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Patterns Of Care And Outcomes Of Patients With Myelofibrosis: A Population-Based Study

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Patterns of Care and Outcomes of Older Patients with Myelofibrosis: A Population-based Study

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Abstract

Background: Current treatments for Myelofibrosis (MF) are largely palliative, with ruxolitinib being the breakthrough treatment approved for higher-risk patients by the Food and Drug Administration in November of 2011. Little is known about the "real-world" patterns of care and outcomes of MF patients since the introduction of ruxolitinib. **Patients and Methods:** The SEER-Medicare database was used to identify older patients diagnosed with MF from 2007 through 2015. Treatment patterns were assessed using Medicare part B and D claims, and multivariate cox proportional hazards regression models were used to assess the effect of ruxolitinib use on survival in MF patients. **Results:** A total of 773 patients were identified. The median age of our study population (N=773) was 76 years (IQR, 70, 80), and 88.9% of the population was non-Hispanic white. Of 342 patients who were diagnosed during 2012-2015 (i.e., the ruxolitinib era), 127 (37.1%) were ruxolitinib users. The median duration of ruxolitinib use was 16.21 months. Most ruxolitinib users started with doses of 5 (23.6%), 10 (27.0%), or 20 (23.6%) mg twice a day (BID). Among the patients who started treatment at 5 mg BID, 56.6% were never able to increase the dose above 5 BID. Only 3.1% were able to use the maximum dose of 25 mg BID. 54.3% of patients were taking hydroxyurea or prednisone during the same time period that they took ruxolitinib. Medications to manage anemia were used more commonly by MF patients diagnosed before 2012. Among patients diagnosed in 2012-2015, there was no difference in survival between ruxolitinib users and non-users. **Conclusion:** Older MF patients treated with ruxolitinib had similar survival when compared to patients who did not receive this medication but possibly belonged to the lower disease risk group. For many ruxolitinib users, the dose of ruxolitinib could not be escalated, additional medications were used concurrently, and the drug was discontinued quickly after initiation. Optimization of ruxolitinib use may be necessary to accomplish better outcomes. Furthermore, development of new drugs which may be used together with ruxolitinib or after its discontinuation is needed.

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Introduction

Myelofibrosis (MF) is a type of Philadelphia chromosome negative myeloproliferative neoplasm (MPN), characterized by bone marrow fibrosis, systemic and splenomegaly-related symptoms, cytopenias and abnormal extramedullary hematopoiesis (Barosi 1999, Cervantes *et al.* 2009). MF can be primary or secondary when it develops after Polycythemia Vera (PV) or Essential Thrombocythemia (ET). It is a rare disease with incidence of approximately 0.1 to 1 per 100,000 people per year (Moulard *et al.* 2014). The median age of diagnosis is approximately 67 years, and the median survival is 3 to 7 years (Mesa *et al.* 1999, Kvasnicka *et al.* 2000). Arterial and venous thrombosis, the common feature in MPNs, may occur among patients with MF with the rate of 0.95% to 1% patients per year (Guglielmelli *et al* 2020).

There are a variety of treatments used to manage MF, however, most of them fall into the category of supportive care. The only known disease-modifying treatment capable of curing MF is allogeneic hematopoietic stem cell transplantation (allo HSCT) which, due to its high morbidity and mortality, is reserved for younger patients who have higher-risk disease based on clinical and laboratory parameters including cytogenetic and molecular data (Tefferi 2016). Other treatments are used to control disease-related symptoms including hydroxyurea, prednisone and spleen-directed therapies such as splenectomy and splenic irradiation. Also, erythropoiesis-stimulating agents, androgens (e.g. danazol), and immunomodulatory IMID drugs (IMIDs, with or without steroids) are used to improve anemia (Tefferi 2016).

Since the early 2000s, discovery of driver mutations and an improved understanding of the molecular pathophysiology of MF have led to the development of new therapeutic approaches to this disease (Wadleigh and Tefferi 2010). In November 2011, the United States Food and Drug Administration

(FDA) approved an oral JAK-inhibitor, ruxolitinib, for treatment of MF patients who are considered intermediate- or high- risk based on the International Prognostic Scoring System (IPSS). This was based on the results of two phase 3 randomized studies which showed significant reduction of spleen size and improvement of symptoms among IPSS intermediate-2 and high-risk patients with MF when compared to placebo (Verstovsek *et al.* 2012) and to best available therapy (Harrison *et al.* 2012). Ruxolitinib was also shown in post-hoc analyses to improve overall survival (Mesa *et al.* 2014, Verstovsek 2012 and Verstovsek 2015).

