blood advances

A prognostic model to predict survival after 6 months of ruxolitinib in patients with myelofibrosis

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Key Points

- RUX dose, spleen response, and transfusion requirement in the first 6 months of RUX treatment predict overall survival in MF.

- The RR6 model overcomes conventional risk stratification in RUX-treated MF.

Ruxolitinib (RUX) is extensively used in myelofibrosis (MF). Despite its early efficacy, most patients lose response over time and, after discontinuation, have a worse overall survival (OS). Currently, response criteria able to predict OS in RUX-treated patients are lacking, leading to uncertainty regarding the switch to second-line treatments. In this study, we investigated predictors of survival collected after 6 months of RUX in 209 MF patients participating in the real-world ambispective observational RUXOREL-MF study (NCT03959371). Multivariable analysis identified the following risk factors: (1) RUX dose <20 mg twice daily at baseline, months 3 and 6 (hazard ratio [HR], 1.79; 95% confidence interval [CI], 1.07-3.00; $P = .03$), (2) palpable spleen length reduction from baseline ≤30% at months 3 and 6 (HR, 2.26; 95% CI, 1.40-3.65; $P = .0009$), (3) red blood cell (RBC) transfusion need at months 3 and/or 6 (HR, 1.66; 95% CI, 0.95-2.88; $P = .07$), and (4) RBC transfusion need at all time points (ie, baseline and months 3 and 6; HR, 2.32; 95% CI, 1.19-4.54; $P = .02$). Hence, we developed a prognostic model, named Response to Ruxolitinib After 6 Months (RR6), dissecting 3 risk categories: low (median OS, not reached), intermediate (median OS, 61 months; 95% CI, 43-80), and high (median OS, 33 months; 95% CI, 21-50). The RR6 model was validated and confirmed in an external cohort comprised of 40 MF patients. In conclusion, the RR6 prognostic model allows for the early identification of RUX-treated MF patients with impaired survival who might benefit from a prompt treatment shift.

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

Introduction

Among myeloproliferative neoplasms (MPNs), myelofibrosis (MF) is characterized by the most heterogeneous clinical picture and the most severe prognosis.[1-3] The disease can occur as primary myelofibrosis (PMF) or secondary to an antecedent diagnosis of essential thrombocythemia (ET) or polycythemia vera (PV), collectively referred to as secondary myelofibrosis (SMF). This distinction has further clinical and prognostic relevance.[4,5] Most MF patients harbor a somatic driver mutation in *JAK2*, *CALR*, or *MPL*,[6] often coexisting with additional mutations. Both categories of genetic variants impact phenotype and prognosis.[7-12] The addition of genetic information to clinical variables has allowed to update prognostic models,[1,3,5,13,14] which are currently extensively used to inform treatment decisions and enrollment in clinical trials. The JAK inhibitor ruxolitinib (RUX) is the first approved drug for the treatment of MF, with efficacy in terms of spleen volume reduction and symptom relief, mostly obtained within the first 6 months of treatment.[15,16] An improvement of overall survival (OS) with RUX has been reported in a posthoc pooled analysis of the registration trials,[17,18] in a comparison of phase 1/2 trial data with matched historical controls,[19] and in a recently reported registry study.[20]

Nonetheless, RUX therapy is burdened by a substantial proportion of suboptimal responses, loss of response over time, and significant discontinuation rates in clinical trials[18,21-23] and in the real-world setting.[24,25] Pre-RUX factors associated with lower spleen response rates include higher risk MF, large splenomegaly, transfusion-dependency, platelet count $<200 \times 10^9$/L, a time-interval between MF diagnosis and RUX start >2 years, RUX as $\geq$second-line treatment, any genotype other than *JAK2*V617F with $\geq$50% allele burden, and $\geq$3 mutations identified by next-generation sequencing (NGS).[26-29] Data on fatality after RUX discontinuation[30-32] collectively indicate the need for effective second-line treatments.

Multiple trials focusing on RUX-treated patients (ie, individuals who are relapsed/refractory, suboptimal responders, or intolerant to RUX) have been conducted or are underway.[33-35] However, given the absence of clinically relevant endpoints associated with differential responses to RUX and the consequent heterogeneity of trial inclusion criteria, even cautious comparisons of outcomes among studies are unreliable.[36,37] In the real world, the definition of the optimal timing for a treatment shift or stem cell transplant (SCT) after RUX is a recognized unmet medical need.

The aim of the present study is to identify early predictors (after 6 months of RUX) of inferior survival, the most relevant clinical endpoint, in patients with MF receiving RUX in a well-characterized real-world setting.

Methods

Study overview

The Italian health care service is regionally based and is characterized by universal coverage. Drugs are delivered by each regional health authority, with longitudinal monitoring for high-cost treatments such as RUX. In Lombardy, a region of roughly 10 million individuals, we are conducting an ambispective observational study (RUXOREL-MF, clinicaltrials.gov identifier NCT03959371), focusing on RUX-treated MF patients on the basis of real-world data provided by the regional health authority integrated with institutional data, already described at an earlier time point of patient inclusion.[38] The study was approved by the review board of each institution and conducted in accordance with the Declaration of Helsinki.

