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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Efficacy and Safety of Fedratinib in Patients with Myelofibrosis Previously Treated with Ruxolitinib: Results from the Phase 3 Randomized FREEDOM2 Study

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Introduction

Patients (pts) with myelofibrosis (MF) treated with the Janus kinase inhibitor (JAKi) ruxolitinib (RUX) show spleen volume reduction (SVR) and symptom reduction. However, most develop RUX intolerance or relapsed/refractory (R/R) disease and survival rates after RUX discontinuation are poor. Fedratinib (FEDR) delivered SVR and symptom reduction in the JAKARTA2 and FREEDOM studies (C Harrison et al. *Am J Hematol* 2020; V Gupta et al. *Blood* 2022). FREEDOM2 (NCT03952039) was a phase 3, open-label, randomized study to evaluate the safety and efficacy of FEDR compared with best available therapy (BAT) in pts with MF previously treated with RUX.

Methods

Pts aged ≥ 18 years with primary, post-polycythemia vera, or post-essential thrombocythemia MF with Dynamic International Prognostic Scoring System (DIPSS) score ≥ intermediate-2, splenomegaly (≥ 450 cm ^{3}), platelets ≥ 50 x 10 ^{9}/L, peripheral blood myeloblasts < 5%, and normal baseline thiamine, R/R or intolerant to RUX, were randomized 2:1 to FEDR 400 mg/day or BAT in 28-day cycles, with stratification by spleen size, platelet count, and RUX R/R vs intolerant. Crossover to FEDR was permitted for progressive disease or after cycle 6 (EOC6) response assessment. Pts were treated until intolerance or lack of efficacy and followed-up every 3 months until death, withdrawal of consent, or study closure. The primary endpoint was SVR ≥ 35% (SVR35) at EOC6; secondary endpoints included symptom response (≥ 50% reduction in total symptom score measured by Myelofibrosis Symptom Assessment Form), SVR ≥ 25% (SVR25), durability of SVR and symptom response, and safety.

Results

Overall, 201 pts were initially randomized and treated, 134 and 67 pts in the FEDR and BAT arms, respectively; subsequently, 46 (68.7%) pts from the BAT arm crossed over to FEDR. Median (interquartile range) age was 70 (64-74) years, 52.2% were male, and most had primary MF (54.7%) and intermediate-2 DIPSS risk (76.1%). Assessed by aggregated group, most pts in the BAT arm received RUX (70.1%), hydroxyurea (10.4%), or RUX plus hydroxyurea (7.5%).

At the data cutoff of December 27, 2022 (median follow-up, 15 months), pts receiving FEDR had significantly higher rates of SVR35 at EOC6 compared with BAT (35.8% vs 6.0%; $P < 0.0001$), as well as superior SVR25 at EOC6 and SVR35 during the

full treatment course (**Table, Figure**). SVR35 benefit with FEDR was observed across subgroups. The FEDR arm also showed higher rates of symptom response at EOC6 compared with BAT (34.1% vs 16.9%; $P = 0.0033$; **Table**).
Median treatment duration was 43 weeks of FEDR and 24.7 weeks of BAT. During the first 6 cycles in the safety population: 70 (52.2%) pts on FEDR and 20 (29.9%) pts on BAT had dose interruption/reduction; median time to first reduction/interruption was 44.0 days for FEDR and 56.5 days for BAT. Treatment-emergent adverse events (TEAEs) leading to permanent treatment discontinuation occurred in 13 (9.7%) and 4 (6.0%) pts in the FEDR and BAT arms, respectively, during the first 6 cycles.
During the first 6 cycles, 132 (98.5%) pts on FEDR and 65 (97.0%) pts on BAT had ≥ 1 TEAE; treatment-related AEs (TRAEs) occurred in 109 (81.3%) and 23 (34.3%) pts in the FEDR and BAT arms, respectively. The most frequently occurring TRAEs with FEDR were diarrhea (38.1% FEDR vs 0.0% BAT) and nausea (32.1% FEDR vs 1.5% BAT); most cases were grade 1/2. Grade 3/4 TRAEs occurred in 52 (38.8%) pts in FEDR and 8 (11.9%) pts in BAT arms, most frequently thrombocytopenia (11.9% FEDR vs 3.0% BAT) and anemia (9.0% FEDR vs 9.0% BAT). In the FEDR arm, 22 (16.4%) pts had thiamine levels below normal range, compared with 2 (3.0%) pts receiving BAT; most cases occurred prior to the study amendment of prophylactic thiamine supplementation. There was a single grade 1 case of suspected Wernicke's encephalopathy in the FEDR arm during cycle 3, which resolved fully 24 hours after thiamine supplementation (0 cases in BAT arm). Two pts each in FEDR and BAT arms had TRAEs of infection.