One of the common toxicities of ruxolitinib is worsening of anemia, and management is not well defined in this setting. Some patients require short or long-term red blood cell transfusions and others utilize anemia-directed therapies similar to non-ruxolitinib treated patients without good evidence to support this approach (Barbui *et al.* 2018).

There are very limited data on the "real-world" clinical experiences and outcomes of patients with MF who are treated in the JAK inhibitor era (Mascarenhas *et al.* 2020). MF became reportable to population-based cancer registries such as the Surveillance, Epidemiology and End Results (SEER) program in 2001, making it possible to assess the incidence and survival of MF at the population level. Therefore, the objective of this study is to understand the "real-world" patterns of care and outcomes of older adults with MF since ruxolitinib became available for their management.

Methods

Data Source

The SEER-Medicare linked database, developed by the National Cancer Institute (NCI) and the Centers for Medicare and Medicaid Services, links patient-level information from the SEER records with

Medicare enrollment and claims data. The SEER database contains 17 SEER regions, collects data on survival and demographic information and covers approximately 34% of the United States population (NCI 2019). The Medicare database includes data for inpatient, outpatient, physician services and prescription drugs (Warren *et al.* 2002). Since the median age of MF diagnosis is 67 years old, the SEER-Medicare database is a good data source to analyze the outcomes and treatment patterns of older MF patients (Mesa *et al.* 1999). The most recent SEER-Medicare database includes MF patients diagnosed between 2001 and 2015, with Medicare claims through the end of 2016. The Yale Human Investigation Committee determined that this study did not directly involve human subjects.

Study Population

Since we needed to access Medicare Part D claims for the use of oral prescription drugs and Part D was not available until 2006, we assembled a retrospective cohort of patients diagnosed with incident MF (International Classification of Diseases for Oncology, Third Edition codes: 9961) between 2007 and 2015. All patients fulfilled the following eligibility criteria: 1) aged 66-99 years at diagnosis; 2) had known month of diagnosis; 3) were not identified from death certificate or autopsy only; 4) had continuous enrollment in Medicare Part D from diagnosis 5) had continuous enrollment in Medicare Parts A, B and no enrollment in health maintenance organizations from 1 year before diagnosis until the end of follow-up (death or 12/31/2016, whichever came first); and 6) bone marrow biopsy claim from 1 year before diagnosis to end of follow up.

Treatment Assessment

Prescription drug use was identified from the Medicare Part B and D claims using clinical modification procedure codes (ICD-9 and ICD-10), the Healthcare Common Procedure Coding System (HCPCS)

codes, and brand or generic name for oral drugs from Medicare claims. Prescription drug users were defined as any patient that used the drug between the date of diagnosis and end of follow up. Allo HSCT, splenectomy and splenic irradiation were assessed using ICD-9, ICD-10 and HCPCS codes. Anemia drugs included: Darbepoeitin, Epogen, androgens [testosterone and danazol] and IMIDs [lenalidomide and thalidomide].

The daily dose of ruxolitinib at initiation was assessed by using the patient's first ruxolitinib prescription via the formula [daily dose = (dose strength (mg)*quantity dispensed)/ number of days supplied]. We calculated the end date of last dispense as dispense date plus number of days supplied, if the end date exceeded the end of follow-up, we censored at the date of end of follow-up. Duration of ruxolitinib was calculated as the difference between the first prescription date and end date of last dispense. We restricted calculation of duration among patients with more than one ruxolitinib prescription. To understand the use of concurrent drugs with ruxolitinib, we also assessed patients' prescriptions on prednisone and hydroxyurea within 1 month after ruxolitinib initiation and 1 month before discontinuation of ruxolitinib, which was designated as the patient's last prescription.

Outcome and Variable Assessment

Our primary outcome of interest was overall survival (OS). Patients were followed from the date of their diagnosis until death or the end of the study period (December 31st, 2016), whichever came first.