Patients

At the time of data cutoff for the current analysis (February 2021), the study database comprised 288 MF patients regularly followed at 17 centers (training cohort). A validation cohort comprised of 91 MF patients treated with RUX at Moffitt Cancer Center (Florida) was employed. Since responses to RUX are typically seen within the first 6 months of therapy, and drug discontinuation has been advocated in the absence of splenomegaly reduction or symptom improvement in the same time frame,[39-41] we focused on the first 6 months of treatment to evaluate early predictors of impaired survival. Patient selection criteria for enrollment in our study, therefore, included subjects with $\geq$6 months of follow up after RUX initiation, along with the following parameters at the beginning of RUX: platelet count $>50 \times 10^9$/L, spleen enlargement of $\geq$5 cm below the left costal margin (LCM), and International Prognostic Scoring System (IPSS) intermediate-1 risk or higher, reflecting current indications and reimbursement policies. PMF was defined or diagnosis was reassessed by World Health Organization (WHO) 2016 criteria,[42] whereas diagnoses of post-PV MF and post-ET MF were made according to the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria.[43] Leukemic transformation was diagnosed according to WHO criteria, considering a 20% bone marrow or peripheral blood (PB) blast threshold.[42] Given the observational ambispective real-world nature of the study, decisions regarding RUX dosing and treatment cessation were made by the treating physicians at the participating sites.

Data collection

The RUXOREL-MF study was designed to collect clinical and laboratory data at MF diagnosis, at the time of RUX initiation, and subsequently at regular time intervals (patient visits 3, 6, 12, 18, 24, 36, and 48 months post-RUX start are recorded). Risk category was assessed at RUX start and at the 6-month time point according to the Dynamic IPSS (DIPSS)[1] for PMF patients and the MYelofibrosis SECondary to polycythemia vera and essential thrombocythemia Prognostic Model (MYSEC-PM)[5] for SMF patients. Given the real-world nature of the study and the pursuit of meaningful evidence readily transferable to daily patient care, no spleen imaging studies nor symptom assessment scales were required. Splenomegaly was measured by palpation, assessing spleen length in cm from LCM. Constitutional symptoms were recorded as absent or present, in line with most prognostic scoring systems currently used in clinical practice.[1,3,5,13,44] RUX dose was recorded at the time of each patient visit. The need for red blood cell (RBC) transfusions (any quantity of units) in the 3 months preceding the start of RUX (included) was captured as "presence of baseline RBC requirement"; the need for RBC transfusions (any quantity of units) in the time interval ranging from the start of RUX to the 3-month visit (included) was captured as "presence of RBC requirement at 3 months"; and the need for RBC transfusions (any quantity of units) in the time interval ranging from the 3-month visit to the 6-month visit (included) was captured as "presence of RBC requirement at 6 months." Investigated components of RUX response, readily available in all patients everywhere (eg, hemoglobin [Hb] value, white blood cell [WBC] count, platelet

[PLT] count, PB blasts, spleen length from LCM, constitutional symptoms, transfusion requirement) were evaluated individually, given the exploratory nature of the analysis and its real-world makeup. Since we aimed to identify dynamic predictors of survival under RUX treatment, we focused on the changes of clinical and laboratory variables between the 6-month time point and baseline, including 3-month data in order to have a more fine-grained picture and to minimize the risk of considering transient modifications as clinically meaningful.

Statistical methods

Concerning the statistical methods, continuous variables are expressed as median and interquartile range (IQR) (except for age, conveyed as median and range). Categorical variables are presented as frequency distribution. Given the temporal focus of the analysis, clinical parameters are described at baseline, 3 months, and 6 months (descriptive statistics, Kaplan-Meier estimates, and Sankey flow diagrams are performed on complete case data). Follow-up and OS are censored at the date of SCT. We used multiple imputation to maximize the use of the available covariates in the presence of missing data (generally not exceeding 5%, and in any case never exceeding 10%, for any individual covariate). The missing values of all covariates were imputed, by assuming that data were missing at random, with 10 imputations. Discriminant function and predictive mean matching were applied to impute binary responses and continuous variables, respectively. All analyses except for the descriptive statistics, Kaplan-Meier curves, and Sankey flow diagrams are performed on imputed data. Differences from baseline are evaluated with a paired t test for continuous variables and McNemar's test for categorical variables. The performance of disease-specific prognostic models was assessed at baseline and after 6 months of treatment, and their agreement between the 2 time points was evaluated using Cohen's κ coefficient.

