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Retrospective Analysis of Efficacy and Safety Outcomes in Patients with Primary and Secondary Myelofibrosis Treated with Ruxolitinib: JUMP Study

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INTRODUCTION

- Ruxolitinib, a JAK inhibitor, has been shown to provide spleen, symptom and overall survival benefits in patients with MF[1–5] and is approved for MF, including PMF, post-ET MF and post-PV-MF[6,7]
- Evidence from real-world data indicates that patients with SMF are less frequently treated with JAK inhibitors such as ruxolitinib in clinical practice (data not published), despite being a standard of care treatment for MF
- The phase IIIb, single arm, open-label JUMP study (NCT01493414) assessed the safety and efficacy of ruxolitinib in patients with symptomatic MF without access to ruxolitinib outside of a clinical trial setting[8]

Objective

- To compare efficacy and safety of ruxolitinib in patients diagnosed with PMF and SMF, differentiating also between two types of SMF: post-ET and post PV

METHODS

- This study was a post hoc subgroup analysis of 2232 patients treated with ruxolitinib in the JUMP study; 1326 had a PMF diagnosis, 532 a post-PV diagnosis, and 374 a post-ET diagnosis
- Outcomes included spleen length response, PFS, LFS, OS, patient-reported outcomes (FACIT-fatigue score) and incidence of AEs

Definitions

- Spleen length response was defined as a ≥50% reduction from baseline in spleen length at any post-baseline visit
- Spleen best response was defined as the largest percentage reduction from baseline in spleen length achieved at any time
- FACIT-fatigue score response was defined as ≥3 point increase from baseline at any visit

Analyses

- Spleen length response and spleen best response were compared across diagnoses by logistic and linear regression, respectively, of the response variable against diagnosis, adjusting for confounders
- FACIT-fatigue score response was compared across diagnoses using logistic regression of the response variable against diagnosis, adjusting for confounders
- PFS, LFS and OS were compared across diagnoses using a Cox proportional hazards regression analysis adjusting for confounders
- Due to the post-hoc nature of this analysis, nominal p values are provided only for hypothesis generation purposes
- Confounders included age, gender, Hb, baseline blast cells and baseline WBC and prior use of MF medications as well as baseline spleen length only for spleen-related analysis, and baseline FACIT-fatigue score only for FACIT-related analysis
  - Patients with missing values in any of the confounder variables were excluded from the analysis
- Models were repeated for PMF vs SMF diagnosis and further differentiating by SMF type
- Incidences of AEs were descriptively analyzed

RESULTS

Patient characteristics

- A comparison of baseline characteristics is shown in **Table 1**. For the PMF vs SMF group:
  - The mean age was 66.1 vs 65.0 years
  - Proportions of female patients (40.6% vs 51.8%) as well as baseline levels of Hb, platelets and WBCs were lower
  - Mean time between MF diagnosis and treatment start was longer (54.9 vs 47.2 months) [data not shown]

Table 1. Comparison of baseline patient characteristics

	PMF (N=1326)	SMF (N=906)	Post-ET MF (N=374)	Post-PV MF (N=532)
Age, mean ± SD,	66.1 ± 10.6	65.0 ± 10.1	65.1 ± 11.0	64.9 ± 9.5
IQR	60.0–74.0	59.0–72.0	59.0–73.0	60.0–72.0
N	1295	906	373	529
Gender, N	1302	897	370	527
Female, n (%)	529 (40.6)	465 (51.8)	205 (55.4)	260 (49.3)
Male, n (%)	773 (59.4)	432 (48.2)	165 (44.6)	267 (50.7)
Hb (g/L), mean ± SD	105.9 ± 21.9	114.2 ± 23.4	107.1 ± 20.9	119.1 ± 23.8
IQR	91.0–119.0	95.8–131.0	91.5–120.0	100.0–136.0
N	1325	900	371	529
Platelets (x10^9/L), mean ± SD	298.1 ± 224.4	349.8 ± 255.2	392.5 ± 281.7	319.7 ± 230.4
IQR	147.0–376.0	173.0–446.5	199.5–498.5	153.8–406.0
N	1325	899	371	528
WBCs (x10^9/L), mean ± SD	15.7 ± 16.1	17.6 ± 16.0	14.8 ± 14.8	19.5 ± 16.5
IQR	6.2–19.2	7.7–21.3	6.4–18.0	9.2–24.2
N	1324	898	371	527
Blast Cells (%), mean ± SD	1.0 ± 2.1	1.1 ± 2.0	1.4 ± 2.2	0.9 ± 1.8
IQR	0.0–1.0	0.0–2.0	0.0–2.0	0.0–1.0
N	1205	819	338	481
Spleen Length (cm) by palpation, mean ± SD	12.6 ± 7.2	12.9 ± 7.1	11.1 ± 6.8	14.1 ± 7.0
IQR	7.0–18.0	8.0–18.0	6.0–15.0	8.8–19.0
N	1295	882	362	520
Number of prior MF medications, N	1327	910	376	534
0, n (%)	481 (36.3)	248 (27.3)	114 (30.3)	134 (25.1)
1, n (%)	846 (63.8)	662 (72.8)	262 (69.7)	400 (74.9)