We obtained information on the following patient characteristics: age at diagnosis, sex, race/ethnicity, marital status, comorbidities, SEER region (West, South, Midwest, or Northeast) and census tract median household income. To assess comorbidities, we used ICD-9 and ICD-10 diagnosis codes within 1 year prior to MF diagnosis in inpatient claims or at least 2 outpatient claims, 30 days apart. A modified

Elixhauser score was developed previously by our research group by removing prior thrombosis from the original Elixhauser score (Wang *et al.* 2017).

Statistical Analysis

Categorical variables were presented using frequencies and percentages. Continuous variables were summarized by median and interquartile range (IQR). F-test for continuous variables and χ^2 test for categorical variables was used to compare treatment groups. Consistent with the SEER-Medicare requirement to preserve confidentiality, all categories with $\leq$ 10 patients were reported as <11. Kaplan-Meier curves and log-rank tests were used to compare the incidence of death between treatment groups. Multivariable Cox proportional hazards regression models with time dependent variables were used to identify potential predictors of survival. A ruxolitinib user would only be considered as a user after the initiation. Aside from treatments, we considered the possible influence of several patient characteristics on OS, including age of diagnosis, sex, race/ethnicity, marital status, and comorbidities. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, North Carolina) with two-sided tests and a type I error of 0.05 as the threshold for statistical significance.

Results

Study Population and Baseline Characteristics

We identified a total of 773 patients who fulfilled the eligibility criteria. The median age at diagnosis was 75 years (IQR, 70-80 years), 88.9% were non-Hispanic white, 55.1% were male, and 55.8% (N= 431) were diagnosed before 2012.

Since ruxolitinib was approved to treat MF in November 2011, we further categorized our study population into two groups: early era (diagnosed during 2007- 2011) and late era (diagnosed during 2012-2015). Patients diagnosed in the two eras were similar with respect to all characteristics except for death at the end of the study period ($p<0.001$), comorbidities ($p<0.001$), SEER region ($p=0.03$) and median household income ($p<0.001$) (Table 1).

The 342 patients who were diagnosed in the later era were further categorized into two groups based on ruxolitinib use. A total of 127 (37.1%) patients ever used ruxolitinib after diagnosis. As shown in Table 2, there was no difference among any evaluated characteristics.

Treatment Patterns and Outcomes

To compare the pattern of treatment between the two eras, we censored the patients diagnosed in the early era at the end of 2011. More patients diagnosed in the later era used hydroxyurea (39.2%) than those diagnosed earlier (26.7%). However, more patients diagnosed in the early era used anemia-directed therapies (34.3% vs. 19.9%) and prednisone (36.2% vs. 30.1%) compared to those diagnosed later (Figure 1).

Only a limited number (<11) of ruxolitinib users and non-users received splenic irradiation. There were 27 patients (7.9%) in the ruxolitinib era group who were 70 or younger at the time of MF diagnosis, and out of these 27, less than 11 patients received allo HSCT.

The median time to initiation of ruxolitinib after MF diagnosis was 107 days (IQR, 47, 341.7 days, N=127), and the majority of patients started at daily doses of 10, 20 or 40 milligrams (mg), which is 5, 10 and 20 mg per time twice a day (BID) (Figure 2). Of the 30 patients who started at 5 mg BID, 17 (56.7%) never had their dose of ruxolitinib escalated above 5 mg BID. Also, less than 11 patients were

able to go up to the highest dose of 25 mg BID. The median amount of time patients stayed on ruxolitinib was 16.21 months (Figure 3). While on ruxolitinib treatment, 28 (22%) and 17 (13%) also took hydroxyurea and prednisone, respectively. In addition, 12 (10%) ruxolitinib treated patients took both hydroxyurea and prednisone during the same time period (Figure 4).

Ruxolitinib users had similar survival to non-user survival, with a median survival of 2.93 years in the ruxolitinib treatment group and a median survival of 2.59 years in the non-ruxolitinib treatment group (Figure 5). The percent of patients that died in each group was also similar: 48.84% died in the non-ruxolitinib treatment group and 52% died in the ruxolitinib treatment group. In the multivariable analysis, the risk of death among ruxolitinib users compared to non-users was not statistically significant (p=0.33, Figure 5).

