Check for updates

Received: 26 May 2023 | Revised: 11 October 2023 | Accepted: 12 October 2023

DOI: 10.1111/ejh.14124

ORIGINAL ARTICLE

European Journal of Haematology

WILEY

Ruxolitinib in patients with polycythemia vera resistant and/or intolerant to hydroxyurea: European observational study

Alexandre Theocharides[1] | Heinz Gisslinger[2] | Valerio De Stefano[3] | Vincenzo Accurso[4] | Alessandra Iurlo[5] | Timothy Devos[6] | Miklos Egyed[7] | Eric Lippert[8] | Regina Garcia Delgado[9] | Nathan Cantoni[10] | Anders E. A. Dahm[11] | Damianos Sotiropoulos[12] | Erik Houtsma[13] | Aoife Smyth[14,15] | Amir Iqbal[13] | Paola Di Matteo[16] | Mike Zuurman[14] | Peter A. W. te Boekhorst[17]

[1]Department of Medical Oncology and Hematology, University Hospital Zurich and University of Zurich, Zurich, Switzerland

[2]Department of Internal Medicine I, Hematology, Medical University of Vienna, Vienna, Austria

[3]Section of Hematology, Department of Radiological and Hematological Sciences, Catholic University, Fondazione Policlinico A Gemelli IRCCS, Roma, Italy

[4]U.O.C. Ematologia AZ.Osp.Univ. Policlinico Paolo Giaccone Palermo, Palermo, Italy

[5]Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[6]Department of Hematology, University Hospitals Leuven and Department of Microbiology and Immunology, Laboratory of Molecular Immunology (Rega Institute), KU Leuven, Leuven, Belgium

[7]Hematológiai Osztály, Somogy Megyei Kaposi Mor Oktato Korhaz, Kaposvar, Hungary

[8]Service Hématologie, CHU de Brest, Brest, France

[9]Servicio de Hematologia, Hospital Virgen de la Victoria, Malaga, Spain

[10]Division of Oncology, Hematology and Transfusion Medicine, Kantonsspital Aarau, Aarau, Switzerland

[11]Avdeling for Blodsykdommer, Akershus Universitetssykehus, Lørenskog, Norway

[12]Heamatology Clinic, General Hospital of Thessaloniki G Papanikolaou, Thessaloniki, Greece

[13]Novartis Global Service Center, Dublin, Ireland

[14]Novartis Pharmaceuticals AG, Basel, Switzerland

[15]Novartis Pharmaceuticals UK Limited, London, UK

[16]Novartis Farma SpA, Origgio, Italy

[17]Department of Hematology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence
Peter A. W. te Boekhorst, Department of Hematology, Erasmus Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.
Email: p.teboekhorst@erasmusmc.nl

Funding information
Novartis Pharma

Abstract

Background: Hydroxyurea (HU) is a commonly used first-line treatment in patients with polycythemia vera (PV). However, approximately 15%–24% of PV patients report intolerance and resistance to HU.

Methods: This phase IV, European, real-world, observational study assessed the efficacy and safety of ruxolitinib in PV patients who were resistant and/or intolerant to HU, with a 24-month follow-up. The primary objective was to describe the profile and disease burden of PV patients.

Results: In the 350 enrolled patients, 70% were >60 years old. Most patients (59.4%) had received ≥1 phlebotomy in the 12 months prior to the first dose of ruxolitinib.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2023 The Authors. *European Journal of Haematology* published by John Wiley & Sons Ltd.

Overall, 68.2% of patients achieved hematocrit control with 92.3% patients having hematocrit <45% and 35.4% achieved hematologic remission at month 24. 85.1% of patients had no phlebotomies during the study. Treatment-related adverse events were reported in 54.3% of patients and the most common event was anemia (22.6%). Of the 10 reported deaths, two were suspected to be study drug-related.

Conclusion: This study demonstrates that ruxolitinib treatment in PV maintains durable hematocrit control with a decrease in the number of phlebotomies in the majority of patients and was generally well tolerated.

KEYWORDS

hematocrit, phlebotomy, polycythemia vera, ruxolitinib, splenomegaly

1 | INTRODUCTION

Polycythemia vera (PV) is a *BCR-ABL1*-negative myeloproliferative neoplasm (MPN) associated with dysregulated Janus kinase (JAK) signaling pathways, specifically JAK1 and JAK2. The predominant characteristic of PV is an increase in red blood cell (RBC) mass but increased white blood cell (WBC) and platelet count are common as well.[1–4]

Patients with PV have an increased risk of morbidity and mortality relative to the respective general population (e.g., same sex/age), often resulting from thromboembolic events or fibrotic progression/leukemic disease evolution. PV is associated with a substantial symptom burden, most commonly pruritus and fatigue, affecting patients' quality of life. Additionally, 30%–40% of PV patients may experience splenomegaly.[5–9] It has been demonstrated that PV patients with a hematocrit level <45% suffer four times fewer thromboembolic events compared to those unable to reach hematocrit control,[10] recommending a hematocrit level <45% to prevent thromboembolic events. Platelet aggregation inhibition is also widely recommended to prevent thromboembolic events.[11,12]

The choice of treatment for PV is based on the individual patient's risk.[4] Globally, hydroxyurea (HU) is the most common first-line treatment for high-risk patients with PV (patients aged >60 years and/or with a history of thromboembolic events).[13,14] However, the PV-associated symptom burden is frequently not well controlled with HU treatment as demonstrated by the high Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) in patients with HU treatment (range, 27.7–32.5; the mean MPN-SAF TSS of patients with PV is 21.8).[15,16] Furthermore, HU treatment can be associated with toxicities which necessitate discontinuation of HU,[15,17] and approximately 15%–24% of patients become HU resistant or intolerant.[18,19] Finally, HU resistance correlates with reduced survival and risk of progression to myelofibrosis and acute myeloid leukemia.[2,18] The European LeukemiaNet (ELN) 2021 recommendations advocate the replacement of HU with another cytoreductive agent for PV patients who develop HU intolerance, indicated by hematological/non-hematological (prolonged grade 2 or grade 3–4) toxicity or inappropriate clinical response to HU (≥1.5 g/day) for ≤4 months.[20] For the treatment of adult PV patients resistant and/or intolerant to HU, ruxolitinib, a targeted JAK1/JAK2 therapy, was approved by the United States Food and Drug Administration (FDA) in December 2014 and by the European Medicines Agency (EMA) in January 2015. Approval of ruxolitinib has been granted based on the RESPONSE and RESPONSE-2 clinical studies in which significantly more patients who were treated with ruxolitinib achieved hematocrit control compared to the best available treatment.[21,22] However, it is important to gain insights into treatment administration and outcomes in the real-world setting beyond the clinical experience of registrational trials. Here, we present the final results from a non-interventional study to gain an understanding of the profile and the disease burden of patients with PV who were resistant and/or intolerant to HU and treated with ruxolitinib according to the respective approved local label and daily practice in Europe.

2 | MATERIALS AND METHODS

2.1 | Study design

This phase IV, European, multicenter, non-randomized, observational study assessed the efficacy and safety of ruxolitinib in PV patients, with a minimum 24-month follow-up after treatment initiation (Figure S1). Patients were enrolled across 88 sites in 10 European countries. The recommended starting dose of ruxolitinib was 10 mg, administered orally twice daily as per the approved label. The study was conducted in accordance with the principles of the Declaration of Helsinki criteria. The protocol was approved by the relevant independent review board/independent ethics committee/research ethics board at each participating center. The selection of the participating centers was based on their ability to recruit patients and provide reimbursed access to therapies. The study was funded by Novartis Pharma AG/Region Europe.