To assess early predictors of inferior survival the following variables, selected on the basis of clinical plausibility, have been explored using a Cox proportional hazards model: (1) Hb decrease between 6 months and baseline, as a continuous variable adjusted for baseline transfusions; (2) acquisition of leukocytosis, defined as WBC $>25 \times 10^9$/L at 6 months in subjects with WBC $\leq 25 \times 10^9$/L at baseline; (3) worsening thrombocytopenia, considering the following PLT count categories: $\geq 200 \times 10^9$/L, 100 to 199 $\times 10^9$/L, 75 to 99 $\times 10^9$/L, 50 to 74 $\times 10^9$/L, $<50 \times 10^9$/L between 6 months and baseline; (4) increase of PB blasts as a continuous variable between 6 months and baseline; (5) acquisition of constitutional symptoms at 6 months; (6) RUX dose as a categorical variable, considering individuals "never treated with ≥ 20 mg twice daily over the course of the first 6 months of therapy" (20 mg twice daily being the most frequently employed RUX starting dose in our cohort) vs those "treated with ≥ 20 mg twice daily on at least 1 occasion (baseline, 3 months, and/or 6 months)"; (7) reduction of palpable spleen length within the first 6 months categorically defined as "reduction always $\leq 30\%$" vs "reduction $>30\%$ at 3 and/or 6 months of treatment" (cutoff defined through a spline function analysis); (8) RBC transfusion requirement, considering the following categories "never transfused with RBC," "RBC transfusions only at baseline," "RBC transfusions at 3 and/or 6 months," and "RBC transfusions at all time points (baseline, 3 months, and 6 months)."

Regressors associated with OS with $P < .10$ in univariate analysis were jointly tested in a multivariate model. Independent predictors of survival with $P < .10$ were used to define a prognostic model. For

the sake of simplicity, a rounded weight was associated with each risk factor based on its hazard ratio (HR). Sums of scores recognizing patients with a similar OS were unified in risk categories. To test the quality of our model, the Akaike information criterion (AIC) value was calculated for the baseline disease-specific risk score, for the newly defined prognostic model, and for the combination of both scores. All statistical analyses were performed with SAS (Cary, NC) version 9.4; R software version 3.2.0 was used to produce the plots.

Results

Patient characteristics

Within the RUXOREL-MF database, 209 RUX-treated MF patients entered the analysis (Figure 1). Median follow-up from RUX start was 30.5 months (IQR, 9.7-50.0 months) and median time on RUX was 28.2 months (IQR, 14.3-44.6 months). Patient demographics, disease-specific features, and RUX dose at treatment initiation are summarized in Table 1 and supplemental Figures 1-4. Driver mutation frequency was as expected given the makeup of the patient population under study. When applying disease-specific risk scores (ie, DIPSS for PMF and MYSEC-PM for SMF), 44.5% of patients
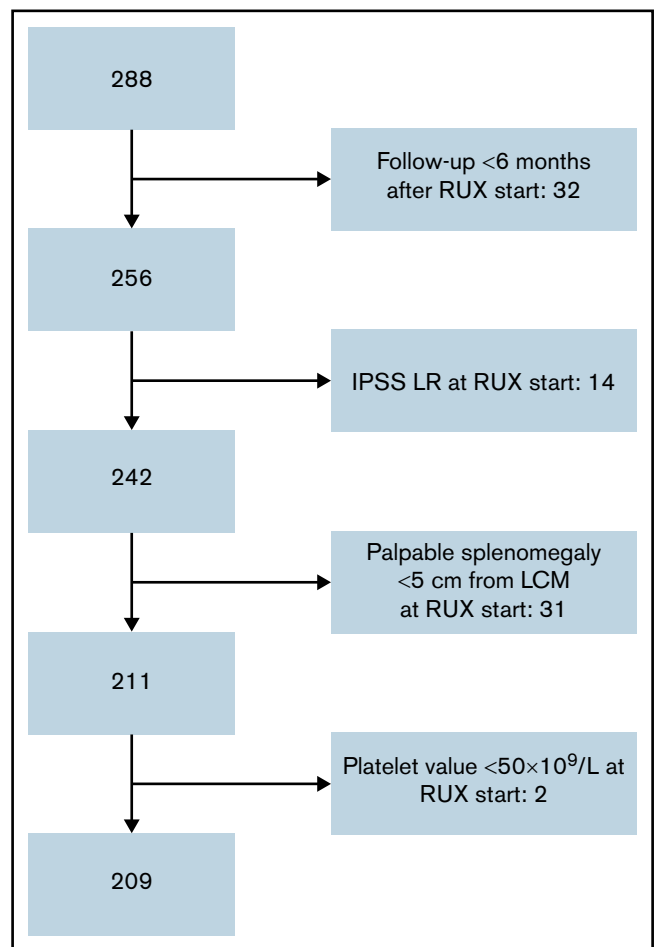

Figure 1. Patient disposition flowchart (training cohort). Patient flowchart reporting the total number of patients included in the RUXOREL-MF database and the number of patients excluded from the analysis with the corresponding motivations, in line with selection criteria. IPSS, International Prognostic Scoring System; LR, low risk; RUX, ruxolitinib.

