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ORAL ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Transform-1: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib Plus Placebo in Patients with Untreated Myelofibrosis

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Background: Janus kinase inhibitors (JAKis) provide symptom improvement and spleen volume reduction in patients with primary, post-polycythemia vera, and post-essential thrombocythemia myelofibrosis (MF). There remains a substantial unmet need for therapies that alter disease trajectory, improve outcomes, and enhance survival. The COMFORT-1 and -2 studies established JAKi monotherapy as standard-of-care with spleen volume reduction of ≥35% at Week 24 (SVR $_{35W24}$) of 42% and SVR $_{35W48}$ of 29%, respectively. In combination with the JAKi ruxolitinib, navitoclax, an orally available inhibitor of antiapoptotic B-cell lymphoma 2 proteins (BCL-X $_L$, BCL-2, BCL-W), was shown to have pronounced antitumor activity in patients with MF in the phase 2 REFINE trial (NCT03222609). TRANSFORM-1 is an ongoing, phase 3, double-blind, placebo-controlled, multicenter, international study evaluating the safety and efficacy of navitoclax plus ruxolitinib (NAV + RUX) compared with placebo plus ruxolitinib (PBO + RUX) in JAK2i-naïve adults with MF.
Methods: TRANSFORM-1 (NCT04472598) enrolled adult patients with intermediate-2 or high-risk MF with measurable splenomegaly, evidence of MF-related symptoms, no prior JAK2i treatment, and ECOG Performance Score ≤2. Patients were randomized 1:1 to receive NAV (starting dose of 200 mg [platelet {PLT} >150 × 10^9/L] or 100 mg escalated to 200 mg once daily if tolerated after ≥7 days [PLT ≤150 × 10^9/L]) or PBO, plus RUX at label dose, based on stratification factors of intermediate-2 vs high-risk MF and PLT ≤200 × 10^9/L vs >200 × 10^9/L. The primary endpoint was SVR $_{35W24}$. Secondary endpoints included change in total symptom score at Week 24 (TSS $_{W24}$) assessed using 7-item MFSAF v4.0 (scale 0-70), SVR $_{35}$ at any time, duration of SVR $_{35}$, anemia response (per International Working Group criteria), reduction in marrow fibrosis, overall survival, leukemia-free survival, reduction in PROMIS Fatigue scale, and improvement in EORTC QLQ-C30 physical functioning scale. Exploratory endpoints include progression-free survival.
Results: At data cutoff, April 13, 2023, 252 patients were enrolled with a median (range) follow-up of 14.9 (0.0-29.5) months; 125 patients were randomized to receive NAV + RUX and 127 to receive PBO + RUX. Most patients were male (57%), median (range) age was 69 (37-87) years, and patient demographics were similar between treatment arms (**Table 1**). TRANSFORM-1 met its primary endpoint, with 79 patients (63.2%) in the NAV + RUX arm achieving SVR $_{35W24}$ compared with 40 patients (31.5%) in the PBO + RUX arm (P<0.0001). Notably, SVR $_{35}$ at any time was achieved by 96 patients (77%) with NAV + RUX compared with 53 patients (42%) with PBO + RUX. Median (range) time to SVR $_{35}$ response was 12.3 (10.1-48.3) weeks with NAV + RUX versus 12.4 (11.3-72.3) weeks with PBO + RUX. Median duration of SVR $_{35}$ was not reached (NR) in the NAV + RUX arm compared with 19.4 months (95% CI 16.8, NR) in the PBO + RUX arm. At Week 24, the mean change in TSS from baseline was -9.7 (95% CI: -11.8, -7.6) with NAV + RUX compared with -11.1 (95% CI: -13.2, -9.1) with PBO + RUX arm (P=0.2852). Grade ≥3 adverse events (AEs) were experienced by 85% of patients with NAV + RUX and 70% with PBO + RUX. The most common AEs (>30% of patients receiving NAV; **Table 2**) were thrombocytopenia, anemia, diarrhea, and neutropenia. Serious AEs were experienced by 26% of patients with NAV + RUX and 32% with PBO + RUX, including anemia (NAV + RUX: n=2; PBO + RUX: n=1), thrombocytopenia (NAV + RUX: n=2), and neutropenia (NAV + RUX: n=1). With NAV + RUX, AEs led to NAV dose reduction in 101 (81%) patients and NAV interruption in 87 (70%) patients of which 83 (67%) and 65 (52%) were due to thrombocytopenia, respectively. Of all enrolled patients, 83 (33%) discontinued study treatment; most common (>5% total patients) reason for NAV/PBO discontinuation were AEs (n=32; 39% of discontinuations) and physician decision (n=14; 17% of discontinuations). In each arm, 13 (10%) patients died; 6 with NAV + RUX and 5 with PBO + RUX died ≤30 days post-final dose.
Conclusions: This first randomized trial in JAKi-naïve MF with NAV + RUX combination led to an SVR $_{35W24}$ rate that was twice as high as PBO + RUX (P<0.0001). The responses were durable; AEs of thrombocytopenia and anemia were common but manageable with dose modification without any clinically significant sequalae. Additional evaluation is ongoing.