2.2 | Study population

Eligibility criteria were adult patients aged ≥18 years with a diagnosis of PV according to the 2008 World Health Organization (WHO)

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

criteria, who were resistant/intolerant to HU (Supplementary appendix; Data S1) and treated with ruxolitinib according to the approved local label. The WHO (2008) diagnostic parameters for PV were an accurate reflection at the time of the start of the study and recognized by the investigators, who accepted and conducted the trial. As defined by the inclusion and exclusion criteria of the study protocol, patients with a short course of ruxolitinib treatment could be included, to evaluate a larger cohort of PV patients since ruxolitinib has recently been approved in multiple participating countries. Accordingly, in addition to the prospective patients who were going to be prescribed ruxolitinib, retrospective patients who had already initiated treatment ≤6 months before the date of the informed consent signature were also included.

Data from these patients were retrospectively collected from the period prior to starting ruxolitinib, and their prospective observational period was to last until a total of 24 months (between retrospective and prospective) was reached. Signed informed consent was collected from all patients prior to entering the study. Patients were managed at the discretion of the treating physician following the approved local label and the local treatment recommendations in terms of visit frequency and types of assessments performed. Access to ruxolitinib was limited to patients resistant or intolerant to HU in 9 of 10 countries, whereas patients in Switzerland resistant or intolerant to any cytoreductive treatment (e.g., interferon) prior to ruxolitinib qualified for enrollment.

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

2.3 | Objectives and assessments

The primary objective of the study was to describe the profile and disease burden of PV patients with HU resistance and/or intolerance who were treated with ruxolitinib according to the respective approved local label in daily practice in Europe.

The secondary objectives included the evaluation of the effectiveness and safety of ruxolitinib, characterizing the clinical routine management of patients, the impact of ruxolitinib from a pharmacoeconomic perspective (i.e., frequency and reasons for hospitalization), and the evaluation of the cardiovascular risk in PV patients who are resistant and/or intolerant to HU.

The primary variables were collected as baseline data prior to and on the day of the first dose of ruxolitinib. The secondary variables were collected during the period of treatment after the first dose of ruxolitinib.

Patient-reported outcomes were assessed with the MPN-SAF TSS, the Pruritus Symptom Impact Scale (PSIS), and the EuroQol-5 dimension-5 level (EQ-5D-5L) and work productivity and activity impairment: polycythemia vera (WPAI: PV) questionnaires.[16,23] PSIS questionnaire is presented as Table S1.

Hematocrit control was defined by the absence of phlebotomy eligibility (hematocrit ≤45%) starting at week 8 and continuing through all subsequent time points, with no more than one phlebotomy eligibility occurring post-enrollment and prior to week 8.

Hematology parameters include hematocrit (%), RBC count, RBC distribution width (%), hemoglobin (g/L), WBC (total/ 10^9/L) with differential count, and platelet counts (10^9/L).

Phlebotomy eligibility was defined by confirmed hematocrit >45% that was at least 3% higher than the hematocrit obtained at baseline or confirmed hematocrit >48%.

Complete hematologic remission at any time point (starting at week 8) was defined by hematocrit control, WBC count ≤10 × 10^9/L, and platelet count ≤400 × 10^9/L.

Spleen enlargement (cm) was assessed by manual palpation.

Safety assessments included vital signs, evaluation of frequency of adverse events (AEs) and serious adverse events (SAEs) and concomitant medications/therapies used to treat them, incidence of the major adverse cardiovascular event (MACE; a clinical composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), dosing and dose modifications, and treatment discontinuation or interruption and reason for permanent discontinuation or interruption.

Patients were treated according to the routine medical practice of the treating physician in terms of visit frequency and types of assessments performed. The treating physician was asked to complete the appropriate case report form (CRF) at every patient visit.

Final analysis was performed when the last patient completed the 24-month observation period or prematurely discontinued.

2.4 | Statistical analyses

Data were summarized with respect to demographic and baseline characteristics, safety observations, and measurements, as well as effectiveness assessments using descriptive statistics. Categorical data are presented as frequencies and percentages. Continuous variables were summarized by mean, standard deviation, minimum, median, and maximum. Baseline assessment refers to the last assessment prior to the patient's first recorded dose of ruxolitinib. No statistical hypotheses were tested.

3 | RESULTS

3.1 | Patients' disposition, demographics, and disease history

A total of 357 patients were screened, of which 351 patients completed the screening phase and were treated with ruxolitinib. Six patients completed the screening phase and were not treated, reasons for which were not recorded on the CRF (Figure 1). Of the 351 patients treated, one patient started ruxolitinib 210 days prior to the informed consent and therefore was not included in the enrolled set.

Of the 350 patients enrolled and treated with ruxolitinib in the study, 197 retrospective patients (56.3%) had been treated within

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

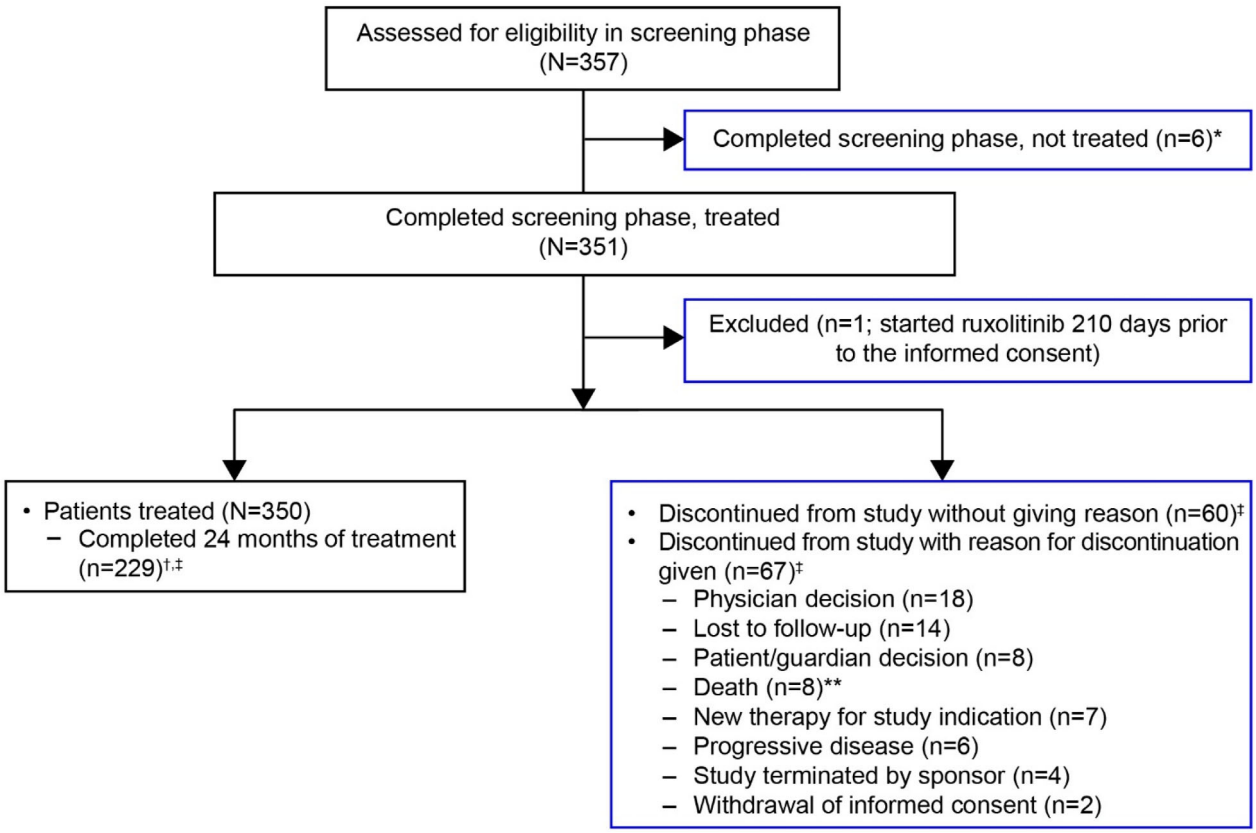

FIGURE 1 Screening phase patient disposition. *n*, number of subjects where data were recorded; *N*, number of subjects in the relevant analysis set. *Reasons were not recorded on case report form (CRF). †Completed 24 months of treatment is defined as 104 weeks on treatment. On-treatment duration is defined as (last date of treatment—first date of treatment) + 1. ‡A patient can be included in both the counts for "completed 24 months of treatment" and "discontinued from study". **The counts for discontinuation category of death only include patients who discontinued due to death and may not contain all adverse events of death.