Table 1. Patient demographics, disease-specific characteristics, and RUX dose at treatment initiation (training cohort)

	At RUX treatment initiation
Median age, years (range)	67 (37-85)
Sex M / F, n (%)	131 (62.7) / 78 (37.3)
Median time between diagnosis and enrollment, months (IQR)	29.0 (5.8-59.8)
PMF, n (%)	96 (45.9)
SMF, n (%)	113 (54.1)
PET-MF, n (%)	35 (16.8)
PPV-MF, n (%)	78 (37.3)
BM fibrosis grade 0 / 1 / 2 / 3 / UNK, n (%)	1 (0.5) / 22 (10.5) / 86 (41.2) / 74 (35.4) / 26 (12.4)
JAK2V617F-mutated, n (%)	151 (72.2)
CALR-mutated, n (%)	31 (14.8)
MPL-mutated, n (%)	11 (5.3)
Triple-negative*, n (%)	4 (1.9)
Driver mutational status not available, n (%)	12 (5.7)
Normal / abnormal karyotype, n (%)†	55 (62.5) / 33 (37.5)
Favorable / unfavorable / very high-risk karyotype, n (%)†	68 (77.3) / 14 (15.9) / 6 (6.8)
PMF, DIPSS LR / int-1 R / int-2 R / HR / UNK, n (% of PMF patients)	0 (0) / 42 (43.8) / 37 (38.5) / 17 (17.7)/ 0 (0)
SMF, MYSEC-PM LR / int-1 R / int-2 R / HR / UNK, n (% of SMF patients)	10 (8.8) / 55 (48.7) / 24 (21.2) / 15 (13.3) / 9 (8.0)‡
Disease-specific risk score§ LR and int-1 R / int-2 R and HR / UNK, n (%)	107 (51.2) / 93 (44.5) / 9 (4.3)
Median WBC, ×10⁹/L (IQR)	11.1 (6.5-18.7)
Median Hb, g/dL (IQR)	10.6 (9.4-12.3)
Median PLT, ×10⁹/L (IQR)	220 (153-348)
Median peripheral blood blasts, % (IQR)	1 (0-2)
Constitutional symptoms Y / N, n (%)	146 (69.9) / 63 (30.1)
Median palpable splenomegaly, cm below LCM (IQR)	12 (8-15)
RBC transfusions 3 mo prior to RUX start Y / N / UNK, n (%)	49 (23.4) / 156 (76.6) / 4 (1.9)
RUX dose 5 mg bid (10 mg total daily dose), n (%)	31 (14.8)
RUX dose 10 mg bid (20 mg total daily dose), n (%)	45 (21.5)
RUX dose 15 mg bid (30 mg total daily dose), n (%)	55 (26.3)
RUX dose 20 mg bid (40 mg total daily dose), n (%)	78 (37.3)

bid, twice a day; BM, bone marrow; F, female; HR, high risk; int-1 R, intermediate-1 risk; int-2 R, intermediate-2 risk; LCM, left costal margin; LR, low risk; M, male; N, no; PET-MF, post-essential thrombocythemia myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; UNK, unknown; Y, yes; PMF, primary myelofibrosis; SMF, secondary myelofibrosis; RUX, ruxolitinib; WBC, white blood cells; Hb, hemoglobin value; PLT, platelet count; RBC, red blood cell; IQR, interquartile range; mo, months; DIPSS, Dynamic International Prognostic Scoring System; MYSEC-PM, MYelofibrosis SECondary to polycythemia vera and essential thrombocythemia Prognostic Model.

*To define a patient as triple-negative, all 3 driver mutations had to have tested negative.
†Percentages calculated on the 88 patients with available karyotype (≥20 metaphases analyzed) at or before RUX start. Definition of favorable, unfavorable, and very high-risk karyotype according to Tefferi A et al.[62]
‡MYSEC-PM category was not available in 9 patients due to missing molecular data.
§Disease-specific risk score (ie DIPSS for PMF and MYSEC-PM for SMF).

belonged to the higher risk categories at RUX start; 23.4% of patients had received RBC in the 3 months before treatment initiation. The most represented RUX starting dose was 20 mg twice daily, given to 78 (37.3%) patients. A dose strictly adherent to the drug label with respect to baseline platelet count was delivered to 122 (58.4%) patients, whereas in 77 (36.8%) patients the starting dose was lower than what would have been indicated based on baseline platelets (detailed in supplemental Table 1). Only 7 out of 46 patients with a baseline platelet count >200 × 10⁹/L who started ruxolitinib at a dose <20 mg twice daily were eventually treated with a dose ≥20 mg twice daily at 3 and/or 6 months.