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Table 1. Baseline demographics and disease characteristics

Characteristics	NAV + RUX (N=125)	PBO + RUX (N=127)
Age, median (range), years	70 (42–87)	69 (37–85)
Sex, male	63 (50)	81 (64)
Time from last MF diagnosis to study entry, median (range), months	8 (0.3–181.6)	6 (0.3–198.8)
Type of myelofibrosis		
Primary	63 (50)	72 (57)
Post-PV-MF or Post-ET-MF	62 (50)	55 (43)
Number of prior lines of therapy, median (range)	1 (1–3)	1 (1–4)
Spleen volume, median (range), cm^3	1441 (419–8020)	1639 (219–5664)
Transfusion dependent at BL	5 (4)	4 (3)
Transfusion independent at BL	120 (96)	123 (97)
Hemoglobin (g/dL), median (range)	10 (4–18)	10 (6–18)
Platelet count (10^9/L), median (range)	289 (100–1278)	286 (94–1847)
150×10^9/L to $\leq 200 \times 10^9$/L	31 (25)	34 (27)
$>200 \times 10^9$/L	94 (75)	93 (73)
WBC (10^9/L), median (range)	14 (2–95)	14 (2–117)
Risk group calculated by DIPSS+ at study entry		
Intermediate-1	8 (6)	5 (4)
Intermediate-2	104 (83)	110 (87)
High	13 (10)	12 (9)
HMR mutations, n/N (%)	57/120 (48)	50/117 (43)

Data are n (%) unless otherwise stated.

Table 2. Safety data

	NAV + RUX (N=124)	PBO + RUX (N=125)
Any AE	124 (100)	121 (97)
Any AE grade ≥3	105 (85)	87 (70)
Most common AEs (>30% patients receiving NAV)		
Thrombocytopenia, any grade [grade ≥3]	112 (90) [63 (51)]	62 (50) [19 (15)]
Anemia, any grade [grade ≥3]	74 (60) [57 (46)]	61 (49) [49 (39)]
Diarrhea, any grade [grade ≥3]	42 (34) [6 (5)]	17 (14) [0]
Neutropenia, any grade [grade ≥3]	56 (45) [47 (38)]	7 (6) [5 (4)]
Any serious AE	32 (26)	40 (32)
All deaths	13 (10)	13 (10)
Deaths <30 days following last dose of study drug	6 (5)	5 (4)

Data are n (%) unless otherwise stated.

AE, adverse event; BL, baseline; DIPSS, Dynamic International Prognostic Scoring System; HMR, high molecular risk (defined as mutations in *ASXL1, EZH2, SRSF2, IDH1/2,* or *U2AF1*); MF, myelofibrosis; NAV, navitoclax; PBO, placebo; Post-PV, post-polycythemia vera; Post-ET, post-essential thrombocythemia; RUX, ruxolitinib; WBC, white blood cell.

Figure 1

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