Discussion

In this retrospective population-based study that reflects real-world clinical practice, we assessed the management of older patients diagnosed with MF in the real-world setting with a focus on the impact of ruxolitinib, which was approved by the FDA in November 2011. Among patients diagnosed in 2012-15, 127 (37.1%) patients received ruxolitinib, with a median of 107 days to treatment initiation, and a median duration of use of 16.21 months. About half of ruxolitinib users initiated treatment at low doses (up to 10 mg BID). Although we did not observe any difference in survival between ruxolitinib users and non-users, taking into consideration that ruxolitinib has been approved for higher risk MF patients, our findings may imply that ruxolitinib could have had a positive effect on the outcomes of the treated population.

We found that lower initiation doses were common among older MF patients. Over half of ruxolitinib users started at 5 or 10 mg BID, and only about 23% started at 20 mg BID, which is a maximal initiating dose based on FDA approved drug prescription information (FDA 2019). The recommended dose at the time of treatment initiation is based on patient's platelet count: 20 mg, 15 mg and 5 mg BID for those with platelets >200,000/mm^3, 100,000 to 200,000/mm^3, and 50,000 to <100,000/mm^3, respectively (FDA 2019). A dose of 5 mg BID is less effective than higher doses to accomplish symptom control and decrease spleen size (Talpaz *et al.* 2013). However, 13.4% of ruxolitinib users in our study were never prescribed a dose above 5 mg BID. This could be related to low platelet counts or concerns about side effects, including anemia. Less than 11 (3.1%) patients were able to escalate their dosing to the highest recommended dose of 25 mg BID, which should be considered if treatment results with lower doses are unsatisfactory and if the patient is expected to tolerate dose escalation.

Many patients received both ruxolitinib and other symptom-directed therapies (including hydroxyurea and/or steroids) at the same time, pointing to less than acceptable symptom control by ruxolitinib alone. This could be related to lower doses of ruxolitinib being used by our patients. It is interesting that more patients diagnosed after 2011 used hydroxyurea more than patients managed in the pre ruxolitinib era. A more focused approach by providers to symptom control in ruxolitinib era can explain the wider use of symptom-directed therapies. Even though ruxolitinib was added to management and hydroxyurea use increased, anemia-directed drug therapies, expected to have higher demand in the setting of these cytoreductive treatments, were used less frequently after 2011. This may be related to lack of evidence behind concurrent use of these drugs with ruxolitinib, which is antagonistic to erythropoietin analogues based on its mechanism of action.

As expected, very few patients in our cohort (N<11, 1.5%) received spleen-directed therapies before and after introduction of ruxolitnib. Splenectomy is associated with high morbidity, including liver

enlargement and failure, thrombocytosis, thrombosis, intrabdominal infection and increased rate of blast transformation as well as 30% perioperative morbidity and 10% mortality. Splenic irradiation is associated with long-lasting cytopenias and transfusion dependence (Tefferi *et al.* 2000). The number of cases receiving spleen-directed therapies is expected to decrease in the era of ruxolitinib due to its successful ability to decrease spleen size, but we could not perform this analysis due to low frequency of the above described procedures.

Even though allo HSCT is the only disease modifying treatment for MF, very few patients received transplant in our study. Only 27 among 342 patients (7.9%) were transplanted. The average age of our patient population was 76 years, which may explain infrequent allo HSCT use, as it is usually reserved for younger ($\leq$70 years old) patients due to high procedure-related morbidity and mortality which increases with age. Allo HSCT was not reimbursed by Medicare for MF patients until 2016, which may be another reason for low prevalence of this treatment in our patient population.

Our study has several strengths. Its population-based design allowed us to evaluate real-world treatment of older patients with MF and helped to assemble a large cohort of patients with this rare disease. Limitations include short observation period as follow up duration could not exceed 5 years due to ruxolitinib only being approved for MF patients since 2011. We also used Medicare claims to identify treatments and procedures received by our patients. Therefore, any drugs or procedures not covered by Medicare could not be factored into our analyses. As clinical and laboratory variables necessary to estimate patients' risk based on prognostic models utilized in clinical practice (IPSS) were not available, we could not factor these risks into multivariable survival analysis. Also, the age of our population is about 10 years older than the average age of MF patients at diagnosis which may lead to different

outcomes among our patients when compared to the general population with this disease. Finally, patterns of care might have been affected by a variety of unknown confounders.