At the time of data cutoff, 100 (47.8%) patients were still on treatment. Seventy-five patients discontinued RUX, none before completing the 6-month visit. Causes of treatment cessation reported by investigators included absence of spleen response or progression of splenomegaly in 17 (22.7%), absence of symptom response in 1 (1.3%), leukemic transformation in 8 (10.7%), infection in 8 (10.7%), hematologic toxicity in 9 (12.0%), vascular complications in 1 (1.3%), clinical trial inclusion in 3 (4.0%), SCT in 20 (26.7%), and other in 8 (10.7%). During follow-up, blast phase (BP) occurred in 21 (10.0%) patients, at a median time from RUX start of 23.8 months (IQR, 13.4-30.3 months). Twenty-three out of 209 (11.0%) patients underwent SCT after a median time of 14 months (IQR, 9.5-40.5 months) from RUX initiation. Overall, 71 (34.0%) patients had died, and cause of death was BP in 21 (29.6%), MF progression in 17 (23.9%), infection in 16 (22.5%), second primary malignancy in 6 (8.5%), bleeding event in 1 (1.4%), other in 6 (8.5%), and missing in 4 (5.6%). RUX was ongoing at the time of death in 34 (47.9%) subjects. The estimated median OS from diagnosis and from RUX start was 145.0 months (95% CI, 124.2-196.8 months) and 59.4 months (95% CI, 50.5-83.2 months), respectively.

Modifications of parameters over time

Changes over time of disease-specific features and RUX dose are reported in Table 2 and are further illustrated in supplemental Figures 1-4. At 6 months from treatment initiation, patient distribution within disease-specific risk categories underwent significant changes (Cohen's κ = 0.40; 95% CI, 0.30-0.51), quite expectedly given that individual risk factors composing the DIPSS and MYSEC-PM, particularly symptoms and leukocyte and Hb values, are typically impacted by RUX. Among patients belonging to the lower risk categories at baseline, 35% underwent a shift to higher risk categories at 6 months, approximately three-quarters of whom through the acquisition of anemia, which has been demonstrated to be exempt of negative prognostic effect when related to RUX treatment.[45] In our series, DIPSS/MYSEC-PM at baseline were shown to effectively dissect outcomes of low/intermediate-1, intermediate-2, and high-risk patients (maximum P = .0006). On the other hand, after 6 months of RUX, their predictive power was reduced, in particular with respect to the correct identification of intermediate-2 risk patients (P = .09). Table 3 summarizes the results of univariate and multivariate analyses in the RUXOREL-MF training cohort. The multivariable Cox proportional hazard regression confirmed the following risk factors associated with shorter survival: (1) RUX treatment at a dose <20 mg twice daily at baseline, month 3, and month 6 (HR, 1.79; 95% CI, 1.07-3.00; P = .03); (2) palpable spleen length reduction ≤30% with respect to baseline at months 3 and 6 (HR, 2.26; 95% CI, 1.40-3.65; P = .0009); (3) the need for RBC transfusions at month 3 and/or 6 (HR, 1.66; 95% CI,

Table 2. Disease-specific characteristics and RUX dose at 3 and 6 mo from treatment initiation (training cohort)

	At 3 mo of RUX treatment	At 6 mo of RUX treatment
PMF, DIPSS LR / int-1 R / int-2 R / HR / UNK, n (% of PMF patients)	–	5 (5.2) / 28 (29.2) / 49 (51.0) / 8 (8.3) / 6 (6.3)
SMF, MYSEC-PM LR / int-1 R / int-2 R / HR / UNK, n (% of SMF patients)	–	10 (8.8) / 45 (39.8) / 27 (23.9) / 14 (12.4) / 17 (15.0)
Disease-specific risk score* LR and int-1 R / int-2 R and HR / UNK, n (%)	–	88 (42.1) / 98 (46.9) / 23 (11.0)
Median WBC, ×10⁹/L (IQR)	8.5 (5.8-14.2)	9.8 (5.6-15.3)
Median Hb, g/dL (IQR)	9.5 (8.7-10.6)	9.8 (8.9-10.9)
Median PLT, ×10⁹/L (IQR)	168 (116-266)	152 (101-237)
Median peripheral blood blasts, % (IQR)	0.5 (0-2)	1 (0-2)
Constitutional symptoms Y / N / UNK, n (%)	27 (12.9) / 174 (83.3) / 8 (3.8)	22 (10.5) / 175 (83.7) / 12 (5.7)
Median palpable splenomegaly, cm below LCM (IQR)	7 (4-11)	8 (4-10)
Spleen length reduction ≤30% with respect to baseline, n (%)	87 (41.6)	90 (43.1)
Spleen length reduction >30%-50% with respect to baseline, n (%)	58 (27.8)	47 (22.5)
Spleen length reduction >50% with respect to baseline, n (%)	57 (27.3)	58 (27.8)
Spleen length reduction with respect to baseline not available, n (%)	7 (3.3)	14 (6.7)
RBC transfusions 0-3 mo after RUX start Y / N / UNK, n (%)	91 (43.5) / 113 (54.1) / 5 (2.4)	NA
RBC transfusions 3-6 mo after RUX start Y / N / UNK, n (%)	NA	84 (40.2) / 116 (55.5) / 9 (4.3)
RUX dose <20 mg bid (<40 mg total daily dose), n (%)	163 (78.0)	161 (77.0)
RUX dose ≥20 mg bid (≥40 mg total daily dose), n (%)	44 (21.1)	41 (19.6)
RUX dose not available, n (%)	2 (1.0)	7 (3.4)

bid, twice a day; HR, high risk; int-1 R, intermediate-1 risk; int-2 R, intermediate-2 risk; LCM, left costal margin; LR, low risk; N, no; UNK, unknown; Y, yes; PMF, primary myelofibrosis; SMF, secondary myelofibrosis; RUX, ruxolitinib; WBC, white blood cells; Hb, hemoglobin value; PLT, platelet count; RBC, red blood cell; IQR, interquartile range; mo, months; DIPSS, Dynamic International Prognostic Scoring System; MYSEC-PM, MYelofibrosis SECondary to polycythemia vera and essential thrombocythemia Prognostic Model.

