An International Multicentric Observational Study on the Use of Ruxolitinib in Patients With Polycythemia Vera Resistant or Intolerant to Hydroxyurea: Results From Interim Analysis

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Introduction

- **Polycythemia vera (PV)**, the most common myeloproliferative neoplasm, is a result of mutations predominantly in the JAK2 gene and is characterized by erythrocytosis, thrombocytosis, and splenomegaly[1]
- PV patients have a higher risk of thrombotic and hemorrhagic complications and, in the long term, disease transformation to myelofibrosis and acute leukemia[1-3]
- The main objective of PV therapy is to maintain the hematocrit (HCT) <45% with hydroxyurea (HU) being the most common drug employed in first-line treatment. Patients developing resistance/intolerance to HU are at higher risk of thrombosis due to inadequate HCT control
- Ruxolitinib (RUX) was approved for the treatment of PV patients after development of resistance/intolerance to HU

Here, we present the interim analysis of 150 patients included in an ongoing phase IV, international multicentric non-interventional study who were treated with RUX for at least 52 weeks and with a follow-up of 24 months after treatment initiation

JAK, Janus kinase; HCT, hematocrit; HU, hydroxyurea; PV, polycythemia vera; RUX, ruxolitinib

1. Spivak JL. *N Engl J Med*. 2017;376:2168-2181; 2. Marchioli, et al. *J Clin Oncol.* 2005 Apr 1;23(10):2224-2232; 3. Griesshammer, et al. *Ann Hematol.* 2015 Jun;94(6):901-910;

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Methods

Current analysis

150 adult patients with PV (aged ≥18 years)

Treated with RUX for **52 weeks**[a]

Resistant and/or intolerant to HU (as per ELN criteria[1])

Objectives

- **Primary:** Describe the profile and disease burden (including symptom and HRQoL assessment) of PV patients with HU resistance and/or intolerance who were treated with RUX according to the approved local label in Europe
- **Secondary:** To evaluate the safety, efficacy, and impact of RUX (HCT, phlebotomy) in PV patients who are resistant and/or intolerant to HU

Inclusion criteria

- Patients who initiated RUX treatment ≤6 months before obtaining informed consent
- Treatment was not started for the purpose of including patient in the study
- Patients from Switzerland who were resistant and/or intolerant to other cytoreductive first-line therapy
- Informed consent was obtained from all patients

Exclusion criteria

- Hypersensitivity to active substance or any of the excipients listed in the approved label
- Pregnancy, lactation, and women of childbearing potential who were not on effective contraception during the treatment period

[a]Recommended starting dose of 10 mg was administered orally twice daily per the approved label

ELN, European LeukemiaNet; HCT, hematocrit; HRQoL, health-related quality of life; HU, hydroxyurea; MPN-SAF TSS, myeloproliferative neoplasm symptom assessment form total symptom score; PSIS, pruritus symptom impact scale; PV, polycythemia vera; RUX, ruxolitinib

1. Barosi G, et al. *Br J Haematol.* 2010;148(6):961-963.

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Baseline characteristics and demographic data

Characteristic	RUX (N=150)
Age (years), mean (min-max)	**65.6 (38-87)**
Age >60 years, n (%)	101 (67.3)
Duration of PV, months, median (min-max)	**67.2 (0.5-361.4)**
Female, n (%)	74 (49.3)
Caucasian, n (%)	114 (76.0)
HU resistant, n (%)	**92 (61.3)**
HU intolerant, n (%)	**98 (65.3)**
HCT (n)	**133**
HCT %, mean (SD)	44 .9 (4.9)
HCT category, n (%)	
<40%	12 (9.0)
≥40%-≤45%	59 (44.4)
>45%-<48%	**28 (21.1)**
≥48%	**34 (25.6)**
Phlebotomies 12 months before RUX, n (%)	
0	55 (38.5)
1-2	**34 (23.8)**
≥3	**54 (37.8)**
ECOG status, n (%)	
0	34 (66.7)
1	16 (31.4)
2	0
3	1 (2.0)

Characteristic	RUX (N=150)
Platelets x 10^9/L, mean (SD)	415.4 (254.8)
Platelet category x 10^9/L, n (%)	
<100	2 (1.5)
≥100-<400	77 (57.0)
≥400-<600	33 (24.4)
≥600	23 (17.0)
WBC x 10^9/L, n	135
WBC x 10^9/L, mean (SD)	13.1 (9.7)
WBC x 10^9/L, n (%)	
≤10	65 (48.1)
>10-≤ 15	34 (25.2)
>15	36 (26.7)
Splenomegaly (by palpation), n (%)	
No enlargement (0 cm)	28 (45.9)
Mild (<4 cm)	**12 (19.7)**
Moderate (4-8 cm)	**11 (18.0)**
Massive (>8 cm)	**10 (16.4)**
Medical history of patients, n (%)	
Infections	**28 (18.6)**
SNP	**19 (12.6)**
Bleeding	**8 (5.3)**
TE events	**44 (29.3)**