Conclusion

This large population-based study of older patients with MF assessed their pattern of care in the ruxolitinib era and showed similar survival of ruxolitinib users to non-users who are expected to have lower risk disease. Ruxolitinib dose was not escalated above the lowest dose and to the highest permitted dose in a large number of patients and treatment was discontinued quickly after initiation. Optimization of ruxolitinib use may be necessary to accomplish better outcomes. Furthermore, development of new drugs, which may be used with ruxolitinib or after its discontinuation, is needed.

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Appendix

Table 1. Characteristics of 773 older adults with MF, 2007-2015

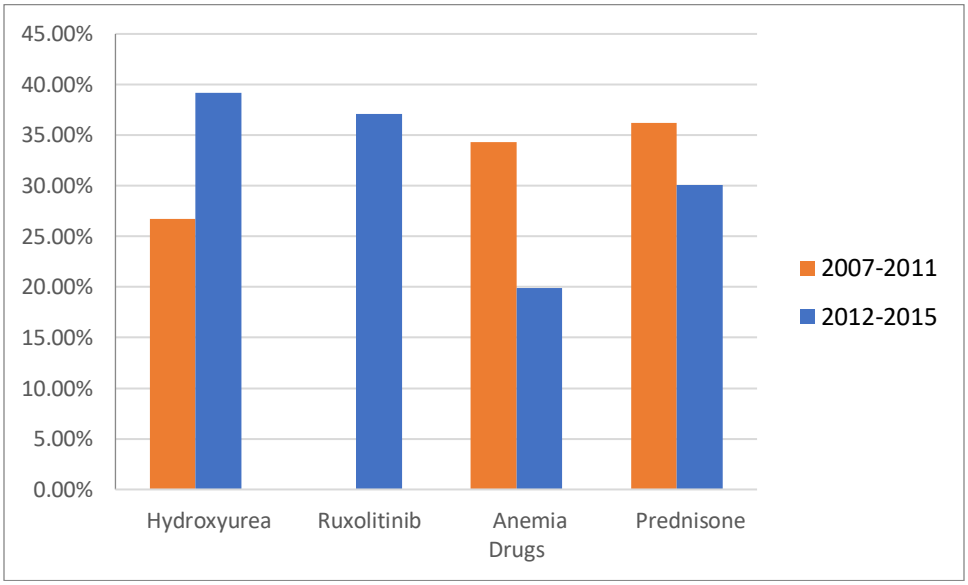
Characteristic	Overall		Year of diagnosis		
			2007-2011	2012-2015	p†
	N (%)		N (%)	N (%)	
Total	773		431	342	
Race/ethnicity					0.20
Non-Hispanic white	687(88.9)		383(88.9)	304(88.9)	
Other	86(11.1)		48(11.1)	38(11.1)	
Age at diagnosis (years)					0.31
Median (IQR)	76(70-80)		76(71-80)	75(70-80)	
Sex					0.46
Male	425(55.0)		232(53.8)	193(56.4)	
Female	348(45.0)		199(46.2)	149(43.6)	
Marital status					0.33
Married	417(53.9)		233(54.1)	184(53.8)	
Unmarried	258(33.4)		154(35.7)	104(30.4)	
Unknown	98(12.7)		44(10.2)	54(15.8)	
Death at End of Study Period					<0.001
Yes	496(64.2)		330(23.4)	166(48.5)	
No	277(35.8)		101(76.6)	176(51.5)	
Comorbidities					<0.001
0	211(27.3)		118(28.6)	93(27.2)	
1-2	306(39.6)		175(40.6)	131(38.3)	
3+	256(33.1)		138(32.0)	118(34.5)	
SEER Region					0.03
West	331(42.8)		181(42.0)	150(43.9)	
South	149(19.3)		81(18.8)	68(19.9)	
Midwest	133(17.2)		89(20.7)	44(12.9)	
Northeast	160(20.7)		80(18.7)	80(23.4)	
Census tract median household income					
<33,000	138(17.9)		118(27.4)	20(5.9)	<0.001
33,000-40,000	56(7.2)		29(6.7)	27(7.9)	
40,000-50,000	123(15.9)		71(16.5)	52(15.2)	
>50,000	456(59.0)		213(49.4)	243(71.1)	

* Numbers may not sum to totals due to missing data, and column percentages may not sum to 100% due to rounding.
† P-value for analysis of variance F-test (continuous variable) or χ^2 test (categorical variable).