Spleen length response

- Similar outcomes for ruxolitinib effect on spleen length reduction across MF diagnoses were observed (**Table 2**)
  - Patients with SMF, and patients with post-ET and post-PV were as likely to have a spleen length response as patients with PMF
  - Patients with SMF, and patients with post-ET and post-PV best spleen responses were not different from patients with primary MF

FACIT-fatigue response score

- Mean FACIT-fatigue scores were similar between diagnosis at baseline and week 48 (**Table 3**)
- Mean improvement in FACIT-fatigue scores from baseline to Week 48 was comparable between PMF and SMF; however, it was slightly lower for post-ET when differentiating by SMF type (**Table 3**)
- A similar outcome for ruxolitinib effect was observed for FACIT-fatigue response across MF diagnoses (**Table 3**)
  - Patients with SMF, and patients with post-ET and post PV, were as likely to respond as patients with primary MF

Table 2. Comparison of spleen response across diagnoses

	Spleen length responders (%)	Comparison vs PMF Odds ratio (95% CI), p value
PMF (N=1066)	71.4	-
SMF (N=738)	74.5	1.1 (0.83–1.3), 0.48
Post-ET MF (N=292)	75.7	1.2 (0.78–1.5), 0.38
Post-PV MF (N=446)	73.8	1.0 (0.75–1.3), 0.76
	Spleen length best response (median)	**Least Square Means from Linear Regression model**
PMF (N=1066)	-75.0	-
SMF (N=738)	-76.9	-0.33 (-3.1–2.4), 0.82
Post-ET MF (N=292)	-80.0	-0.95 (-4.7–2.8), 0.62
Post-PV MF (N=446)	-75.6	0.11 (-3.2–3.4), 0.95

Patients with a palpable spleen at baseline and at least one post-baseline spleen assessment were eligible for this analysis.

Table 3. Comparison of FACIT-fatigue mean score across diagnoses

	Mean FACIT-fatigue score		FACIT-fatigue score mean (SD) improvement from baseline to Week 48	Comparison vs PMF Odds ratio (95% CI), p value
	Baseline	Week 48		
PMF (N=1063)	33.0 (11.8)	36.9 (10.3)	25.1 (88.7)	-
SMF (N=716)	32.3 (11.8)	37.3 (10.2)	22.2 (58.5)	1.18 (0.95–1.48), 0.14
Post-ET MF (N=292)	31.8 (11.7)	36.3 (10.0)	18.7 (56.8)	1.14 (0.84–1.54), 0.39
Post-PV MF (N=424)	32.6 (11.8)	38.0 (10.2)	24.5 (59.6)	1.22 (0.93–1.60), 0.15

For FACIT-fatigue, a score of 0–52 is reported. A score of 52 represents no fatigue. FACIT-fatigue score at baseline must have been below 52 to be eligible for this analysis.

Survival outcomes

- Similar outcomes for the effect of ruxolitinib across diagnoses were observed in time-to-event survival outcomes (PFS, LFS and OS) (**Table 4**)

Table 4. Comparison of survival outcomes across diagnoses

Survival outcome	Events, n (%)	Censored, n (%)	Hazard ratio (95% CI), p value
PFS			
PMF (N=1326)	227 (17.1)	1099 (82.9)	-
SMF (N=906)	127 (14.0)	779 (86.0)	1.00 (0.95–1.05), 0.85
Post-ET MF (N=374)	56 (15.0)	318 (85.0)	1.02 (0.97–1.07), 0.54
Post-PV MF (N=532)	71 (13.3)	461 (86.7)	0.98 (0.93–1.03), 0.47
LFS			
PMF (N=1326)	181 (13.7)	1145 (86.3)	-
SMF (N=906)	99 (10.9)	807 (89.1)	1.00 (0.96–1.05), 0.95
Post-ET MF (N=374)	41 (11.0)	333 (89.0)	1.02 (0.97–1.07), 0.51
Post-PV MF (N=532)	58 (10.9)	474 (89.1)	0.99 (0.94–1.04), 0.69
OS			
PMF (N=1326)	158 (11.9)	1168 (88.1)	-
SMF (N=906)	84 (9.3)	822 (90.7)	1.01 (0.96–1.06), 0.78
Post-ET MF (N=374)	35 (9.4)	339 (90.6)	1.02 (0.97–1.07), 0.42
Post-PV MF (N=532)	49(9.2)	483 (90.8)	1.00 (0.95–1.04), 0.83

Median survival times were not reached for any event.
PFS was defined as the time from first study drug administration to the date of documented progression (based on International Working Group for Myelofibrosis Research and Treatment Response Criteria) or death.
LFS was defined as the duration from first study drug administration to the date of documented leukemia.
OS was defined as the duration from first dose of study drug administration to the date of death due to any cause.

