Ruxolitinib Re-Treatment in Patients with Myelofibrosis: Real-World Evidence on Patient Characteristics and Outcomes

Aaron T. Gerds\textsuperscript{a}, Jingbo Yu\textsuperscript{b} Robyn M. Scherber\textsuperscript{b} Dilan Paranagama\textsuperscript{b} Jonathan K. Kish\textsuperscript{c} Jay Visaria\textsuperscript{d} Mukul Singhal\textsuperscript{d} Srdan Verstovsek\textsuperscript{e} Naveen Pemmaraju\textsuperscript{e}

\textsuperscript{a}Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; \textsuperscript{b}Incyte Corporation, Wilmington, DE, USA; \textsuperscript{c}Cardinal Health Specialty Solutions, Dublin, OH, USA; \textsuperscript{d}HealthCore, Inc., Wilmington, DE, USA; \textsuperscript{e}The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Abstract
Ruxolitinib is an FDA-approved treatment of intermediate- and high-risk myelofibrosis. In the phase 3 COMFORT studies, ruxolitinib reduced spleen volume in patients with myelofibrosis, with a median time to response of 3 months. However, nearly 20% of patients discontinued by month 4 with few treatment options available following discontinuation of ruxolitinib treatment. In this study, 2 independent patient care data sources were queried (Cardinal Health Oncology Provider Extended Network [OPEN] and HealthCore Integrated Research Environment [HIRE\textsuperscript{e}]), and a retrospective review of medical charts was conducted. Patients aged ≥18 years with a diagnosis of myelofibrosis (primary or secondary), use of ruxolitinib for myelofibrosis, and documented physician-directed ruxolitinib interruption were included. Among 26 included patients, pre-interruption median (interquartile range [IQR]) ruxolitinib treatment duration was 123 (57–391, OPEN) and 110 (37–148, HIRE) days. Half the patients interrupted treatment within 3 months, commonly for adverse events (42% and 71%, respectively). After restarting ruxolitinib, median (IQR) re-treatment duration was 196 (54–553) and 166 (108–262) days, respectively. Consistent with previous reports, symptoms and spleen size improved in (OPEN/HIRE) 45%/43% and 40%/33% of evaluable patients, respectively. Further studies investigating the management of dose modifications and interruptions are needed to optimize benefit from ruxolitinib therapy.

Introduction
Ruxolitinib is a Janus kinase (JAK)1/JAK2 inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of intermediate- or high-risk myelofibrosis (MF) [1]. In the phase 3 COMFORT studies, ruxolitinib reduced spleen volume in patients with MF (primary endpoint), with a median time to response of 3 months [2, 3]. Ruxolitinib discontinuation rates in these studies were 14% (follow-up duration, 36 weeks) to 18% (follow-up duration, 48 weeks), and approximately 50% of patients discontinued ruxolitinib treatment by 3
Medical charts for 26 patients were included in this analysis (OPEN, N = 12; HIRE, N = 14; Table 1). Median (IQR) age at the time of ruxolitinib treatment interruption was 69 (60–72) years in the OPEN analysis set and 73 (69–76) years in the HIRE analysis set.

Median (IQR) ruxolitinib treatment duration before interruption was 123 (57–391) days among patients from OPEN (shown in Fig. 1) and 110 (37–148) days among those from HIRE, with half of the patients (50.0%) from each analysis set experiencing a treatment interruption within 3 months of initiation. The most common reason for treatment interruption in both analysis sets was adverse events (AEs; OPEN, 41.7%; HIRE, 71.4%), followed by, in the OPEN patients, initiation of alternative treatment (16.7%), disease progression (8.3%), no response (8.3%), loss of response (8.3%), patient request (8.3%), and aggressive skin cancer surgery (8.3%), and in HIRE patients, enrollment in clinical trial (14.3%), interruption due to course of antibiotics (7.1%), and mouth sores attributed by the patient to ruxolitinib but not visible to the provider (7.1%). AEs that led to ruxolitinib interruptions were thrombocytopenia in 33.3% and 50.0% of patients in OPEN and HIRE, respectively; anemia in 8.3% and 35.7%, respectively; and among HIRE patients, neutropenia (7.1%), ST-elevation myocardial infarction (7.1%), and acute kidney injury with pneumonia (7.1%).

