

389 Safety and Tolerability of Fedratinib (FEDR), an Oral Inhibitor of Janus Kinase 2 (JAK2), in Patients with Intermediate- or High-Risk Myelofibrosis (MF) Previously Treated with Ruxolitinib (RUX): Results from the Phase 3b FREEDOM Trial

Authors:

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INTRODUCTION:

Ruxolitinib (RUX) has demonstrated efficacy in patients (pts) with MF, but many pts discontinued (D/C) RUX due to loss of response or treatment (Tx)-related cytopenias. Fedratinib (FEDR) is an oral, selective JAK2 inhibitor approved for Tx of pts with MF, including those previously treated with RUX. In the single-arm, phase 2 JAKARTA2 trial of FEDR 400 mg/day (d) in pts with MF resistant/intolerant to prior RUX, 31% of pts achieved a spleen volume response and 27% achieved a symptom response with FEDR. The most common adverse events (AEs) in JAKARTA2 were gastrointestinal (GI) events, including diarrhea in 62% of pts, nausea in 56%, and vomiting in 41%. A temporary clinical hold was placed on FEDR in 2013 due to suspected cases of Wernicke's encephalopathy (WE).

The ongoing, single-arm, phase 3b FREEDOM trial (NCT03755518) further evaluates the safety and efficacy of FEDR in pts with MF previously treated with RUX. Unlike JAKARTA2 and other early FEDR trials, FREEDOM includes prospective strategies for preventing or mitigating GI AEs, thiamine level decreases, and potential WE. We investigated the safety of FEDR 400 mg/d in FREEDOM, including the effectiveness of these strategies.

METHODS:

Eligible pts are aged ≥ 18 years with DIPSS-defined intermediate- or high-risk, primary or post-PV/ET MF, ECOG PS ≤ 2 , platelet count $\geq 50 \times 10^9/L$, and spleen volume $\geq 450 \text{ cm}^3$ by MRI/CT or palpable spleen $\geq 5 \text{ cm}$ below the left costal margin (LCM). Pts must have previously received RUX for ≥ 3 months (mo), or for ≥ 28 d with development of RBC transfusion requirement (≥ 2 units/mo for 2 mo) or grade ≥ 3 thrombocytopenia, anemia, hematoma, or hemorrhage. All pts received FEDR 400 mg QD in continuous 28d cycles. AE mitigation strategies include prophylactic and symptomatic use of anti-nausea/vomiting and anti-diarrheal Tx, thiamine supplementation, FEDR dosing modifications, and administration of FEDR with food. All pts who received ≥ 1 FEDR dose were evaluated for safety. AEs were coded using MedDRA v24.0 and graded (G) by CTCAE v5.0.

RESULTS:

At data cutoff (April 9, 2021), 34 pts had been enrolled and 16 pts continued to receive FEDR. Reasons for FEDR Tx D/C in > 1 pt were lack of efficacy ($n = 5$) AEs ($n=4$; 1 was Tx-related [G3 thrombocytopenia]), disease progression ($n = 2$), pt decision ($n = 2$), and to undergo transplant ($n = 2$). Median FEDR Tx duration was 28.3 weeks (range 1.6–101.3); 20 pts (59%) had received > 6 Tx cycles and 14 pts (41%) completed > 12 cycles. Median average FEDR dose was 400 mg/d (range

298–400). At BL, median (range) age was 68.5 years (49–82), time from MF diagnosis was 3.4 years (0.1–17.4), and spleen size was 15 cm (3–31). Most pts (62%) had primary MF, and all pts had received ≥ 3 mo of prior RUX Tx; the most common reason for prior RUX D/C was loss of response/Tx failure (41%).

During FEDR Tx, 22 pts (65%) received ondansetron and 11 (32%) received loperamide. GI AEs reported in $> 10\%$ of pts were constipation (47%), diarrhea (35%), nausea (26%), abdominal pain (24%), and vomiting (18%). The frequency of nausea, vomiting, and diarrhea decreased as Tx continued (Figure). Most GI AEs were G1/2 (including all events of nausea, vomiting and diarrhea) and there were no Tx-related G3/4 GI AEs. No pt required FEDR dose-reduction, interruption, or D/C due to a Tx-related GI AE

Overall, Tx-related G3/4 AEs were reported in 11 pts (32%), including anemia in 7 pts (21%), and neutropenia, thrombocytopenia, and hyperkalemia in 2 pts each (6%). The cases of hyperkalemia occurred in the setting of acute renal failure or of relevant concomitant conditions.

At BL, 1 pt had a thiamine level below the lower limit of normal (LLN; 70 nmol/L); thiamine level was normalized before the pt received FEDR Tx. Thiamine levels dropped below the LLN during FEDR Tx for 4 pts between cycles 2–3 (and for 1 pt at end of Tx); levels returned to normal for these pts with thiamine supplementation and did not require FEDR interruption or reduction. Five other pts received prophylactic thiamine supplementation. There were no reported cases of WE.

CONCLUSIONS:

FEDR was generally well tolerated. These data suggest the frequency and severity of GI AEs may be reduced via early implementation of GI prophylaxis. Use of GI-directed therapies may have increased the incidence of low-grade constipation. Monitoring thiamine levels before FEDR initiation and periodically during FEDR therapy is recommended.