AEs

- An overview of AE incidence is presented in **Table 5**
- Compared to PMF:
  - A >5% higher incidence of any grade asthenia was observed in patients with post-ET (**Table 5**)
  - A >5% lower incidence of Grade 3/4 anemia was observed in patients with SMF and post-PV (**Table 5**)

Table 5. Overview of AE incidence and comparison of AEs (≥10%) across diagnoses

AE incidence, n (%)	PMF All grades (N=1326)	PMF Grades 3/4 (N=1326)	SMF All grades (N=906)	SMF Grades 3/4 (N=906)	Post-ET MF All grades (N=374)	Post-ET MF Grades 3/4 (N=374)	Post-PV MF All grades (N=532)	Post-PV MF Grades 3/4 (N=532)
All	**1274 (100.0)**	**913 (100.0)**	**884 (100.0)**	**558 (100.0)**	**367 (100.0)**	**246 (100.0)**	**517 (100.0)**	**312 (100.0)**
Drug-related*	1059 (83.12)	612 (67.03)	710 (80.32)	335 (60.04)	287 (78.20)	154 (62.6)	423 (81.82)	181 (58.01)
Serious	518 (40.66)	448 (49.07)	325 (36.76)	270 (48.39)	141 (38.42)	125 (50.81)	184 (35.59)	145 (46.47)
Drug-related*	126 (9.89)	107 (11.72)	73 (8.26)	61 (10.93)	29 (7.90)	28 (11.38)	44 (8.51)	33 (10.58)
Leading to discontinuation	268 (21.04)	211 (23.11)	146 (16.52)	102 (18.28)	69 (18.80)	52 (21.14)	77 (14.89)	50 (16.03)
Drug-related*	139 (10.91)	104 (11.39)	78 (8.82)	50 (8.96)	32 (8.72)	22 (8.94)	46 (8.90)	28 (8.97)
Requiring dose adjustment or interruption	831 (65.23)	424 (46.44)	577 (65.27)	253 (45.34)	229 (62.40)	113 (45.93)	348 (67.31)	140 (44.87)
Drug-related*	721 (56.59)	333 (36.47)	500 (56.56)	177 (31.72)	191 (52.04)	80 (32.52)	309 (59.77)	97 (31.09)
Requiring concomitant medication and non-drug therapies	277 (21.74)	209 (22.89)	159 (17.99)	103 (18.46)	72 (19.62)	53 (21.54)	87 (16.83)	50 (16.03)
Drug-related*	117 (9.18)	92 (10.08)	78 (8.82)	53 (9.50)	38 (10.35)	29 (11.79)	40 (7.74)	24 (7.69)
AEs (≥10%) by preferred term, n (%)								
Anemia	799 (62.72)	509 (55.75)	555 (62.78)	280 (50.18)	247 (67.30)	149 (60.57)	308 (59.57)	131 (41.99)
Thrombocytopenia	597 (46.86)	235 (25.74)	402 (45.48)	141 (25.27)	160 (43.60)	56 (22.76)	242 (46.81)	85 (27.24)
Pyrexia	214 (16.8)	30 (3.29)	153 (17.31)	25 (4.48)	70 (19.07)	14 (5.69)	83 (16.05)	11 (3.53)
Asthenia	189 (14.84)	24 (2.63)	165 (18.67)	26 (4.66)	73 (19.89)	12 (4.88)	92 (17.79)	14 (4.49)
Diarrhea	184 (14.44)	19 (2.08)	105 (11.88)	7 (1.25)	35 (9.54)	NR	70 (13.54)	7 (2.24)
Fatigue	148 (11.62)	14 (1.53)	91 (10.29)	13 (2.33)	38 (10.35)	4 (1.63)	53 (10.25)	9 (2.88)

*Suspected. AEs were coded using MedDRA version 26.1.

KEY FINDINGS & CONCLUSIONS

- Ruxolitinib shows comparable effects for spleen length response, FACIT-fatigue response, PFS, LFS, OS and safety in patients diagnosed with PMF, and SMF
- The findings support that, as for PMF, ruxolitinib is a viable treatment option for SMF regardless of SMF type

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Abbreviations

AE, adverse event; CI, confidence interval; ET, essential thrombocythemia; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; IQR, interquartile range; JAK, Janus Kinase; LFS, leukemia-free survival; MedDRA, Medical Dictionary for Regulatory Activities; MF, myelofibrosis; NE, not estimable; NR, not recorded; OS, overall survival; PFS, progression-free survival; PMF, primary myelofibrosis; PV, polycythemia vera; SD, standard deviation; SMF, secondary myelofibrosis; WBC, white blood cell.

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