6 months of signing the informed consent, and 153 prospective patients (43.7%) had been treated after signing the informed consent. At the predetermined cutoff date of the study, a total of 229 (65.4%) patients had completed the total 24-month observation period and 67 (19.1%) patients discontinued the study.

The median age of patients was 68.0 years and the majority ($n = 245$, 70.0%) were >60 years of age. Most patients were male ($n = 195$, 55.7%) and Caucasian (n = 259, 74.0%). The median weight was 74.0 kg ($n = 163$), and median body mass index (BMI) was 25.974 kg/m^2 ($n = 88$) (Table 1).

3.2 | Concomitant medications

The most commonly (>10%) reported concomitant medications by preferred term after starting treatment with ruxolitinib included acetylsalicylic acid ($n = 215$, 61.4%), HU ($n = 115$, 32.9%), allopurinol ($n = 92$, 26.3%), paracetamol ($n = 54$, 15.4%), pantoprazole sodium sesquihydrate ($n = 49$, 14.0%), omeprazole ($n = 42$, 12.0%), and acyclovir ($n = 37$, 10.6%). These co-medications were administered as per the clinicians' decision, which affirmed the additional value of ruxolitinib in this patient subgroup. The predominant reasons for concomitant HU administration were: (1) hydroxycarbamide terminated and ruxolitinib initiated on the same day, (2) hydroxycarbamide initiated after initiating ruxolitinib, (3) hydroxycarbamide initiated after terminating ruxolitinib, or (4) end date of hydroxycarbamide treatment was unknown. In total, 145 (41.4%) patients received concomitant medications affecting the blood and blood forming organs of the body with 34 (9.7%) patients receiving clopidogrel.

3.3 | Primary variables

3.3.1 | Baseline characteristics and disease history

At baseline, 345 patients (98.6%) were resistant or intolerant to HU treatment. The majority ($n = 222$, 63.4%) of patients were intolerant to HU treatment, 57.7% ($n = 202$) were resistant to HU, and 23.4% ($n = 82$) were both resistant and intolerant to HU. Resistance to HU was observed in the following patients: (1) patients (n = 198, 57.2%) who had undergone at least 12 weeks of HU (2 g/day) treatment or at the maximally tolerated dose; (2) patients ($n = 148$, 42.8%) who had the need for phlebotomy to maintain their hematocrit levels below 45%; (3) patients ($n = 91$, 26.3%) with uncontrolled myeloproliferation

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Baseline patient characteristics.

Baseline characteristics	**N = 350**
Age, years, median (min–max)	68.0 (27–90)
Age, >60 years, *n* (%)	245 (70.0)
Female, *n* (%)	155 (44.3)
Male, *n* (%)	195 (55.7)
Race, *n* (%)	
Caucasian	259 (74.0)
Unknown	36 (10.3)
Other	55 (15.7)
Duration of PV, months, median (min–max)	74.0 (0.5–449.0)
Medical history of patients, *n* (%)	
Thromboembolic events	69 (19.7)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	57 (16.3)
Infections and infestations	45 (12.9)
Disease characteristics	**N = 350**
Resistance and/or intolerance to HU[a], *n* (%)	345 (98.6)
HU intolerant	222 (63.4)
HU resistant	202 (57.7)
HU resistant and intolerant	82 (23.4)
Hematocrit, %, *N* (mean ± SD)	318 (45.1 ± 4.9)
Hematocrit category, *n* (%)	**N = 318**
<40%	39 (12.3)
≥40%–≤45%	115 (36.2)
>45%–<48%	70 (22.0)
≥48%	94 (29.6)
WBC, $\times 10^9$/L, *N* (mean ± SD)	318 (11.9 ± 8.5)
WBC count category, $\times 10^9$/L, *n* (%)	**N = 318**
≤10	173 (54.4)
>10–≤15	71 (22.3)
>15	74 (23.3)
Platelet count, $\times 10^9$/L, *N* (mean ± SD)	316 (420.9 ± 249.7)
Platelet count category, $\times 10^9$/L, *n* (%)	**N = 316**
<100	7 (2.2)
≥100–<400	171 (54.1)
≥400–<600	76 (24.1)
≥600	62 (19.6)
Red blood cell count, $\times 10^{12}$/L, *n* (mean ± SD)	292 (5.2 ± 1.3)
Hemoglobin, g/L, *n* (mean ± SD)	320 (142.5 ± 17.5)
Phlebotomies 12 months prior to first dose of ruxolitinib, *n* (%)	**N = 337**
0	142 (42.1)
≤2	88 (26.1)
>2–≤4	57 (16.9)
>4–≤6	29 (8.6)
>6–≤8	10 (3.0)
>8	11 (3.3)
Splenomegaly, *n* (%)	**N = 164**
No enlargement (0 cm)	81 (49.4)
Mild (<4 cm)	36 (22.0)
Moderate (4–8 cm)	27 (16.5)
Massive (>8 cm)	20 (12.2)
ECOG performance status, *n* (%)	
Grade 0	106 (67.9)
Grade 1	49 (31.4)
Grade 2	0
Grade 3	1 (0.6)
Grade 4	0
	N = 350
Relevant medical histories, *n* (%)	312 (89.1)
Surgical and medical procedures, *n* (%)	256 (73.1)
Phlebotomy, *n* (%)	211 (60.3)
Current medical conditions, *n* (%)	324 (92.6)
Vascular disorders	215 (61.4)
Hypertension	202 (57.7)
Non-melanoma skin cancer history, *n* (%)	17 (4.9)
Previous infectious diseases, *n* (%)	51 (14.6)
Summary of PV history, *n* (%)	
Bone marrow biopsy	221 (63.1)
Reticulin fibrosis, Grade[b]	
Grade 0	94 (26.9)
Grade 1	104 (29.7)
Grade 2	10 (2.9)
Grade 3	2 (0.6)
Hypercellular bone marrow	182 (52.0)
Genetic analysis	326 (93.1)
JAK2 V617F mutation	325 (92.9)
JAK2 exon 12 mutation	18 (5.1)
JAK2 V617F allelic burden, *n* (mean ± SD)	94 (49.3 ± 26.8)
Framingham cardiovascular risk score, *n* (%)	
<10%	14 (4.0)
≥10%–<20%	1 (0.3)
SCORE risk, *n* (%)	
<5%	10 (2.9)
≥5%	7 (2.0)

Note: The denominator used for percentages is the number of non-missing data. Concomitant or prior medications were coded using the WHO Drug Reference List. Medical history/current medical conditions and AEs were coded using the MedDRA terminology.
Abbreviations: AE, adverse event; BMI, body mass index; CRF, case report form; ECOG, Eastern Cooperative Oncology Group; HU, hydroxyurea; MedDRA, Medical Dictionary for Regulatory Activities; *n*, number of subjects where data were recorded; *N*, number of subjects in the relevant analysis set. PV, polycythemia vera; SCORE, systematic coronary risk evaluation; SD, standard deviation; WBC, white blood cell; WHO, World Health Organization.
[a]Resistance and/or intolerance to HU is reported from the "Assessment of Resistance/Intolerance to HU" CRF. Patients can be counted as both resistant/intolerant to HU, and other cytoreductive therapy other than HU.
[b]PV patients with grade 2–3 fibrosis were included in the study by the prescribing hematologists.