ECOG, Eastern Cooperative Oncology Group; HCT, hematocrit; HU, hydroxyurea; PV, polycythemia vera; RUX, ruxolitinib; SD, standard deviation; SNP, secondary neoplasm, TE, thromboembolic; WBC, white blood cells

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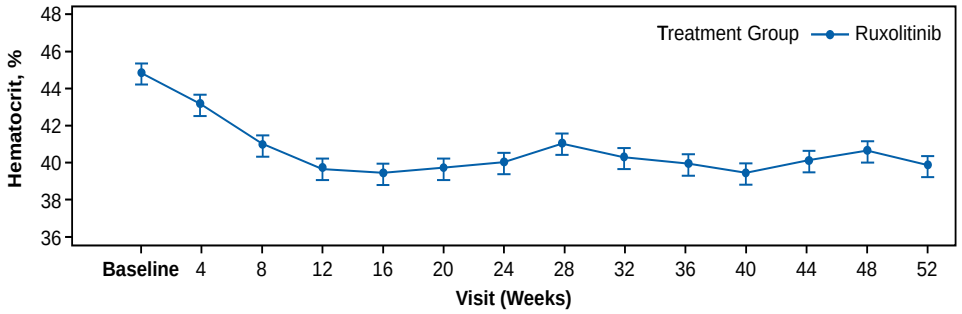
Hematocrit and phlebotomy

Mean hematocrit (%) by week since baseline[a]

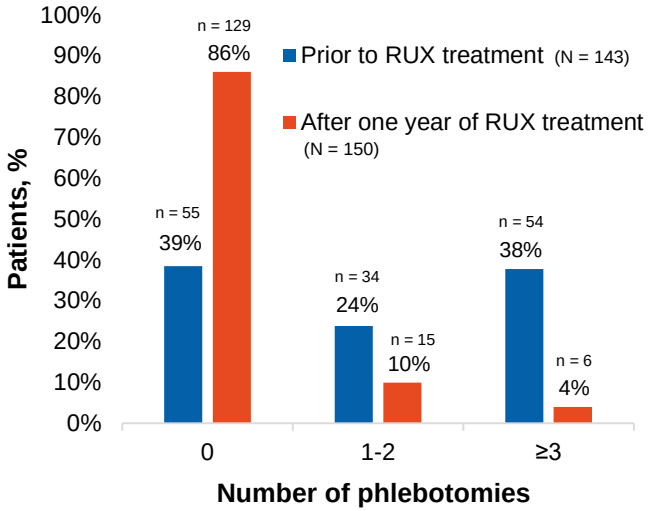


Number of patients at each timepoint

Ruxolitinib	133	102	96	78	67	72	71	70	77	60	64	68	59	106

HCT levels dropped to 40% during weeks 8 to12 and were sustained for the remaining period, as observed in IA2

Distribution of phlebotomy frequency



The dependency of patients requiring 1 to 2 and ≥3 phlebotomies decreased from 24% and 38% at baseline to 10% and 4%, respectively, after 1 year of RUX treatment

[a]Error bars denote standard error of mean
HCT, hematocrit; IA, interim analysis; RUX, ruxolitinib

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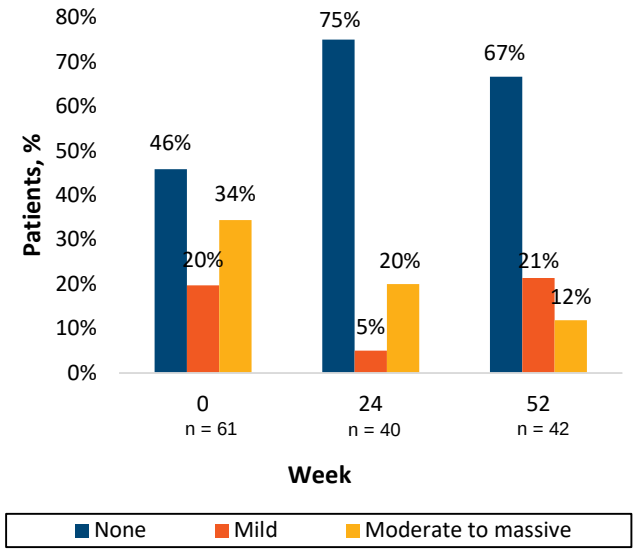
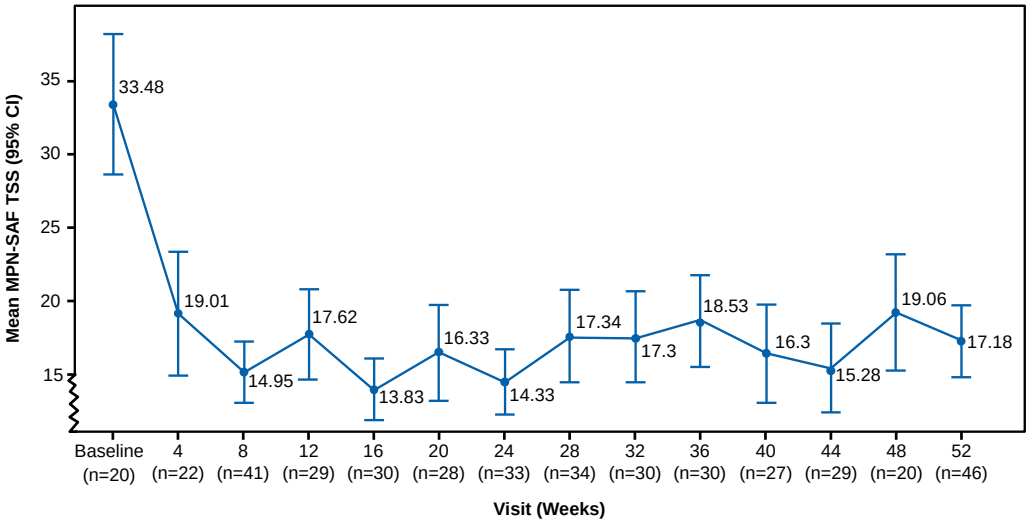
Splenomegaly and MPN-SAF TSS