*Disease-specific risk score (ie, DIPSS for PMF and MYSEC-PM for SMF).

0.95-2.88; $P = .07$); and (4) the need for RBC transfusions confirmed at all time points, ie, baseline and months 3 and 6 (HR, 2.32; 95% CI, 1.19-4.54; $P = .02$). Estimated Kaplan-Meier survival curves for these risk factors, calculating OS from the 6-month time point onward, are shown in supplemental Figure 5A-C.

Development of a model to predict survival based on clinical response after 6 months of ruxolitinib

In order to concurrently capture the prognostic information provided by all the identified variables, we decided to build a comprehensive prognostic model, the Response to Ruxolitinib After 6 Months (RR6)

Table 3. Results of univariable and multivariable Cox regressions in the training cohort

Variable	Univariate, HR (95%CI); P value	Multivariate, HR (95%CI); P value
Hb decrease at 6 mo vs baseline*	1.02 (0.87-1.21); .77	
WBC count increase to >25 × 10⁹/L at 6 mo vs baseline†	1.20 (0.38-3.84); .76	
PLT count decrease at 6 mo vs baseline		
Worsening of 1 grade‡	0.81 (0.44-1.47); .48	
Worsening of 2 grades‡	2.57 (1.25-5.25); .01	
Worsening of ≥2 grades‡ at 3 mo and/or 6 mo	1.07 (0.67-1.73); .77	
Circulating blast cell increase at 6 mo vs baseline	1.42 (0.85-2.37); .18	
Acquisition of constitutional symptoms at 6 mo§	not feasible‖	
Splenomegaly reduction ≤30% by palpation at 3 and 6 mo	2.54 (1.58-4.08); <.0001	2.26 (1.40-3.65); .0009
RBC transfusion need only at baseline	0.42 (0.10-1.75); .23	
RBC transfusion need at 3 and/or 6 mo	1.80 (1.05-3.09); .03	1.66 (0.95-2.88); .07
RBC transfusion need all time points (baseline, 3 mo, and 6 mo)	2.88 (1.49-5.54); .002	2.32 (1.19-4.54); .02
RUX dose <20 mg bid at all time points (baseline, 3 mo, and 6 mo)	2.18 (1.31-3.63); .003	1.79 (1.07-3.00); .03

bid, twice a day; HR, hazard ratio; CI, confidence interval; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; mo, months; RUX, ruxolitinib; RBC, red blood cell.

*Adjusted for RBC transfusion requirement.

†In patients with WBC ≤25 × 10⁹/L at baseline.

‡PLT count categories: ≥200 × 10⁹/L; 100 to 199 × 10⁹/L; 75 to 99 × 10⁹/L; 50 to 74 × 10⁹/L; <50 × 10⁹/L.

§In those without symptoms at baseline.

‖Only 3 patients acquire constitutional symptoms at 6 mo vs baseline.
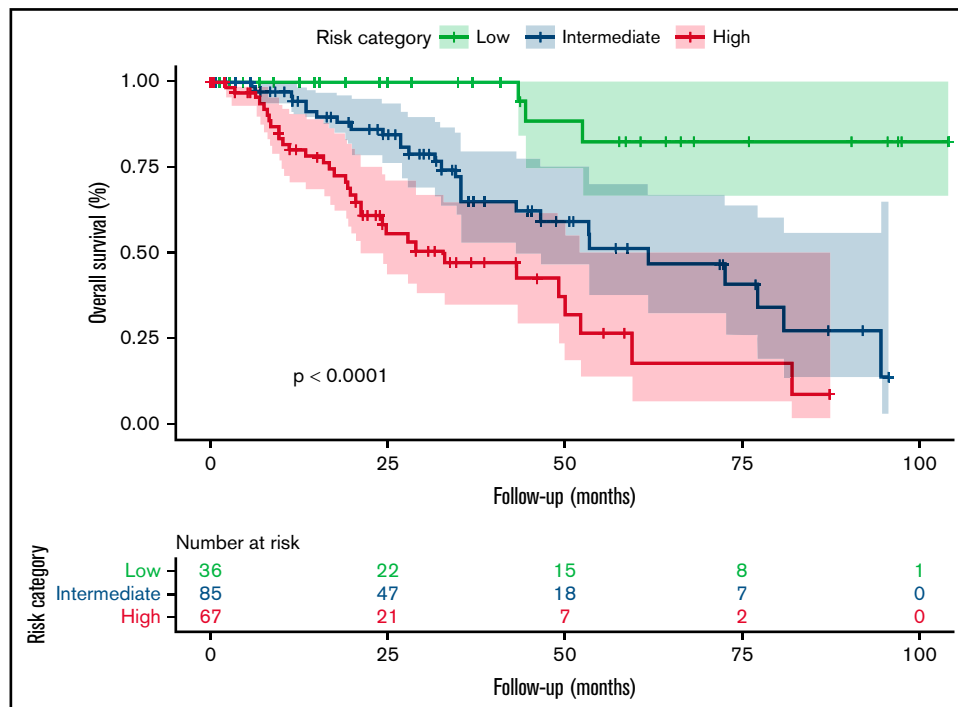
Figure 2. Actuarial survival curves of the 3 risk groups of patients according to the Response to Ruxolitinib After 6 Months (RR6) model developed in RUX-treated MF patients (training cohort).

