patients who discontinued or changed treatment was numerically higher among patients who received HU as 1L than among those who received RUX as 1L or RUX as 2L. Notably, patients who received HU instead of RUX as 1L may be in a lower risk group, because RUX approval varies between countries and in some cases only patients with intermediate- or high-risk MF who are not candidates for SCT are eligible.[10] In addition, the median duration of 1L therapy and rates of discontinuation/change varied regionally with the North American, Latin American, and Oceanian regions demonstrating numerically longer median treatment durations and the North American, Oceanian, and Asian regions having the numerically highest rates of discontinuation/change. Multivariable analyses determined that risk classification at diagnosis, BMF grade, and receipt of SCT were factors significantly associated with treatment duration. Specifically, patients treated with HU as 1L with high- or intermediate-2–risk classification or with MF ≥2 BMF had higher chances of discontinuation or change of 1L treatment than those with low- or intermediate-1–risk classification or with MF <2 BMF at

diagnosis. Among patients treated with RUX as 1L or 2L, those who underwent SCT had a higher chance of treatment discontinuation or change than patients who did not receive an SCT. Although these data show an association, they do not indicate a causal relationship. There could be various reasons to explain why patients who received SCT had a greater chance of RUX discontinuation or change, including the use of RUX as bridging therapy for SCT or because RUX may be discontinued before receipt of SCT in clinical practice. These findings suggest that risk status and SCT option are integral for selecting an optimal treatment for patients with MF, which is important given that, in this study and similarly in others, risk classification is missing for many patients.[28]

Previous studies also assessed real-world treatment patterns and clinical characteristics associated with treatment duration. In a US-based retrospective study that used administrative claims data, 60% of included patients had ≥1 LoT; of these, 46% had ≥2 LoT during the 6-month post-MF diagnosis period.[29] Similar to our study, RUX was the most commonly prescribed 1L therapy, followed by HU. Patients who received lower RUX doses (ie, <30 mg/d) had higher rates of discontinuation and shorter therapy duration than patients who received higher RUX dosage (ie, ≥30 mg/d).[29] Notably, poor outcomes have been reported for patients with MF who discontinue RUX.[30] In a recent US-based analysis, patients with MF had an OS of 11 months following RUX discontinuation; the risk for death increased with age, Charlson Comorbidity index score, and female sex.[31] Together, these findings highlight the importance of understanding potential factors that influence treatment change in clinical settings.

In the METER study, although the estimated median OS of 79.1 months showed a positive trend when compared with historic cohorts,[32] there still was a high number of hospitalizations and transfusion events in this real-world patient population, suggesting that unmet medical needs in MF persist. After adjusting for the patient characteristics, the factors of male sex, age >65 years, high-risk classification, MF ≥2 BMF, and transfusion dependence at index date were statistically significantly associated with a shorter survival, whereas patients with secondary MF had a significantly longer survival. The median OS varied regionally, which could be driven by differences in ethnicity and clinical characteristics, including cancer type (ie, proportion with primary vs secondary MF), transfusion dependency, number of high-risk patients, and BMF level, which varied among different geographic regions. The numerically longer OS observed for patients who did not receive RUX, when compared with those who did receive RUX as 1L or 2L+, and for patients who received only 1L vs 2L+ treatment, may be attributed, in part, to the presence of less aggressive disease in the non-RUX and 1L only groups. Patients who received HU instead of RUX as 1L may have been classified in a lower risk group.[10] Furthermore, patients who received more LoT might similarly have had more aggressive disease that did not respond easily to treatment. A post hoc analysis of pooled data from the COntrolled MyeloFibrosis Study With ORal JAK Inhibitor Treatment (COMFORT)-I and COMFORT-II studies evaluated the treatment effect on OS among patients with intermediate-2 or high-risk MF treated with RUX, placebo, or the best available therapy.[33] With 3 years of follow-up, patients who received RUX trended toward longer OS when compared with patients who received placebo or the best available therapy, which was in contrast with our findings. Furthermore, the most recent 5-year data from COMFORT-1 demonstrated prolonged survival with RUX.[34] Note that the COMFORT studies were not specifically powered to show effects on OS. The European Registry for Myeloproliferative Neoplasms: Toward a Better Understanding of Epidemiology, Survival, and Treatment (ERNEST) project prospectively enrolled patients with MF to assess real-world data across international centers that specialized in MF management,[32,35] and in a recent analysis of 1010 patients, the median OS was approximately 74.4 months.[32] In the ERNEST study, the median OS was longer among patients who were treated with RUX than among those treated with HU (80.4 vs 61.2 months), and a multivariable analysis predicted that age, male sex, and high DIPSS were factors that negatively impacted OS, whereas a more recent diagnosis and treatment with RUX were protective.[32] It should be noted that within the ERNEST study population, RUX exposure was mostly restricted to patients who were in higher risk DIPSS categories at index. Differences in patient populations and criteria for receipt of RUX treatment may partially explain the differences in the trends of OS outcomes for those studies and the METER study.