(defined as platelet count >400 × 10^9/L and WBC count >10 × 10^9/L); (4) patients ($n = 60$, 17.3%) with failed massive splenomegaly reduction by >50% (as measured by palpation); and (5) patients ($n = 43$, 12.4%) with failure to completely relieve symptoms related to splenomegaly. Intolerance to HU was observed in the following patients: (1) patients

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

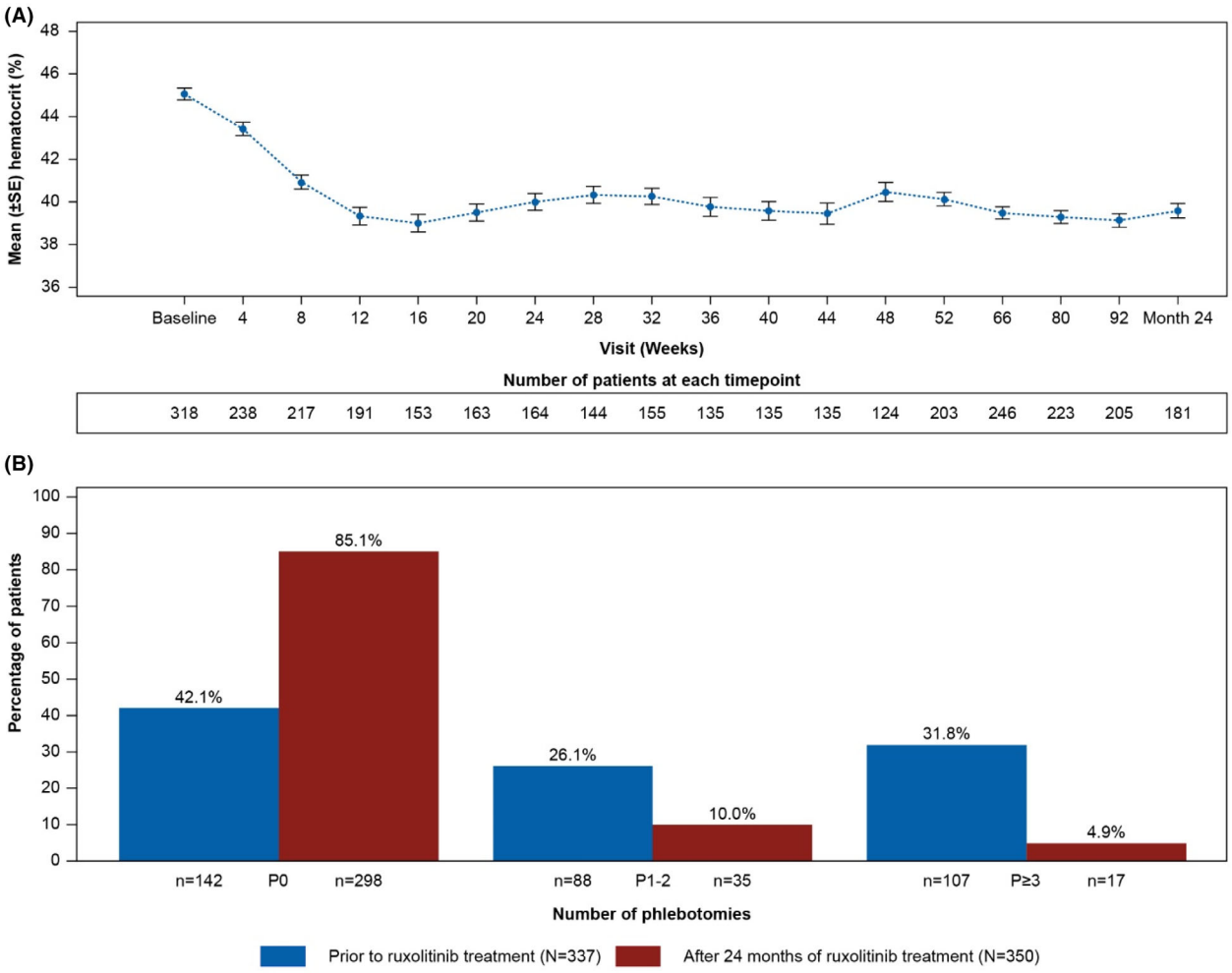

FIGURE 2 (A) Mean (±SE) hematocrit (%) by visit; (B) Comparison of phlebotomies before and after 24 months treatment with ruxolitinib. Prior refers to the period of 12 months preceding the first dose of ruxolitinib. P0, P1–2, and P ≥ 3 is the number of phlebotomies. *n*, number of subjects where data were recorded; *N*, number of subjects in the relevant analysis set; SE, standard error.

($n = 6$, 1.7%) with absolute neutrophil count <1 × 10^9/L (platelet count <100 × 10^9/L [$n = 15$, 4.3%], hemoglobin level < 10 gm/dL [$n = 8$, 2.3%]) at the lowest dose of HU required to achieve a complete or partial clinicohematologic response and (2) patients ($n = 207$, 59.8%) with the presence of leg ulcers or other HU-related non-hematologic toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of HU. Table S2 describes the intolerant/resistant assessment in 350 patients who received ruxolitinib therapy.

In the 350 enrolled patients, reasons for treatment switch included resistance to previous treatment ($n = 109$, 31.1%), intolerance to previous treatment ($n = 190$, 54.3%), unsatisfactory response to previous treatment ($n = 47$, 13.4%), and other reasons ($n = 4$, 1.1%). The median time since diagnosis of PV was 74.0 (min–max, 0.5–449.0) months. Most patients (59.4%) had received ≥1 phlebotomy in the 12 months prior to the first dose of ruxolitinib. The median hematocrit value at baseline was 45.2% and 29.6% of patients had a hematocrit value ≥48%. (Figure 2A). The median RBC count was 5.2 × 10^{12}/L and the median hemoglobin value was 141.0 g/L (Figure 3A). The median WBC count was 9.4 × 10^9/L, and 23.3% patients had a WBC count >15 × 10^9/L (Figure 3B). The median platelet count was 362.5 × 10^9/L, and 19.6% had a platelet count ≥600 × 10^9/L (Figure 3C). Of the 164 patients with spleen measurement by palpation, 49.4% patients had no spleen enlargement and 28.7% had moderate (4–8 cm) or massive (>8 cm) splenomegaly (Figure 4). Of the 47 patients with moderate or massive splenomegaly, bone marrow sampling was done to exclude the diagnosis of post-PV myelofibrosis. The Eastern Cooperative Oncology Group (ECOG) performance status grade was 0 for 106 patients (67.9%) (Table 1).

At baseline, 89.1% ($n = 312$) of patients had relevant medical histories by primary system organ class, of these 73.1% ($n = 256$) had surgical and medical procedures. The most commonly (>10%) reported relevant medical histories by preferred term included phlebotomy ($n = 211$, 60.3%). Current medical conditions were reported in 92.6% ($n = 324$) of patients, of which 61.4% ($n = 215$) had vascular disorders (Table 1). The most commonly (>10%) reported current medical conditions by preferred term included hypertension ($n = 202$, 57.7%) and splenomegaly ($n = 57$, 16.3%). Prior to study entry, 4.9% ($n = 17$) of patients had non-melanoma skin cancer history, 14.6% ($n = 51$) had