Table 2. Characteristics of 342 older adults with MF by ruxolitinib status, 2012-2015

	Ruxolitinib		**p**[†]
	Ever	**Never**	
Characteristic	**N (%)**	**N (%)**	
Total	**127**	**215**	
Race/ethnicity			0.50
Non-Hispanic white	114(89.8)	190(88.4)	
Other	10(10.2)	25(11.6)	
Age at diagnosis (years)			0.44
Median (IQR)	75(70-80)	75(70-80)	
Sex			0.33
Male	76(59.8)	117(54.4)	
Female	51(40.2)	98(45.6)	
Marital status			0.79
Married	69(54.3)	115(53.5)	
Not married	38(29.9)	66(30.7)	
Unknown	20(15.7)	34(15.8)	
Death at End of Study Period			0.89
Yes	66(52.0)	105(51.2)	
No	61(48.0)	110(48.8)	
Comorbidities			0.93
0	36(28.3)	57(26.5)	
1-2	48(37.8)	83(38.6)	
≥ 3	43(33.9)	75(34.9)	
SEER Region			0.67
West	58(45.7)	92(42.8)	
South	23(18.1)	45(20.9)	
Midwest	19(15.0)	25(11.6)	
Northeast	27(21.3)	53(24.7)	
Census tract median household income			0.45
<33,000	5(3.94)	15(7.0)	
33,000-40,000	11(8.66)	16(7.4)	
40,000-50,000	23(18.1)	29(13.5)	
>50,000	88(69.3)	155(72.1)	

* Numbers may not sum to totals due to missing data, and column percentages may not sum to 100% due to rounding.
[†] P-value for analysis of variance F-test (continuous variable) or χ^2 test (categorical variable).



*Censored patients after 2011 for patients diagnosed before 2012

Figure 1. MF related treatments among 773 older adults by era of diagnosis, 2007-2015

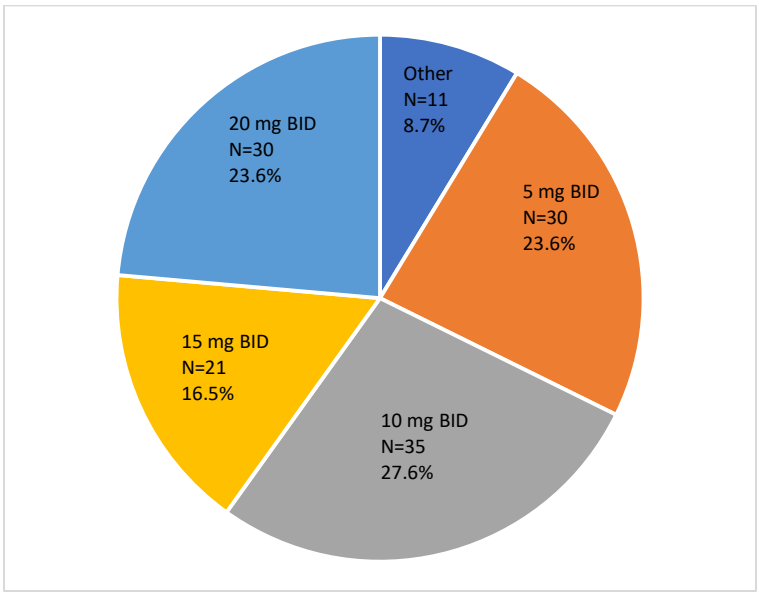


Figure 2. Daily ruxolitinib dose (BID) at treatment initiation (N=127)