Spleen enlargement



The proportion of patients with no splenomegaly increased from 45.9% at baseline to 75.0% at week 24 and 66.7% at week 52

MPN-SAF TSS



The mean MPN-SAF TSS declined rapidly from a score of 33.5 at baseline (n=20) to 19.0 (n=22) at week 4 and reached 17.2 (n=46) by week 52

CI, confidence interval; MPN-SAF TSS, myeloproliferative neoplasm symptom assessment form total symptom score; RUX, ruxolitinib

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Safety

Adverse events

- AEs reported during the study included infections in 43.3%, TEs and bleeding in10% each, and SNP in 6% of patients
- Grade ≥3 AEs reported during the study included infections in 4.6%, TEs in 2%, SNP in 1.3%, and bleeding in 0.7% patients

AE	All grade, n (%)	Grade ≥3, n (%)
Bleeding events	**15 (10.0)**	**1 (0.7)**
Esophageal varices hemorrhage	1 (0.7)	1 (0.7)
Hematoma	5 (3.3)	-
Epistaxis	3 (2.0)	-
Ecchymosis	2 (1.3)	-
Anal hemorrhage	2 (1.3)	-
Secondary neoplasm	**9 (6.0)**	**2 (1.3)**
Basal cell carcinoma	4 (2.7)	1 (0.7)
Acute myeloid leukemia	1 (0.7)	1 (0.7)
Thyroid mass	2 (1.3)	-
Vocal cord leucoplakia	2 (1.3)	-
Squamous cell carcinoma	2 (1.3)	-
Thromboembolic events	**9 (6.0)**	**2 (1.3)**
Colitis ischemic	1 (0.7)	1 (0.7)
Peripheral embolism	1 (0.7)	1 (0.7)
Peripheral vascular disorder	2 (1.3)	-

AE	All grade, n (%)	Grade ≥3, n (%)
Infections	65 (43.3)	7 (4.6)
Nasopharyngitis	15 (10.0)	-
Bronchitis	9 (6.0)	
Influenza	7 (4.6)	-
Respiratory tract infection	7 (4.6)	1 (0.7)
Cystitis	6 (4.0)	-
Herpes zoster	5 (3.3)	-
Pneumonia	4 (2.7)	1 (0.7)
Diverticulitis	2 (1.3)	1 (0.7)
Eye infection	2 (1.3)	-
Colitis	2 (1.3)	-
Urinary tract infection	2 (1.3)	-
Aphthous ulcer	2 (1.3)	-
Tooth abscess	2 (1.3)	-
Pharyngitis	2 (1.3)	-
Oral herpes	2 (1.3)	-
Gastroenteritis	2 (1.3)	-
Wound infection	2 (1.3)	2 (1.3)
Gastrointestinal infection	2 (1.3)	-
Sepsis	2 (1.3)	1 (0.7)
Appendicitis	1 (0.7)	1 (0.7)
Lymph node tuberculosis	1 (0.7)	1 (0.7)
Campylobacter gastroenteritis	1 (0.7)	1 (0.7)
Cholangitis	1 (0.7)	1 (0.7)

Note: Only AEs occurring in ≥2 patients or of grade ≥3 intensity are presented here

AE, adverse events; SNP, secondary neoplasm; TE, thromboembolic events

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Conclusions

RUX treatment achieved a HCT level of 40% during weeks 8 to 12 and was sustained for the remaining period

Symptom and spleen responses were observed in the majority of patients presenting with these abnormalities at baseline

Infections were the most common adverse events with the majority of them being <grade 2

Phlebotomy dependency was reduced from 62% at baseline to 14% after one year of treatment, with a strong reduction in patients requiring 3 or more per year

HCT, hematocrit; RUX, ruxolitinib

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