model, assigning a weight to each risk factor based on its HR. For the sake of simplicity, 1 point was assigned to receiving RUX at a dose <20 mg twice daily at all time points and to RBC transfusion requirement at 3 and/or 6 months, whereas 1.5 points were assigned to obtaining a palpable spleen length reduction ≤30% with respect to baseline at months 3 and 6 and to needing RBC transfusions at all time points. As a result, the patients' score (ie, the sum of points assigned to the risk factors the patient carries) ranges from a minimum of 0 to a maximum of 4. To avoid risk categories comprised of very few patients and to unify scores with similar OS, patients with scores 1, 1.5, and 2 were pooled into a single group, as well as patients with scores 2.5, 3, 3.5, and 4. As a result, 3 prognostic groups were considered: low risk (no poor prognostic factor [ie, score 0], including 19.1% of the patients; median OS, not reached); intermediate (score 1 to 2, comprising 45.2% of the patients; median OS, 61 months; 95% CI, 43-80); and high risk (score 2.5 or more, 35.6% of the patients; median OS, 33 months; 95% CI, 21-50). Kaplan-Meier curves estimating survival from 6 months after RUX start were computed based on the complete case series and are shown in Figure 2 (log-rank test overall $P < .0001$). Univariate Cox proportional hazards regressions showed HRs of 4.27 (95% CI, 1.65-11.07; $P = .003$) and of 8.37 (95% CI, 3.19-21.95; $P < .0001$), respectively, for intermediate- and high- vs low-risk patients. A web-based calculator is made available to clinicians in order to readily compute the patient's RR6 risk category (http://www.rr6.eu/).

The RR6 model vs disease-specific risk scores and its validation

We performed a multivariable Cox proportional hazard regression of the RR6 model adjusting for disease-specific risk category at

baseline, which showed an HR of 3.50 (95% CI, 1.34-9.12; $P = .01$) and 5.92 (95% CI, 2.22-15.82; $P = .0004$), respectively, for intermediate- and high- vs low-risk patients. The AIC value (preferable models have lower AIC values) was 561.55, 524.62, and 481.34, respectively, for the baseline disease-specific risk score, for the dynamic RR6 model, and for the RR6 model when considering the baseline disease-specific risk score. This supports the performance of the new RR6 model, especially in conjunction with baseline data. The RR6 model was then applied to the validation cohort (n = 40 patients after applying the study selection criteria, patient characteristics summarized in supplemental Table 2), and its predictive ability was confirmed (log-rank test overall $P = .0276$).

Discussion

The global approval of RUX has modified the MF treatment scenario. A single-institution study reported an increase in RUX administration from 7.5% preapproval to 30.4% postapproval,[46] and a US-based real-world study from community oncology practices disclosed its frontline use in around 29% and 45% of intermediate- and high-risk MF patients, respectively.[47] The widespread use of RUX on the one hand and its significant discontinuation rates on the other underline the need for aptly-timed and effective second-line treatments. Maintaining RUX beyond exhaustion of activity is not the proper choice in MF, particularly since patients have a dismal outcome after late RUX cessation.[30-32]

The recent approval of fedratinib for patients with MF has started to fill this therapeutic gap.[48,49] In the JAKARTA-2 study exploring fedratinib, 55% of patients who failed RUX, based on investigator judgment, obtained a 35% spleen volume reduction by imaging at