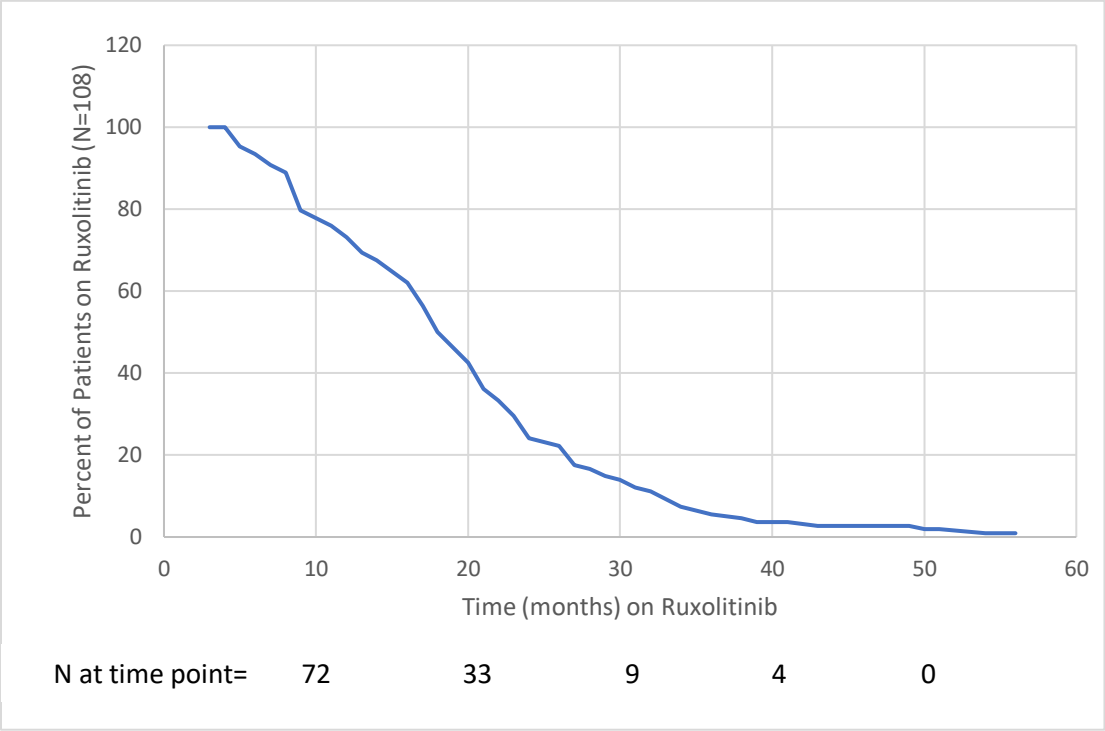


Figure 3. Duration of ruxolitinib treatment among 108 older adults with MF, 2012-2015