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

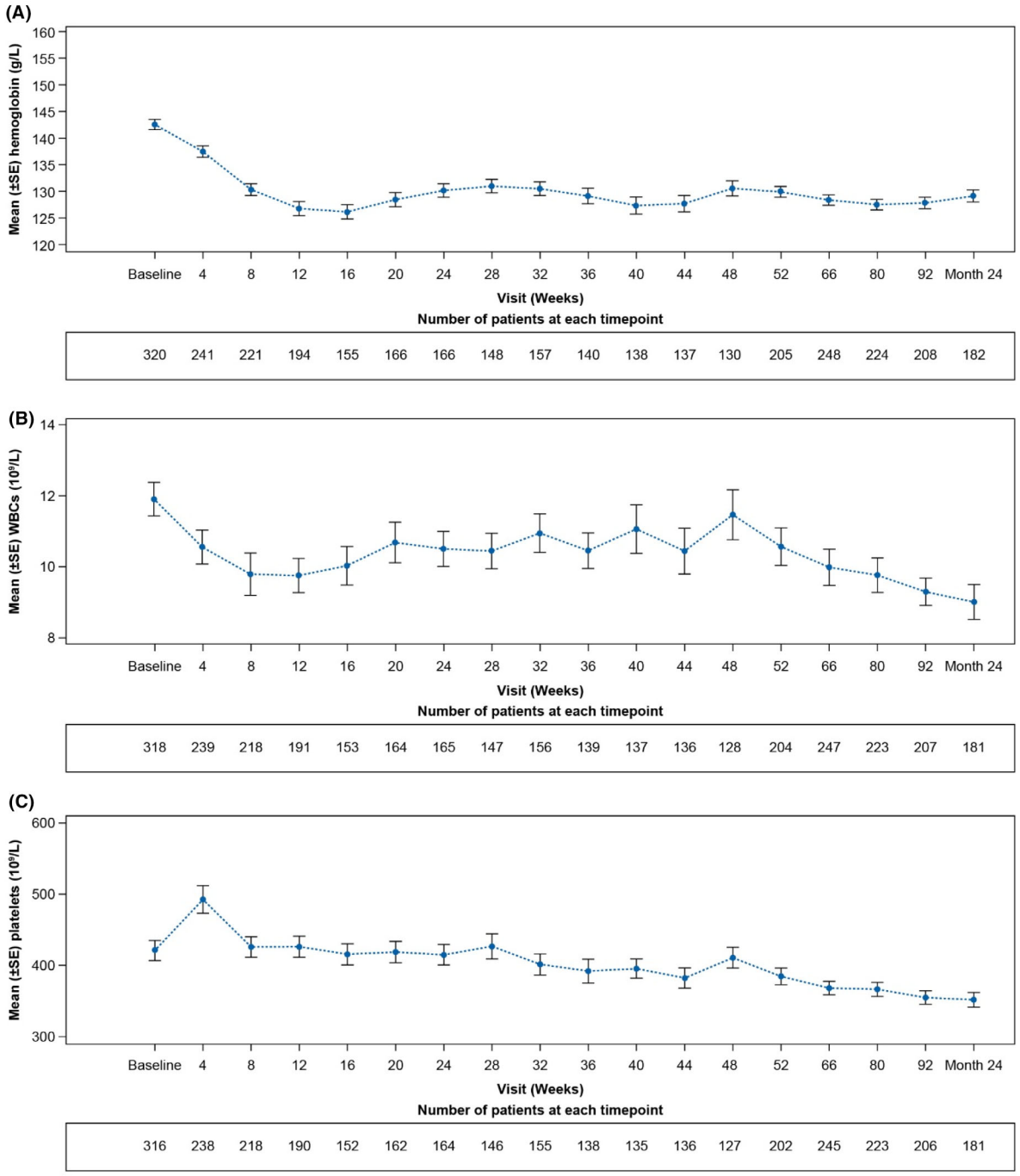

FIGURE 3 (A) Mean (±SE) hemoglobin (g/L) by week from baseline; (B) Mean (±SE) WBCs (10^9/L) by week from baseline; (C) Mean (±SE) platelets (10^9/L) by week from baseline. SE, standard error; WBC, white blood cell.

previous infectious diseases, and 19.7% ($n = 69$) patients had a history of thromboembolic events.

Of the 221 patients (63.1%) with bone marrow analysis data, 29.7% had grade 1, 2.9% had grade 2, and 0.6% had grade 3 reticulin fibrosis. None of the PV patients with grade 2/3 reticulin fibrosis had a medical history of myelofibrosis. Of the 326 patients (93.1%) with genetic analysis data, 92.9% had a JAK2 V617F mutation and 5.1% had a JAK2 exon 12 mutation. The mean JAK2 V617F allelic burden was 49.3% for the 94 patients assessed (Table 1).

3.4 | Secondary variables

3.4.1 | Hematocrit control

Hematocrit levels dropped rapidly in the first 12 weeks and were sustained throughout the observation period to 24 months (Figure 2A). Overall, 141/177 (79.7%) patients at week 24 and 131/192 (68.2%) patients at month 24 achieved hematocrit control with 167/181 (92.3%) patients achieving hematocrit value <45% at month 24.

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

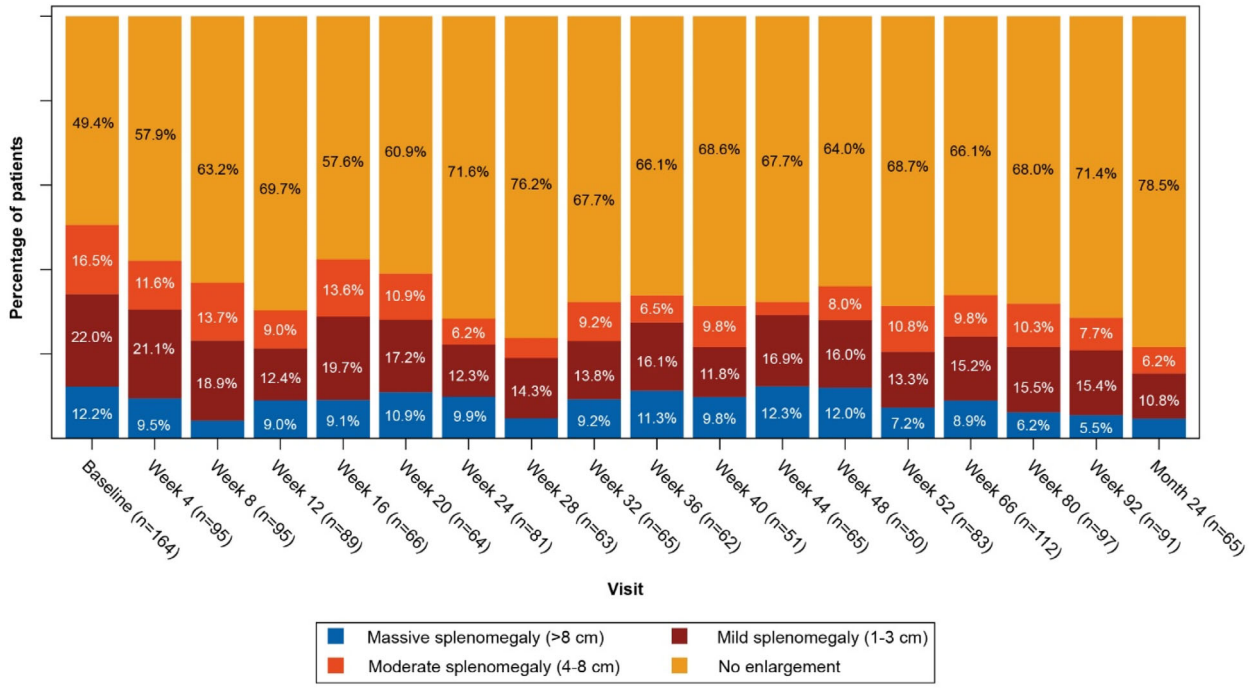

FIGURE 4 Spleen enlargement categories by visit. *n*, number of subjects where data were recorded; *N*, number of subjects in the relevant analysis set. Number of patients with a non-missing spleen enlargement result at each visit is used as the denominator in percentage calculation for each visit. Percentages <5% are not printed within the categories.

At week 24, 52/177 (29.4%) patients achieved hematologic remission, of which 33 patients (16.3%) and 30 patients (13.5%) were resistant and intolerant to HU, respectively. At month 24, 68/192 (35.4%) patients achieved hematologic remission, of which 37 patients (18.3%) and 45 patients (20.3%) were resistant and intolerant to HU before ruxolitinib treatment, respectively.

3.5 | Laboratory data

The mean (SD) hematocrit values were 45.1% (4.9) for 318 patients at baseline and 39.6% (4.5) for 181 patients at month 24 (Figure 2A). The mean (SD) RBC count was 5.2×10^{12}/L (1.3×10^{12}/L) for 292 patients at baseline and 4.5×10^{12}/L (0.8×10^{12}/L) for 161 patients at month 24. The mean (SD) hemoglobin values were 142.5 g/L (17.5) for 320 patients at baseline and 129.1 g/L (15.4) for 182 patients at month 24 (Figure 3A). The mean (SD) WBC count was 11.9×10^9/L (8.5×10^9/L) for 318 patients at baseline and 9.0×10^9/L (6.6×10^9/L) for 181 patients at month 24 (Figure 3B). The mean (SD) platelets count was 420.9×10^9/L (249.7×10^9/L) for 316 patients at baseline and 351.5×10^9/L (138.4×10^9/L) for 181 patients at month 24 (Figure 3C).

