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ORAL ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Ruxolitinib in Patients With Chronic Graft-Versus-Host Disease: 3-Year Final Analysis of Efficacy and Safety From the Phase III REACH3 Study

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Introduction: Corticosteroids (CS) are the standard first-line treatment for patients (pts) with chronic graft-versus-host disease (cGvHD), but pts can be unresponsive or become refractory to or dependent on CS (SR/D).Ruxolitinib (RUX), a JAK1/2 inhibitor, is approved for the treatment of pts ≥12 years of age with SR/D-cGVHD, based on the primary outcomes from the randomized, phase III REACH3 (NCT03112603) study, which demonstrated the superior efficacy of RUX vs best available treatment (BAT) in pts with SR/D-cGVHD. Here, we present the final, long-term efficacy and safety outcomes from REACH3.
Methods: Pts ≥12 years of age with moderate or severe SR/D-cGVHD were randomized 1:1 to receive either RUX 10 mg twice daily (BID) or investigator-selected BAT and followed for 3 years, till discontinuation or death. The primary analysis was conducted at week 24 (Cycle 7 Day 1 [C7D1]) in randomized pts, then pts entered the extension period (C7-39) in which they continued treatment, switched from BAT to RUX (crossover cohort), or discontinued treatment and entered long-term survival follow-up (FU). Failure-free survival (FFS; key secondary endpoint), duration of response (DOR), overall survival (OS), non-relapse mortality (NRM), malignancy relapse (MR), and safety were analyzed at 3 years (week 156; final data cut off 15 Dec 2022). Overall response rate (ORR) and best overall response (BOR) during the crossover treatment period were analyzed for pts who switched from BAT to RUX on or after C7D1.

Results: Of 329 pts randomized, 53 completed the treatment period and 276 discontinued, 115 entered survival FU (RUX: 73/165; BAT:42/164); 70 pts crossed over from BAT to RUX of which 16 completed the crossover treatment period and 24 entered survival FU.

Median FFS was longer in the RUX vs BAT arms (38.4 vs 5.7 months; hazard ratio [HR]=0.361, 95% confidence interval [CI]: 0.268, 0.485) with 12-month FFS probabilities of 64.0% (95% CI: 56.1, 70.8) and 28.8% (95% CI: 21.8, 36.1), respectively. Median OS was not reached and there was no difference in risk of death between the arms (HR=0.851, 95% CI: 0.544, 1.331) [Table 1]. Median DOR was 6.4 months (95% CI: 4.9, 11.4) in the BAT arm but was not reached for the RUX arm; notably, the probability of maintaining DOR at 3 years was higher in RUX (59.6%; 95% CI: 50.4, 67.6) vs BAT (26.7%; 95% CI: 18.5, 35.5). NRM event rates were similar between the arms (RUX: 29/165; BAT 34/164), and MR events were similar and low in both arms (13/156 and 11/160, RUX and BAT respectively) up to 3 years.

The ORR at week 24 after crossover from BAT to RUX was 50.0% (95% CI: 37.8, 62.2), including complete response (CR) in 4 (5.7%) pts and partial response (PR) in 31 (44.3%) pts. The BOR during crossover was 81.4% (95% CI: 70.3, 89.7), including CR of 7.1% and PR of 74.3%; disease progression only occurred in 1 pt.

Almost all pts treated during the main treatment period (RUX: 100%; BAT: 93.7%) experienced ≥1 adverse event (AE) and, in general, AE rates were higher in the RUX vs BAT arms [Table 2], likely due to prolonged FU and exposure to RUX (median exposure to treatment of 52.9 weeks vs. 24.1 weeks for RUX and BAT, respectively).Anemia was the most common AE (RUX: 33.9%; BAT: 15.8%) and grade ≥3 AE for RUX (17.6% vs BAT 9.5%, respectively); grade ≥3 neutropenia, thrombocytopenia, alanine aminotransferase increase, and gamma-glutamyltransferase increase were also ≥5% higher for RUX than BAT. Anemia (24.2%; grade ≥3, 10.3%) and thrombocytopenia (3.8%) were the most common RUX and BAT treatment-related AEs, respectively. Infections, excluding tuberculosis, were the most common AE of special interest (77.6% vs. 68.4%; grade ≥3, 31.5% and 26.6%, for RUX and BAT, respectively). On-treatment deaths were mainly due to cGvHD (n/N, RUX: 10/18; BAT 6/12).

Conclusions: After 3 years of treatment in REACH3, the longer FFS and higher DOR with RUX vs BAT indicated that cGVHD was more in control with RUX treatment. Notably, efficacy was demonstrated in pts who switched from BAT to RUX with an ORR similar to that in pts randomized to RUX. RUX was well tolerated with no unexpected toxicities and safety that was consistent with earlier studies. Overall, the long-term control of cGVHD and tolerability of RUX was demonstrated for pts ≥12 years of age with SR/D-cGvHD.

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Table 1. Risk of death in REACH3 over 3 years from primary analysis to end of study

Data cut-off	Events (deaths), n (%)		HR (95% CI)	p-value*
	RUX (N=165)	BAT (N=164)		
8 May 2020†	31 (18.8)	27 (16.5)	1.09 (0.65, 1.82)	0.38
25 Jun 2021‡	37 (22.4)	36 (22.0)	0.96 (0.60, 1.51)	0.42
15 Dec 2022§	37 (22.4)	40 (24.4)	0.85 (0.54, 1.33)	0.24

*Nominal p-value derived from one-sided stratified log rank test with cGvHD severity as strata; †Primary analysis (Zeiser R, et al. *NEJM* 2021;385:228–38); ‡Data on file; §Final analysis
BAT, best available treatment; cGvHD, chronic graft-versus-host disease; CI, confidence interval; HR, hazard ratio; RUX, ruxolitinib

Table 2. Overview of safety (Grade ≥3 events) in the RUX and BAT arms

AE category	RUX, N=165 Grade ≥3, n (%)	BAT, N=158 Grade ≥3, n (%)
Any AE	123 (74.5)	100 (63.3)
Treatment-related	75 (45.5)	26 (16.5)
SAE	79 (47.9)	65 (41.1)
Treatment-related	40 (24.2)	13 (8.2)
Fatal SAE	17 (10.3)	11 (7.0)
Treatment-related	8 (4.8)	4 (2.5)
AEs l/t discontinuation	30 (18.2)	12 (7.6)
Treatment-related	18 (10.9)	5 (3.2)
AEs l/t dose adjustment/interruption	54 (32.7)	15 (9.5)
AEs requiring additional therapy	104 (63.0)	87 (55.1)

A patient with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 25.1, CTCAE version 4.03. AE, adverse event; BAT, best available treatment; l/t, leading to; RUX, ruxolitinib; SAE, serious adverse event

Figure 1

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