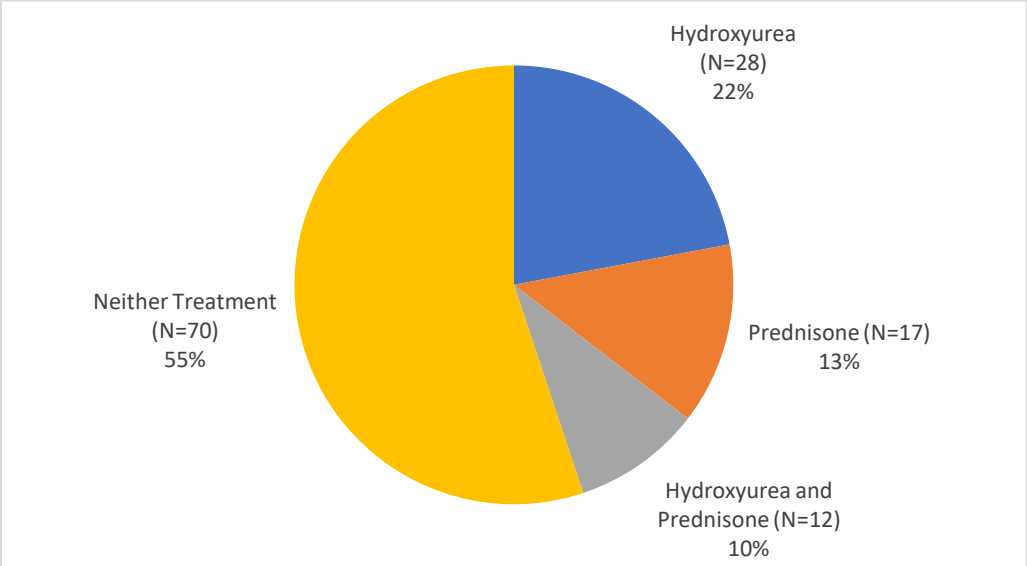
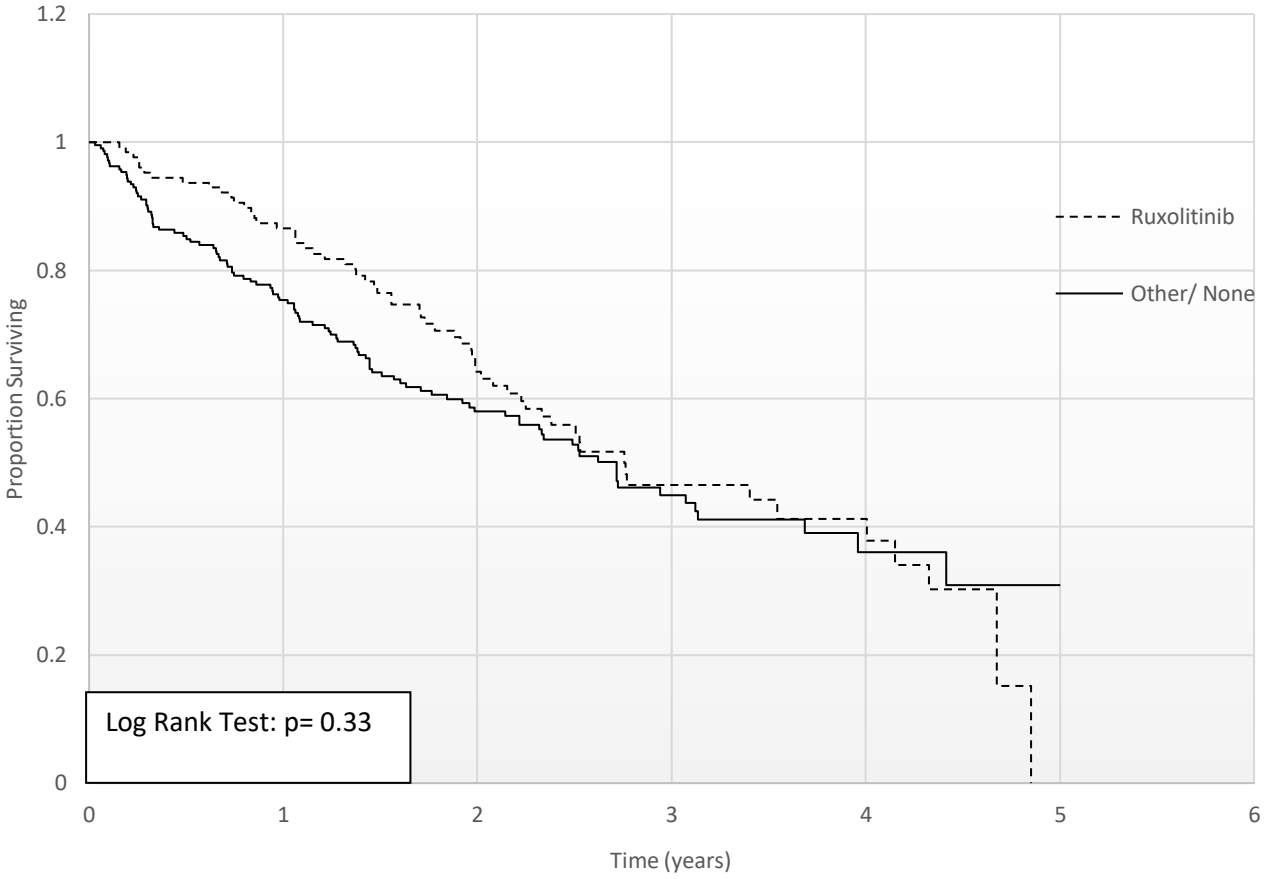


Figure 4. Most commonly used concurrent drugs received by ruxolitinib treated patients (N=127; treatments within one month after ruxolitinib initiation and one month before discontinuation)



N at risk at time point					
Time (years)	*1*	*2*	*3*	*4*	*5*
Total	265	147	59	24	0
Other/None	156	89	37	12	0
Ruxolitinib	109	58	22	12	0

Treatment Group	Total N	Died N (%)	Median Survival	Unadjusted HR	Adjusted HR
Other/None	215	105(48.84)	2.59 yrs.	1	1
Ruxolitinib	127	66(52.00)	2.93 yrs.	0.86(0.62,1.17)	0.86(0.61,1.22)

* Adjusted for age, marital status, gender, comorbidities and race

Figure 5. Kaplan-Meier curves of survival among 342 older adults with MF by ruxolitinib status, 2012-2015