3.6 | Phlebotomy

Most of the patients (85.1%) had no phlebotomies during the study. Of the 52/350 patients (14.8%) with phlebotomies from week 4 to month 24, 10.0% ($n = 35$) had ≤2, 3.4% ($n = 12$) had >2 to ≤4, and 1.4% ($n = 5$) had >4 to ≤6 phlebotomies. The proportion of patients not requiring any phlebotomy increased from 42.1% at baseline to 85.1% after 24 months of treatment with ruxolitinib; conversely, the percentage of patients requiring 1–2 phlebotomies decreased from 26.1% to 10%, and patients requiring ≥3 phlebotomies decreased from 31.8% to 4.9% from baseline to end of ruxolitinib treatment (Figure 2B).

3.7 | Splenomegaly

Spleen measurement by palpation was assessed in 164/350 patients at baseline and 65/350 patients at month 24. The proportion of patients without splenomegaly increased from 49.4% ($n = 81$) at baseline to 78.5% ($n = 51$) at month 24, while the proportion of patients with moderate (4–8 cm) splenomegaly was reduced from 16.5% ($n = 27$) at baseline to 6.2% ($n = 4$) at month 24, and the proportion of patients with massive (>8 cm) splenomegaly was reduced from 12.2% ($n = 20$) at baseline to 4.6% ($n = 3$) at month 24 (Figure 4).

3.8 | Disease progression

During the 24-month observation period, eight patients (2.3%) developed post-PV myelofibrosis, two patients (0.6%) progressed to acute

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

myelogenous leukemia, and one patient (0.3%) transformed to myelodysplastic syndromes.

3.9 | MPN-SAF TSS, PSIS, EQ-5D-5L, and WPAI: PV

Swift and deep improvements in symptoms were reported, as measured by MPN-SAF TSS, PSIS, and EQ-5D-5L visual analog scores, early after initiation of ruxolitinib treatment, and the symptoms improved in a sustainable manner throughout the 24-month period (Figures S2–S4). Of the 62 patients (17.7%) evaluated for PV-related itching since the start of the treatment, 52 patients (83.9%) had improved, 9 patients (14.5%) had no change, and 1 patient (1.6%) was worse at month 24.

We also assessed the percentage of work time missed and the overall work impairment measured using the WPAI: PV questionnaire. The mean (SD) of activity impairment percentage in the past 7 days was 26.1% (29.4) for 86 patients at baseline and 15.5% (21.3) for 60 patients at month 24.

3.10 | Safety variables

3.10.1 | Dosing, exposure, and dose modifications

Patients received a median daily dose of 20.0 mg/day ruxolitinib, with 49.7% of patients receiving 20 to <30 mg/day and 30.3% of patients receiving 10 to <20 mg/day. The median duration of exposure to ruxolitinib was 106.0 weeks.

The majority of patients (82%) did not have dose interruptions, and 12.6% had one dose interruption. Dose increases were more prominent than reductions (56.0% vs. 45.7%, respectively). A total of 795 events required a dose change based on physician decision (60.3%) and due to AEs (28.9%) (Figure S5).

3.11 | Adverse events

Overall, 315 (90.0%) patients experienced at least one AE during the study (Table 2). The most common AEs were anemia (28.9%), followed by asthenia (11.7%), headache (11.1%), fatigue (9.7%), and pruritus (7.7%). A total of 10 patients (2.9%) died during the study; in two patients, the events (anemia) were suspected to be related to study drug. Further reported causes of death during the study included pneumonia ($n = 2$, 0.6%), sepsis, acute myelomonocytic leukemia, anemia, leukocytosis, bronchial carcinoma, myeloid leukemia, prostate cancer, cardiac arrest, post-procedural hematoma, hemorrhagic shock, COVID-19 pneumonia, respiratory failure, and hypovolemic shock ($n = 1$, 0.3% each). AEs considered to be related to study treatment were reported in 190 (54.3%) patients, and the most common study drug-related AEs were anemia ($n = 79$, 22.6%), and weight gain ($n = 21$, 6.0%). SAEs were reported in 67 patients (19.1%), with the most frequent being pneumonia ($n = 6$, 1.7%), COVID-19 pneumonia, prostate cancer, acute myocardial infarction, fall, and anemia ($n = 3$, 0.9% each). AEs requiring dose adjustment/interruption were reported in 147 (42.0%) patients. The most common all grade adverse events of special interest (AESIs) by safety topic were infections excluding tuberculosis (68.9%), erythropenia/anemia (29.4%), and bleeding (14.3%). Overall, thromboembolic events were reported in 13 (3.7%) patients during the study, whereas 19.7% of the patients had experienced an event in their medical history (Table S3). Six (1.7%) patients experienced embolic and thrombotic arterial events, including acute myocardial infarction ($n = 3$, 0.9%), coronary artery thrombosis ($n = 1$, 0.3%), ischemic stroke (n = 1, 0.3%), peripheral embolism ($n = 1$, 0.3%), and transient ischemic attack ($n = 1$, 0.3%). Five (1.4%) patients experienced embolic and thrombotic venous events, including deep vein thrombosis ($n = 1$, 0.3%), portosplenomesenteric venous thrombosis ($n = 1$, 0.3%), pulmonary embolism ($n = 2$, 0.6%), and venous thrombosis ($n = 1$, 0.3%). Two (0.6%) patients experienced embolic and thrombotic mixed arterial and venous events of unspecified vessel type, including disseminated intravascular coagulation ($n = 1$, 0.3%) and splenic infarction ($n = 1$, 0.3%). Non-melanoma skin cancer was reported in 11 patients (3.1%) during the study, of which one patient had reported non-melanoma skin cancer in medical history at baseline. Four patients (1.1%) demonstrated MACE during the study. No clinically relevant abnormalities or safety signals in laboratory evaluations, including liver and kidney function analysis or vital signs, were reported during the study. None of the patients with grade 2/3 reticulin fibrosis developed post-PV myelofibrosis according to the WHO criteria. Overall, 178 patients (50.9%) were hospitalized during the study and the median duration of hospitalization was 3 days (range: 1–52 days). The reasons for hospitalization were AE ($n = 85$, 24.3%), phlebotomy ($n = 58$, 16.6%), and other reasons ($n = 35$, 10.0%). Since weight gain is frequently observed with ruxolitinib treatment we also assessed weight gain in the study. The median percentage change in weight from baseline to month 24 was +3.56 kg (−15.0, +17.74); the patient with maximum percent change was on treatment for 103 weeks.

4 | DISCUSSION

The estimated prevalence rate for PV in Europe is 30 per 100 000 individuals.[24] The initiation of ruxolitinib treatment and positive results observed in the phase III clinical trials were of significant importance for PV patients resistant and/or intolerant to HU who previously had limited treatment options available.[21,22,25] The final analysis of this phase IV observational study provided insights into the profile, disease burden, treatment pattern, and outcomes in patients with PV who were resistant or intolerant to HU and treated with ruxolitinib in the real-world setting in Europe. Patients received a median dose of 20.0 mg/day ruxolitinib during the study, which is in line with the recommended starting dose for PV. Treatment with ruxolitinib lowered hematocrit levels to <45% rapidly and sustainably in patients with PV who are resistant or intolerant to HU, which confirms

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 All grades adverse events (AEs).