week 24.[50] However, when more stringent criteria for resistance/intolerance to RUX were applied, this rate decreased to 30%.[51] As a consequence of the uncertainty surrounding the criteria to define an inadequate response to RUX, the timing of a switch to a second-line therapy is unclear. The response criteria identified by the IWG-MRT and ELN consortium are not directed specifically at RUX-treated patients.[52,53] To better select patients for clinical trial enrollment, experts provided definitions of RUX treatment failure (often encompassing disease progression) and suboptimal response, frequently through the identification of challenging clinical scenarios occurring during RUX therapy.[36,37,54,55] To date, a set of variables robustly identifying patients with inferior survival while on RUX is not available, and this truly remains an unmet medical need in the management of MF. Of further note, currently used clinical prognostic tools, such as the DIPSS in PMF and the MYSEC-PM in SMF, are not specifically geared toward RUX-treated MF patients.[1,5] In this respect, the RUXOREL-MF study clearly demonstrated that applying disease-specific risk scores (DIPSS for PMF or MYSEC-PM for SMF) at 6 months from RUX initiation is not entirely useful, failing to effectively dissect intermediate–2- from low/intermediate–1-risk patients. Molecular data can inform prognosis in RUX-treated individuals.[27,56] A study with NGS analysis applied to 95 patients with MF treated with RUX showed that patients with 3 or more mutations at baseline had a reduced likelihood of achieving a spleen response during therapy and were more likely to experience loss of response.[27] However, to date, NGS is used only in selected patients in routine clinical practice, mainly to direct transplant-related decisions.

While developing the RR6 model, the choice of the 6-month time point to perform our analysis was arbitrary, although based on clinical experience and current recommendations. It is nonetheless quite plausible that, given the availability of an effective second-line treatment, the early identification of inadequate responders to RUX may have prognostic value, considering that risk factors acquired over time, such as the occurrence of thrombocytopenia, clonal evolution, or blast phase transformation, negatively impact patient outcomes.[30-32] The RR6 model was built on the basis of a multivariable analysis that recognized the following risk factors negatively impacting OS: RUX treatment at a dose <20 mg twice daily at baseline, month 3, and month 6; palpable spleen length reduction ≤30% with respect to baseline at months 3 and 6; RBC transfusions requirement at month 3 and/or 6; and RBC transfusions requirement at all time points (ie, baseline and months 3 and 6). Higher RUX dose intensity (≥10 mg twice daily or even more so ≥20 mg twice daily), especially at early time points, has previously been associated with better spleen response rates.[26,29,57] In turn, greater spleen length reductions under RUX are possibly correlated with improved survival.[17,19,27] Concerning the last risk factor identified, whereas anemia developed under RUX doesn't seem to negatively impact prognosis, the need for RBC transfusions is a well-known factor impacting survival in MF.[44,45,58] Furthermore, transfusion dependency negatively correlates with the probability of obtaining a spleen response during RUX therapy and predicts drug discontinuation.[26,31] Overall, the median OS of patients within the RUXOREL-MF cohort was similar to that of patients treated within the COMFORT studies, which were limited to higher risk patients.[18] Importantly, our analysis excluded patients who died before the 6-month visit, thereby possibly balancing out the estimated median outcomes.

The comprehensive prognostic RR6 tool recognizes 3 prognostic groups (low, intermediate, and high risk) that are reasonably well balanced. The model identifies patients with a median OS calculated from 6 months after RUX start varying from not reached in the low risk to <3 years in the high-risk category. Given that within the RUXOREL-MF cohort approximately one-half of patients belonged to the lower disease-specific risk categories at RUX start, this estimated median survival beyond the 6-month time point is clinically significant. In practice, patients belonging to the low RR6 risk category and tolerating RUX can reasonably continue the drug for quite some time without the need for a treatment shift if the clinical picture remains unchanged. Conversely, recognizing patients with a high risk of mortality early during RUX treatment translates into the timely selection of candidates for second-line therapies, which should be ideally disease-modifying, either investigative or commercial, and/or for high-risk procedures such as SCT. Transplant is the only curative option for MF but, because of its high morbidity and mortality rates, the decision of whether to proceed to SCT is often postponed. The RR6 model can aid decision-making, recognizing patients with a high probability of fatality. Based on this model, treating physicians can propose SCT earlier, avoiding deferring the decision after RUX discontinuation due to exhausted activity, a setting associated with a limited likelihood of good outcome post-SCT.[59] Furthermore, given the prognostic relevance of dose intensity and spleen response on the one hand, and of avoiding RBC transfusion requirement on the other, the front-line use of add-on agents mitigating the risk of developing RBC transfusion necessity in the context of RUX-treated MF, such as the BET-inhibitor pelabresib,[60,61] may prove particularly beneficial. Of note, our data suggest that starting with a suboptimal dose of RUX (ie, lower than expected on the basis of the platelet count) frequently precludes the possibility of reaching the prognostically relevant dose of 20 mg twice daily at subsequent time points, thus indicating that optimal RUX dosing from the beginning, whenever clinically feasible, bears great prognostic relevance.

In conclusion, the RR6 model can be applied to MF patients after 6 months of RUX to identify those: (1) candidates for approved second-line treatments (eg, high- and selected intermediate-risk patients); (2) candidates for SCT (eg, high-risk patients in whom the transplant indication at RUX start was not clearcut); (3) in need of investigative second-line interventional trials because of limited survival (eg, high- and selected intermediate-risk patients). Clearly, the benefit of such a strategy will need to be demonstrated.

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Authorship

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