Zanubrutinib Plus Obinutuzumab vs Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study

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Introduction: In an early-phase study, the combination of zanubrutinib plus obinutuzumab was well tolerated and associated with an early signal of efficacy in patients with follicular lymphoma (FL) (Tam et al. *Blood Adv.* 2020). ROSEWOOD (NCT03332017) is a phase 2, randomized study designed to assess the efficacy and safety of zanubrutinib plus obinutuzumab vs obinutuzumab in patients with relapsed/refractory (R/R) FL. Here we present an updated analysis with a median follow-up of 20.2 months.

Material and methods: Patients with R/R FL (grade 1-3a) who received ≥2 lines of therapy including an anti-CD20 antibody and an alkylating agent were randomized 2:1 to receive zanubrutinib plus obinutuzumab or obinutuzumab. Zanubrutinib was given at 160 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) by independent central review. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Time to next treatment (TTNT) was also assessed.

Results: A total of 217 patients were randomized (145 to zanubrutinib plus obinutuzumab; 72 to obinutuzumab). Median age was 64 years. Of the 217 patients, 114 (52.5%) had a high Follicular Lymphoma International Prognostic Index (FLIPI) score at screening, and 123 (56.7%) patients had high tumor burden criteria according to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria. Median number of prior lines of therapy was 3 (range, 2-11). A total of 114 (52.5%) patients were refractory to rituximab; 214 (98.6%) patients received prior immunochemotherapy. Prior anticancer drugs included anthracyclines (80.6%), cyclophosphamide (94.0%), and bendamustine (54.8%). The ORR was 69.0% (zanubrutinib plus obinutuzumab) vs 45.8% (obinutuzumab) (*P*=.0012). The complete response rate was 39.3% (zanubrutinib plus obinutuzumab) vs 19.4% (obinutuzumab) (*P*=.0035); the 18-month DOR rate was 69.3% (zanubrutinib plus obinutuzumab) vs 41.9% (obinutuzumab); median PFS was 28.0 months (zanubrutinib plus obinutuzumab) vs 10.4 months (obinutuzumab) (hazard ratio [HR], 0.50; 95% CI, 0.33-0.75; *P*=.0007). Median TTNT was not estimable for zanubrutinib plus obinutuzumab and 12.2 months for obinutuzumab (HR, 0.34; 95% CI, 0.22-0.52; *P*<.0001). Estimated OS rate at 24 months was 77.3% (zanubrutinib plus obinutuzumab) and 71.4% (obinutuzumab), with median OS not reached (zanubrutinib plus obinutuzumab) and 34.6 months (obinutuzumab) (HR, 0.62; 95% CI, 0.35-1.07; *P*=.0845). Nonhematologic treatment-emergent adverse events of any grade that occurred more frequently with zanubrutinib plus obinutuzumab vs obinutuzumab (>5% difference) were petechiae (6.3% vs 0%) and herpes zoster infection (6.3% vs 0%); in contrast, pyrexia (13.3% vs 19.7%) and infusion-related reaction (2.8% vs 9.9%) occurred more frequently in patients receiving obinutuzumab.

When adjusted for duration of treatment exposure, incidences of infection and cytopenia were similar, and incidence of all grades of hemorrhage was 2.4 (zanubrutinib plus obinutuzumab) vs 1.3 (obinutuzumab) persons per 100 person-months. Two patients in each treatment group reported major hemorrhage. Incidences of atrial fibrillation and hypertension were low and similar in both treatment arms.

Conclusions: Zanubrutinib plus obinutuzumab demonstrated meaningful activity and a manageable safety profile in patients with heavily pretreated R/R FL, representing a potential novel combination therapy.