In addition to clinical benefits, understanding the impact of treatment on HCRU is critical for understanding the full benefits of MF treatments on patients and the health care system. In the METER study, patients who received RUX had a numerically shorter hospital LoS and numerically fewer transfusion events than patients who did not receive RUX. The high number of hospitalizations and transfusion events is notable given that these may factor into the overall economic burden on patients and the health care system. The overall economic burden is not fully understood, however, it is estimated to be as high as $66 000 per patient in the US and $23 863 in Canada, driven primarily by outpatient and inpatient visits.[29,36,37] In a recent US-based administrative claims study, costs increased considerably from 6 months before diagnosis to 6 months after diagnosis (all cause, $24 216-$48 966; MF related, $16 502-$39 383), driven by inpatient stays and pharmacy costs.[29]

Limitations

Although this study, which assessed different regions, included ethnically diverse populations, it is worth noting that the study population was not racially diverse, and ~88% of patients were White. It is also worth noting that no randomization or blinding was performed for this observational study. Inherent biases may potentially confound the results because of the observational nature of the study. In observational studies, patient assessments are not dictated by a strict protocol but based on routine clinical practice, the physician's judgment, and the patient's availability. This creates a problem with unequal duration of treatment and follow-up when assessments at defined time intervals are required. Analyses related to hospitalization and ICU admissions involved all-cause admissions and were not specifically MF related because MF-related hospitalizations and other forms of HCRU were not consistently available across the multiple sites included in the chart review. Because of the retrospective nature of the chart review, there may be data missing from certain charts. Further longitudinal studies are necessary to explore these relationships comprehensively.

Conclusion

This real-world study demonstrates that most patients with MF receive RUX or HU as 1L therapy, and nearly half of these patients remained on this treatment option through 156 weeks. The greatest reduction in duration of MF treatment occurred between 1L and 2L when compared with the transition to later lines, highlighting the importance of optimizing 1L treatment. In everyday clinical practice, failure on RUX therapy continues to be a challenge in the management of patients with MF. Despite improvements in MF treatments, this study also demonstrated that patients with MF in a real-world setting experience hospitalization and required transfusions, suggesting significant unmet medical need. The descriptive findings from this study highlight the need for further studies into treatment patterns, outcomes, and factors associated with outcomes to achieve optimal treatment and disease management in patients with MF.

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Authorship

Contribution: V.G. recruited patients, designed the study protocol, performed data analysis, and contributed to manuscript writing and approval of the manuscript; C.T., G.I.B.L., H.-A.H., G.H., P.V., I.H., K.G., B.M., and D.M.R. contributed to the analysis and interpretation of results, manuscript preparation, and critical review; A.S. contributed to clinical data collection, analysis and interpretation of results, manuscript preparation, and critical review; F.T. and T.V. contributed to study design, analysis and interpretation of results, manuscript preparation, and critical review; A.S.C. contributed to the design, execution, and review of the manuscript; and M.Z. contributed to the design, statistical analysis, analysis and interpretation of the results, manuscript preparation, and critical review. All authors had access to the relevant data and participated in the drafting, review, and approval of this publication.

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ORCID profiles: V.G., 0000-0002-1419-8607; G.I.B.L., 0000-0002-2988-7544; G.H., 0000-0003-3703-1268; P.V., 0000-0001-9779-6217; A.S., 0000-0002-3685-3473; K.G., 0000-0003-1192-9053; A.S.C., 0000-0001-6020-488X; D.M.R., 0000-0001-7171-2935.

Correspondence: Vikas Gupta, Princess Margaret Cancer Centre, 610 University Ave, Toronto, ONM5G 2M9C Canada; email: Vikas.Gupta@uhn.ca.

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