Preferred term, *n* (%)	Ruxolitinib *N* = 350
Total AEs (≥5%)	315 (90.0)
Anemia	101 (28.9)
Asthenia	41 (11.7)
Headache	39 (11.1)
Fatigue	34 (9.7)
Pruritus	27 (7.7)
Arthralgia	25 (7.1)
Weight gain	25 (7.1)
Diarrhea	23 (6.6)
Hypertension	21 (6.0)
Nasopharyngitis	21 (6.0)
Constipation	18 (5.1)
Dizziness	18 (5.1)
Dyspnea	18 (5.1)
AEs considered to be related to study drug (≥1.5%)	190 (54.3)
Anemia	79 (22.6)
Weight gain	21 (6.0)
Fatigue	16 (4.6)
Headache	15 (4.3)
Diarrhea	10 (2.9)
Thrombocytopenia	9 (2.6)
Asthenia	8 (2.3)
Thrombocytosis	6 (1.7)
Blood cholesterol increased	6 (1.7)
Nasopharyngitis	6 (1.7)
Abdominal distension	6 (1.7)
Pruritus	6 (1.7)
Vertigo	6 (1.7)
Serious AEs (≥4%)	67 (19.1)
Infections and infestations	21 (6.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	16 (4.6)
AEs requiring dose adjustment or study drug interruption (≥5%)	147 (42.0)
Anemia	62 (17.7)
AEs requiring significant additional therapy (≥3%)	232 (66.3)
Anemia	20 (5.7)
Hypertension	13 (3.7)
Bronchitis	13 (3.7)
Most common AEs of special interest by safety topic (≥3%)	
Infections excluding tuberculosis	241 (68.9)
Erythropenia/anemia	103 (29.4)
Bleeding	50 (14.3)
Dizziness	32 (9.1)
Lipid abnormalities	26 (7.4)
Urinary tract infections	25 (7.1)
Weight gain	25 (7.1)
Other hemorrhage events	24 (6.9)
Hypertension	22 (6.3)
Long-term safety data, including secondary malignancies—second primary malignancies	21 (6.0)
Bruising	21 (6.0)
Thrombocytopenia	14 (4.0)
Thromboembolic events	13 (3.7)
Herpes zoster	12 (3.4)
Elevated Transaminases	11 (3.1)
Fracture	11 (3.1)
Non-melanoma skin cancers	11 (3.1)
Pneumonia	11 (3.1)

Note: *n*, number of subjects where data were recorded; *N*, number of subjects in the relevant analysis set. A patient with multiple occurrences of an AE is counted only once in the AE category. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. MedDRA version 24.0, Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used for reporting.

findings from the RESPONSE and RESPONSE-2 studies.[21,22,25] The hematocrit control definition used in our study was of a composite primary endpoint from RESPONSE-2.[22] This definition did not allow occurrence of more than one phlebotomy eligibility (confirmed hematocrit >45% and at least 3% higher than baseline or >48%) in the first 8 weeks of ruxolitinib treatment and did not allow phlebotomy eligibility during the rest of the observation period of 22 months. This definition was strict and conservative when applied in the real-world setting, yet the majority of patients were still responding after 24 months. Additionally, ∼85% of patients treated with ruxolitinib were phlebotomy-free and ∼78% were without splenomegaly during the study, further highlighting the real-world benefit provided by ruxolitinib treatment. In this population of mainly high-risk PV patients treated with HU, it was observed that only 61.4% patients received acetylsalicylic acid and 9.7% patients received clopidogrel as concomitant medication after starting treatment with ruxolitinib. This is surprising and in line with the observation that classic cardiovascular risk factors are not regularly checked in this population despite the high-risk cardiovascular profile of these patients and the cardiovascular risk is insufficiently treated which could have affected the outcome in terms of cardiovascular events. Pruritus in PV is associated with a substantial disease burden, leading to a reduced quality of life.[26] This is the first study to systematically assess the PSIS scores in patients with PV during treatment with ruxolitinib and we observed considerable and immediate reduction of pruritus after the start of treatment. Moreover, ruxolitinib led to an improved total symptom burden and

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

quality of life as reflected by other quality of life measures, including MPN-SAF TSS, EQ-5D-5L, and WPAI: PV scores. Thus, patients treated with ruxolitinib experienced improvements in all PV-associated symptoms, including pruritus and fatigue. This outcome emphasizes the importance of reducing PV symptoms in therapeutic practice.

There were few thromboembolic events and few MACE reported during the study. The data on thromboembolic events, although from a short 24-month follow-up, was in line with the results from MAJIC-PV study (ruxolitinib = 93; best available therapy = 87) in which 74 patients were resistant/intolerant to HU in the ruxolitinib arm. Thromboembolic event-free survival was significantly improved with ruxolitinib (hazard ratio [HR], 0.56; 95% CI, 0.32 to 1.00; $p = .05$).[27] The overall safety profile observed in the study was consistent with that observed in prior studies of ruxolitinib, with no new safety signals identified.[21,22,25,28]

Overall, the results from this observational study build on the data and evidence from the earlier pivotal studies RESPONSE and RESPONSE-2 and provide real-world evidence of the efficacy and safety of ruxolitinib in clinical practice. Hematocrit control was achieved in 60.0% of patients in the RESPONSE study at week 32 and in 62% of patients in the RESPONSE-2 study at week 28. In our study, hematocrit levels dropped rapidly in the first 12 weeks and were sustained throughout the observation period to 24 months with 68.2% of patients achieving hematocrit control at month 24 (92.3% patients achieving hematocrit value <45%), which is considerably good control compared to RESPONSE and RESPONSE-2 studies.[21,22,25,28] Our study demonstrated that in routine clinical practice, PV symptoms are not being captured using standardized questionnaires in the majority of patients, and there is a need for more routine use of patient-reported outcome questionnaires. Despite the high-risk criteria met at baseline (70% of patients aged >60 years and 19.7% of patients with a history of thromboembolic events), data on cardiovascular risk parameters such as weight, BMI, and cholesterol were not available in approximately 75% of patients, highlighting the need for more awareness and analysis of these parameters to conduct more comprehensive risk analysis using systematic coronary risk evaluation (SCORE) and Framingham models. Therefore, a multidisciplinary approach to treatment of PV patients is warranted, consisting of a team that includes expert cardiologists.

During the study, rates of transformation to myelofibrosis and acute myelogenous leukemia were consistent with those expected in a high-risk population of patients with PV[21,29] and in those with resistance to HU.[18] Acute myeloid leukemia led to death in two patients. The COVID-19 pandemic had minimal impact on our study milestones; however, COVID-19 pneumonia led to death in one patient, and COVID-19 pneumonia (three [0.9%] patients) and COVID-19 infections (two [0.6%] patients) were among the most commonly reported SAEs. These events were not suspected to be related to ruxolitinib. Of note, 4.9% of patients at the study entry had a confirmed diagnosis of non-melanoma skin cancer, while neoplasms (4.6%) and infections (6%), unrelated to ruxolitinib, were reported during the study. Weight gain is a known phenomenon related to ruxolitinib treatment and the increase in weight from baseline to month 24 and treatment-related AE weight gain reported in 21 (6.0%) patients confirms previous observations.[22]

The advantage of using data obtained from non-interventional studies is that they depict normal clinical settings under real-life conditions and therefore are more representative of both the study population of interest and the clinical outcomes under observation. However, the main foreseen limitations for this observational study were attributed to the observational and partially retrospective character of the study design and involved patient selection bias, lack of control group, incomplete or missing data, difficulty in interpreting or verifying documented information, and variability in the quality of documentation among health care personnel for the retrospective cohort. Every effort was made to confront the reality of inherent bias in patient selection and the difficulty in making sound conclusions introduced by the inability to obtain all pertinent data, aiming at ensuring transparency in terms of the study conduct and data analysis.

This first large scale observational study that assessed real-world benefit for 24 months in patients with PV who were resistant/intolerant to HU demonstrated that ruxolitinib treatment maintained durable hematocrit control with a decrease in the number of phlebotomies, reduction in splenomegaly, improvement in PV symptoms, and improvement in quality of life in the majority of patients. In a real-world setting, ruxolitinib was generally well tolerated, and the safety profile was in line with that reported in previous studies.

