Zanubrutinib plus obinutuzumab (ZO) versus obinutuzumab (O) monotherapy in patients (pts) with relapsed or refractory (R/R) follicular lymphoma (FL): primary analysis of the phase 2 randomized ROSEWOOD trial

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Background: FL is the most common type of indolent non-Hodgkin lymphoma. Approved treatment options are limited for pts with R/R FL. In a phase 1b trial (*Blood Adv*. 2020;4(19):4802-4811), ZO was found to be tolerable and associated with early signal of efficacy. ROSEWOOD (BGB-3111-212) is a phase 2, randomized study designed to assess efficacy and safety of ZO vs O in pts with R/R FL.

Methods: Pts with R/R FL who received ≥2 lines of therapy, including an anti-CD20 antibody and an alkylating agent, were randomized 2:1 to receive either ZO or O. O was given in both arms on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycles 2-6, and then every 8 weeks up to 20 doses maximum. Z (160 mg twice daily) was given until progressive disease (PD) or unacceptable toxicity; Pts with confirmed PD in the O arm were allowed to crossover to ZO. Primary endpoint was overall response rate (ORR) by independent central review. Secondary endpoints included complete response rate (CRR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Exploratory endpoint included ORR by investigator after crossover. Primary analysis cutoff was October 8, 2021.

Results: A total of 217 pts were randomized to ZO (n=145) or O (n=72). Median study follow-up was 12.5 mo; median age was 64 yrs. Incidence of high FL International Prognostic Index score was 53% (ZO) and 51% (O). Pts received a median of 3 prior lines of therapy, with 28% (ZO) and 25% (O) of pts receiving >3 lines. Proportion of pts refractory to rituximab, refractory to the most recent line of therapy, or with PD within 24 mo of initiation of first-line immunochemotherapy was 54%, 32% and 28% with ZO and 50%, 40% and 32% with O, respectively. The study met its primary endpoint: ORR was 68.3% with ZO vs 45.8%

with O (*p*=0.0017). CRR was 37.2% (ZO) vs 19.4% (O); 18-mo DOR rate was 70.9% (ZO) vs 54.6% (O); and median PFS was 27.4 mo (ZO) vs 11.2 mo (O; hazard ratio [HR], 0.51 [95% CI, 0.32-0.81], *p*=0.0040). Median time to new anti-lymphoma therapy or crossover was not evaluable (NE; ZO) vs 12.1 mo (O; HR, 0.37 [95% CI, 0.23-0.60], *p*<0.0001). ORR for 29 pts who crossed over to ZO was 24.1%. Median OS was NE; 18-mo OS probability was 85.4% (ZO) vs 72.6% (O). Most common any grade AEs in the ZO arm were thrombocytopenia (34.3%), neutropenia (27.3%), diarrhea (16.1%), fatigue (14.0%), constipation (13.3%), cough (11.9%), pyrexia (11.2%), and dyspnea (10.5%). Grade ≥3 AEs with incidence >5% with ZO were neutropenia (22.4%) and thrombocytopenia (14.0%); incidence of atrial fibrillation was 0.7% and major bleeding was 1.4%. Incidence of treatment-emergent AEs leading to death was 5.6% (ZO) and 9.9% (O).

Conclusions: ZO demonstrated superior efficacy to O in treatment of pts with R/R FL. ZO had a favorable benefit-risk profile and represents a potential combination therapy for pts with R/R FL.