After ruxolitinib was restarted, patient median (IQR) re-treatment duration was 196 (54–553) days in patients from OPEN and 166 (108–262) days in patients from HIRE. The reasons provided for reintroducing ruxolitinib therapy in the OPEN analysis set were unavailability of an alternative treatment strategy (25.0%), resolution of AEs (16.7%), worsening symptoms (16.7%), increased spleen size (8.3%), and others (33.3%); and in HIRE, reasons for re-starting ruxolitinib were worsening or persistent symptoms (46.7%), resolution of toxicity (46.7%), splenomegaly in some patients on reinitiation of ruxolitinib after treatment interruption; however, data on patient outcomes after reinitiation remain limited [7, 8, 10]. In the current era of novel JAK inhibitors, identifying indicators for treatment changes and dose optimization remain major challenges. This study describes ruxolitinib treatment patterns and clinical outcomes of patients with MF with ruxolitinib re-treatment after interruption in community-based clinical practices.

Methods

A retrospective review of medical charts from 2 national research networks was conducted in parallel. Cardinal Health Oncology Provider Extended Network (OPEN), which uses its database of medical hematology/oncology providers in US community-based practice to perform medical chart reviews, and HealthCore Integrated Research Environment (HIRE®), a repository for administrative claims and provider data from which medical charts can be targeted and collected, were queried to identify patients with MF meeting study entry criteria: age ≥18 years; primary, post-polycythemia vera, or post-essential thrombocytopenia MF diagnosis between January 1, 2012, and December 31, 2016 (OPEN), or July 1, 2013, and November 30, 2017 (HIRE); use of ruxolitinib for MF; and documented physician-directed ruxolitinib interruption. Data on ruxolitinib treatment patterns before, during, and after treatment interruption; reason for the interruption; and MF-related symptoms and spleen response on re-treatment were abstracted by the treating physician at participating sites, collected, and analyzed. Data were summarized using descriptive statistics. Frequencies and percentages were reported for categorical variables; median and interquartile range (IQR) were calculated for continuous variables.

Results

Medical charts for 26 patients were included in this analysis (OPEN, N = 12; HIRE, N = 14; Table 1). Median (IQR) age at the time of ruxolitinib treatment interruption was 69 (60–72) years in the OPEN analysis set and 73 (69–76) years in the HIRE analysis set.
aly (40.0%), failure of alternative treatment (6.7%), and others (33.3%). The most frequent ruxolitinib dose at re-initiation was 15 mg twice daily (BID) (41.7% of patients) in the OPEN patients and 5 mg once daily, 5 mg BID, and 10 mg BID (each 14.3%) in the HIRE patients (shown in Table 2). No patient in the HIRE analysis set received a ruxolitinib dose higher than 10 mg BID.

After patients restarted treatment with ruxolitinib, symptoms improved in 5 of 11 (45.5%) and 3 of 7 (42.9%) evaluable patients in the OPEN and HIRE analysis sets, respectively. Spleen size reductions were observed in 4 of 10 (40.0%) and 3 of 9 (33.3%) evaluable patients in the OPEN and HIRE analysis sets, respectively.

**Discussion**

The results of this study are consistent with those of previous reports. In a phase 3b expanded access study (JUMP), among 207 patients with ≥1 ruxolitinib dose in-
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Table 2. Ruxolitinib dose at reinitiation

| Ruxolitinib dose | OPEN (N = 12) | HIRE (N = 14) |
|------------------|---------------|---------------|
| Median (IQR) total daily dose, mg | 40.0 (10.0–40.0) | 15.0 (10.0–20.0) |
| Dose, n (%) | | |
| 25 mg BID | 1 (8.3) | 0 |
| 20 mg BID | 1 (8.3) | 0 |
| 15 mg BID | 5 (41.7) | 0 |
| 10 mg BID | 2 (16.7) | 2 (14.3) |
| 7.5 mg BID | 0 | 1 (7.1) |
| 5 mg BID | 1 (8.3) | 2 (14.3) |
| 20 mg QD | 0 | 1 (7.1) |
| 15 mg QD | 0 | 1 (7.1) |
| 10 mg QD | 0 | 1 (7.1) |
| 5 mg QD | 2 (16.7) | 2 (14.3) |
| Others | 0 | 1* (7.1) |
| Missing | 0 | 3 (21.4) |