AUTHOR CONTRIBUTIONS

Paola Di Matteo and Mike Zuurman conceived and designed the study; Alexandre Theocharides, Heinz Gisslinger, Timothy Devos, Eric Lippert, Damianos Sotiropoulos, Miklos Egyed, Valerio De Stefano, Vincenzo Accurso, Amir Iqbal, Anders E.A. Dahm, Regina Garcia Delgado, Nathan Cantoni, and Peter AW te Boekhorst provided study materials or patients; PAD and Mike Zuurman collected data; Amir Iqbal and Erik Houtsma extracted the data; Erik Houtsma created the figures and tables; Paola Di Matteo, Mike Zuurman, Peter AW te Boekhorst, and Alexandre Theocharides analyzed and interpreted the data; all authors wrote the manuscript; and all authors finally approved the manuscript.

ACKNOWLEDGMENTS

The authors thank all the patients and investigators who participated in the study. The authors acknowledge Dr Riddhi Sharma, BDS, MSc of Novartis Healthcare Pvt. Ltd. for providing medical writing assistance with this manuscript.

FUNDING INFORMATION

This study was funded by Novartis Pharma AG/Region Europe. Alexandre P.A. Theocharides was supported by the Professor Dr. Max Cloëtta Foundation.

CONFLICT OF INTEREST STATEMENT

AT receives grants or contracts from Prof. Dr. Max Cloëtta foundation, honoraria for presentations and manuscript writing from

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Novartis, support for attending meetings and/or travel from Novartis, and own stock from Novartis. HG receives grant from AOP Orphan, consulting fees from AOP Orphan and BMS/Celgene, payment or honoraria from AOP Orphan, Novartis, and BMS/Celgene, payment for expert testimony from AOP Orphan, and reports leadership/fiduciary role with MPN Austria. VDS is on advisory board of AOP Health, BMS/Celgene, Grifols, GSK, Novartis, SOBI, and Takeda and receives speaker fee from AbbVie, Alexion, Amgen, BMS/Celgene, Novartis, Sanofi, and Takeda. AI receives honoraria from BMS/Celgene, Incyte, Novartis, and Pfizer. TD reports consulting or advisory role from AbbVie, BMS/Celgene, Incyte and Novartis. EL receives honoraria for presentations from Novartis and Incyte, and support for attending meetings and/or travel from Novartis. RGD receives consulting fees from Novartis, honoraria from Novartis and Janssen, payment for expert testimony from Novartis and Janssen, and support for attending meetings from Novartis, and is on advisory board of Novartis. NC receives consulting fees from BMS/Celgene and Novartis, honoraria for lectures and presentations from AbbVie, Astra Zeneca, BMS/Celgene, Gilead, Novartis, OrPha Swiss, Pfizer, Sandoz, Sanofi-Aventis, and Takeda/Shire, support for attending meetings from AbbVie, Amgen, BMS/Celgene, Gilead, and Roche, is on advisory board of AbbVie, Alexion, Amgen, BMS/Celgene, Gilead, Incyte, Janssen-Cilag, Novartis, OrPha Swiss, Roche, Sandoz, Sanofi-Aventis, and Takeda/Shire, and councilor (unpaid) from Stiftung MPN Forschung Schweiz (Foundation). AEAD reports consulting engagement from Pfizer, honoraria for lectures from Pfizer and Novartis, and is on advisory board of Bristol-Myers-Squibb/Pfizer. EH, AS, AI, PDM, and MZ are employees of Novartis. PAWteB receives consulting fees from Novartis and AbbVie and honoraria from Novartis. ME, DS, and VA declare no competing interests.

DATA AVAILABILITY STATEMENT

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The availability of this trial data is according to the criteria and process described on www.clinicalstudydatarequest.com.

ORCID

Heinz Gisslinger https://orcid.org/0000-0002-0295-7629
Alessandra Iurlo https://orcid.org/0000-0002-4401-0812
Timothy Devos https://orcid.org/0000-0002-6881-417X
Miklos Egyed https://orcid.org/0000-0002-5513-5880

REFERENCES

1. Spivak JL. Myeloproliferative neoplasms. *New Engl J Med*. 2017;376(22):2168-2181.
2. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia*. 2013;27(9):1874-1881.
3. Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol*. 2005;23(10):2224-2232.
4. Griesshammer M, Gisslinger H, Mesa R. Current and future treatment options for polycythemia vera. *Ann Hematol*. 2015;94(6):901-910.
5. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic recommendations in polycythemia vera based on polycythemia vera study group protocols. *Semin Hematol*. 1986;23(2):132-143.
6. Stuart BJ, Viera AJ. Polycythemia vera. *Am Fam Physician*. 2004;69(9):2139-2144.
7. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international internet-based survey of 1179 MPD patients. *Cancer*. 2007;109(1):68-76.
8. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood*. 2013;121(23):4778-4781.
9. Kiladjian JJ, Winton EF, Talpaz M, Verstovsek S. Ruxolitinib for the treatment of patients with polycythemia vera. *Expert Rev Hematol*. 2015;8(4):391-401.
10. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368(1):22-33.
11. Panova-Noeva M, Marchetti M, Russo L, et al. ADP-induced platelet aggregation and thrombin generation are increased in essential thrombocythemia and polycythemia vera. *Thromb Res*. 2013;132(1):88-93.
12. Patrono C, Rocca B, De Stefano V. Platelet activation and inhibition in polycythemia vera and essential thrombocythemia. *Blood*. 2013;121(10):1701-1711.
13. Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol*. 2011;29(6):761-770.
14. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an international prognostic score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). *Blood*. 2012;120(26):5128-5133. quiz 5252.
15. Geyer H, Scherber R, Kosiorek H, et al. Symptomatic profiles of patients with polycythemia vera: implications of inadequately controlled disease. *J Clin Oncol*. 2016;34(2):151-159.
16. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. *J Clin Oncol*. 2012;30(33):4098-4103.
17. Randi ML, Ruzzon E, Luzzatto G, Tezza F, Girolami A, Fabris F. Safety profile of hydroxyurea in the treatment of patients with Philadelphia-negative chronic myeloproliferative disorders. *Haematologica*. 2005;90(2):261-262.
18. Alvarez-Larrán A, Pereira A, Cervantes F, et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. *Blood*. 2012;119(6):1363-1369.
19. Alvarez-Larrán A, Kerguelen A, Hernández-Boluda JC, et al. Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythaemia vera. *Br J Haematol*. 2016;172(5):786-793.
20. Marchetti M, Vannucchi AM, Griesshammer M, et al. Appropriate management of polycythaemia vera with cytoreductive drug therapy: European LeukemiaNet 2021 recommendations. *Lancet Haematol*. 2022;9(4):e301-e311.
21. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

22. Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. *Lancet Oncol*. 2017;18(1):88-99.
23. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics*. 1993;4(5):353-365.
24. Moulard O, Mehta J, Fryzek J, Olivares R, Iqbal U, Mesa RA. Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union. *Eur J Haematol*. 2014;92(4):289-297.
25. Verstovsek S, Vannucchi AM, Griesshammer M, et al. Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial. *Haematologica*. 2016;101(7):821-829.
26. Harrison CN, Koschmieder S, Foltz L, et al. The impact of myeloproliferative neoplasms (MPNs) on patient quality of life and productivity: results from the international MPN landmark survey. *Ann Hematol*. 2017;96(10):1653-1665.
27. Harrison CN, Nangalia J, Boucher R, et al. Ruxolitinib versus best available therapy for polycythemia vera intolerant or resistant to hydroxycarbamide in a randomized trial. *J Clin Oncol*. 2023;41(19):3534-3544.
28. Cattaneo D, Iurlo A. Immune dysregulation and infectious complications in MPN patients treated with JAK inhibitors. *Front Immunol*. 2021;12:750346.
29. Finazzi G, Caruso V, Marchioli R, et al. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood*. 2005;105(7):2664-2670.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Theocharides A, Gisslinger H, De Stefano V, et al. Ruxolitinib in patients with polycythemia vera resistant and/or intolerant to hydroxyurea: European observational study. *Eur J Haematol*. 2023;1-13. doi:10.1111/ejh.14124

16000609, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejh.14124 by EVIDENCE AID - BELGIUM, Wiley Online Library on [12/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License