Conclusions

In this phase 3 randomized study in pts with MF and prior RUX treatment, FEDR demonstrated superior SVR and symptom response rates compared with BAT. Most pts on BAT received RUX, highlighting a clinical need for an alternative JAKi. Differences in AE and discontinuation rates in the first 6 cycles are consistent with other studies comparing JAKi with BAT. AE mitigation strategies were effective and no new safety concerns for FEDR were identified.

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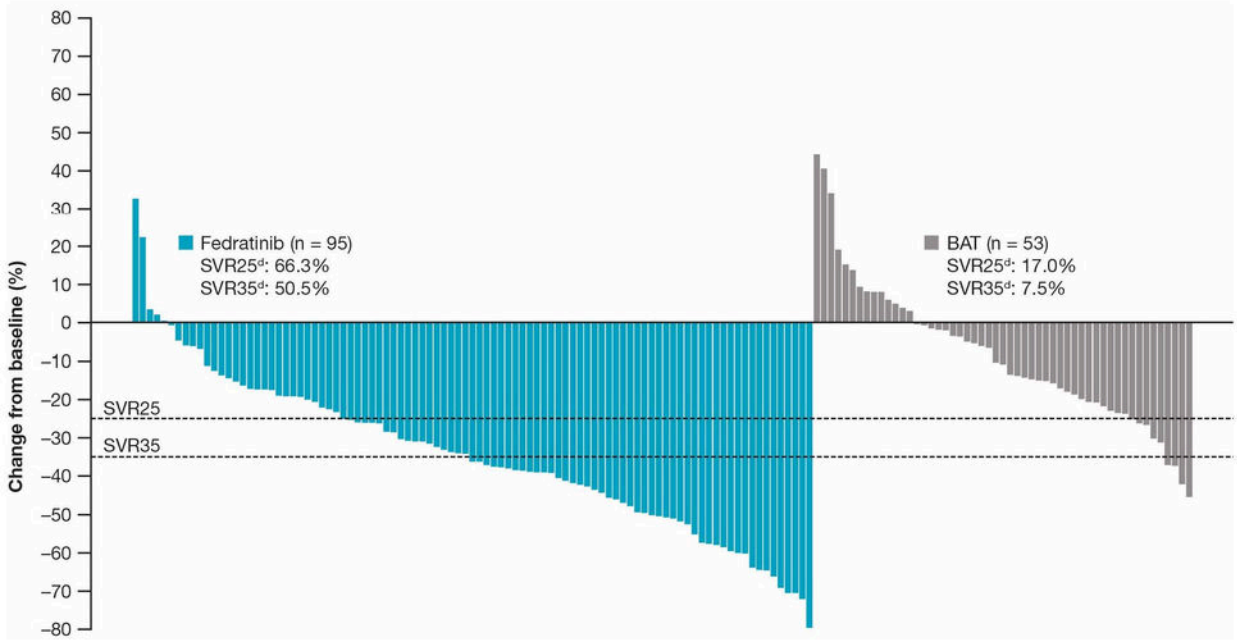
Table. Primary and key secondary endpoints (ITT population)

Response	Fedratinib (n = 134)	BAT (n = 67)	One-sided *P* value[b]
	n (%) [95% CI][a]	n (%) [95% CI][a]	
≥ 35% SVR at EOC6	48 (35.8) [27.7–44.6]	4 (6.0) [1.7–14.6]	< 0.0001
≥ 35% SVR during full treatment course (best overall response)	72 (53.7) [44.9–62.4]	8 (11.9) [5.3–22.2]	< 0.0001
≥ 50% reduction in MFSAF TSS at EOC6[c]	43/126 (34.1) [25.9–43.1]	11/65 (16.9) [8.8–28.3]	0.0033
≥ 25% SVR at EOC6	63 (47.0) [38.3–55.8]	9 (13.4) [6.3–24.0]	< 0.0001

Figure. Percentage change in spleen volume from baseline to EOC6



[a]Two-sided 95% CI is based on the exact Clopper–Pearson method; [b]*P* value is one-sided based on Cochran–Mantel–Haenszel test using the Greenland and Robins method to adjust for stratification factors: spleen size by palpation and platelet counts. The third stratification factor, refractory/relapsed or intolerance to RUX treatment, was dropped due to the small cell count issue; [c]Symptom response was evaluated in the ITT population with non-zero baseline TSS; [d]SVR rates calculated based on evaluable patients with baseline and EOC6 spleen volume measurements (fedratinib, n = 95; BAT, n = 53).

BAT, best available therapy; CI, confidence interval; EOC6, end of cycle 6; ITT, intent to treat; MFSAF; Myelofibrosis Symptom Assessment Form; RUX, ruxolitinib; SVR, spleen volume reduction; SVR25, spleen volume reduction ≥ 25% from baseline; SVR35, spleen volume reduction ≥ 35% from baseline; TSS, total symptom score.

Figure 1

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