BID, twice daily; HIRE, HealthCore Integrated Research Environment; IQR, interquar tile range; OPEN, Oncology Provider Extended Network; QD, once daily. * One patient was receiving 10 and 20 mg alternate daily doses.

In spleen volume (primary endpoint) was approximately 3 months [3]; however, only half of the patients in the current analysis received ≥3 months of ruxolitinib treatment before initial interruption. The presence of ruxolitinib discontinuation syndrome, in which there is a rebound of MF-related symptoms after cessation of ruxolitinib, has been posited to be evidence of ongoing treatment benefit at the time of ruxolitinib discontinuation [14, 15], and may identify patients with the potential to benefit from ruxolitinib re-treatment. Notably, requirement of a ruxolitinib washout period prior to initiation of another JAK inhibitor in clinical trials may affect baseline measurements of spleen size and symptom burden, thereby potentially impacting the achievement of study endpoints.

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BID, twice daily; HIRE, HealthCore Integrated Research Environment; IQR, interquar tile range; OPEN, Oncology Provider Extended Network; QD, once daily. * One patient was receiving 10 and 20 mg alternate daily doses.

In conclusion, findings from this study demonstrate the potential benefit of ruxolitinib re-treatment for some patients with MF in a real-world clinical setting. Future studies are needed to investigate proper management of dose modifications and interruptions to ensure that patients derive optimal therapeutic benefit from ruxolitinib therapy.

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Statement of Ethics

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Because of the retrospective nature and the use of deidentified patient data, the current analysis was exempt from ethical approval, and informed consent was not required per the approving institutional review boards (WCG IRB [Cardinal Health] and New England IRB [HealthCore]).

Conflict of Interest Statement

A.T.G. has a consulting or advisory role with Incyte Corporation, AstraZeneca/MedImmune, CTI, Apexx Oncology, and Celgene; received research funding from Pfizer, CTI, Incyte Corporation, Roche/Genentech, Gilead Sciences, Imago Biosciences, Sierra...
Oncology, and Celgene; and equity ownership in Samus Therapeutics. J.Y., R.M.S., and D.P. are employees and stockholders of Incyte Corporation. J.K.K. is an employee of Cardinal Health, which received study funding from Incyte Corporation. J.V. and M.S. are employees of HealthCore, Inc., which received study funding from Incyte Corporation. S.V. received research support from Incyte Corporation, Roche, NS Pharma, Celgene, Gilead, Promedior, CTI BioPharma Corp., Genentech, Blueprint Medicines Corp., Novartis, Sierra Oncology, Pharma Essentia, AstraZeneca, Ital Pharma, and Protagonist Therapeutics and is a paid consultant for Constellation, Pragmatist, Sierra Oncology, Incyte Corporation, Novartis, and Celgene. N.P. has a consulting role or received honorarium from AbbVie, Celgene, Stemline, Incyte Corporation, Pacylex, Roche Diagnostics, Blueprint Medicines Corporation, and LFB Novartis and received research support from AbbVie, Novartis, Celgene, Stemline, MustangBio, Samus, Cellestics, Plexxikon Daiichi-Sankyo, Affymetrix, and SagerStrong Foundation.

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Author Contributions

A.T.G., J.Y., R.M.S., D.P., J.K.K, J.V., M.S., S.V., and N.P. designed the study, analyzed the data, and participated in the interpretation of the data, as well as drafting and revising the manuscript. All authors read and approved of the final manuscript.

Data Availability Statement

Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase 1 studies) for which the product and indication have been approved on or after 2020 in at least one major market (e.g., USA, EU, and JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte’s clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.