# Final analysis of the randomized phase 2 ROSEWOOD study of zanubrutinib + obinutuzumab vs obinutuzumab monotherapy in patients with relapsed/refractory follicular lymphoma

**Authors:** Pier Luigi Zinzani,[1] Jiří Mayer,[2] Christopher R. Flowers,[3] Fontanet Bijou,[4] Ana C. De Oliveira,[5] Yuqin Song,[6] Qingyuan Zhang,[7] Marco Brociner,[8] Krimo Bouabdallah,[9] Peter S. Ganly,[10] Huilai Zhang,[11] Sam Yuen,[12] Marek Trněný,[13] Rebecca Auer,[14] Sha Huang,[15] Jiayi Shen,[16] Jamie Hirata,[16] Judith Trotman[17]

**Affiliations:** [1]Institute of Hematology “Seràgnoli”, University of Bologna, Bologna, Italy; [2]Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital, Brno, Czech Republic; [3]Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Institut Bergonié, Bordeaux, France; [5]Institut Català d'Oncologia (ICO) Hospital Duran i Reynals, Barcelona, Spain; [6]Peking University Cancer Hospital and Institute, Beijing, China; [7]Harbin Medical University Cancer Hospital, Harbin, China; [8]Hematology, University Hospital "Ospedale di Circolo e Fondazione Macchi" - ASST Sette Laghi, University of Insubria, Varese, Italy; [9]Hôpital Haut-Lévêque, CHU Bordeaux, Pessac, France; [10]Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; [11]Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [12]Calvary Mater Newcastle, Waratah, NSW, Australia; [13]Charles University, General Hospital, Prague, Czech Republic; [14]St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK; [15]BeOne Medicines Ltd, Shanghai, China; [16]BeOne Medicines Ltd, San Carlos, CA, USA; [17]Department of Hematology, Concord Repatriation General Hospital, Sydney, NSW, Australia

**Introduction:** While treatment advances have improved outcomes in follicular lymphoma (FL), many patients experience multiple relapses with decreasing disease control intervals, highlighting the need for new therapies. The phase 2 ROSEWOOD

study (NCT03332017) compared zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, in combination with the anti-CD20 antibody obinutuzumab (ZO) with obinutuzumab monotherapy (O) in patients with relapsed/refractory (R/R) FL who had received ≥2 prior lines of therapy. Data from an analysis with a median follow-up of 20.2 months were previously reported and showed significantly improved overall response rates (ORRs) per independent central review (ICR) with ZO vs O. Here we report the final analysis of ROSEWOOD with a 34.6-month median follow-up.

**Methods:** As previously reported, patients with R/R FL with ≥2 prior lines of therapy (including an anti-CD20 antibody and an alkylating agent) were randomized 2:1 to receive ZO or O. The primary endpoint was ORR, per Lugano 2014 classification, by ICR. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and the incidence and severity of adverse events (AEs) graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

**Results:** As of December 31, 2024, 217 patients with R/R FL were enrolled and 214 had received treatment with ZO (n=143) or O (n=71). Thirty-six patients (50.0%) in the O arm crossed over to receive ZO. Median study follow-up was 34.6 months (range, 0.1-69.7 months). Baseline characteristics were balanced between arms; overall, the median age was 64.0 years, 50.2% were female, and 64.1% were White. Patients had high-risk features at baseline: 114 (53.5%) had a high Follicular Lymphoma International Prognostic Index (FLIPI), 179 (82.5%) had Ann Arbor stage III/IV disease, and 81 (37.3%) had progression of disease ≤24 months after frontline therapy (POD24). The median number of prior lines of therapy was 3 (range, 2-11).

The combination of ZO significantly improved ORR per ICR vs O (70.3% vs 44.4%; risk difference [RD], 25.5%; 95% CI, 11.8%-39.3%; *P*=.0003), with higher complete response (CR) rates (ZO, 42.1%; O, 19.4%). The ORR benefit of ZO over O was generally consistent across subgroups, including those with >3 prior lines of therapy (RD, 28.8%), high FLIPI (RD, 17.7%), and POD24 (RD, 19.4%). Median DOR per ICR was 32.9 months (95% CI, 19.6-43.1 months) in the ZO arm and 14.0 months (95% CI, 9.2-26.5 months) in the O arm; 36-month DOR rates were 47.2% and 20.3%,

respectively, and median duration of CR was 44.2 months (95% CI, 28.4 months-not estimable [NE]) and 26.5 months (95% CI, 2.7 months-NE). Median PFS per ICR was 22.1 months (95% CI, 16.1-34.0 months) vs 10.3 months (95% CI, 6.5-13.8 months) with ZO vs O (hazard ratio [HR], 0.54; 95% CI, 0.37-0.79; *P*=.0012), respectively; 36-month PFS rates were 39.4% and 16.2%. Median OS was not reached (95% CI, 50.0 months-NE) with ZO vs 41.2 months (95% CI, 31.5 months-NE) with O (HR, 0.66; 95% CI, 0.43-1.04).

Median zanubrutinib exposure in the ZO arm was 12.4 months (range, 0.5-67.4 months), and median obinutuzumab exposure was 10.6 months (range, 0.3-35.3 months) in the ZO arm and 6.5 months (range, 0.1-28.7 months) in the O arm. Treatment-emergent AEs (TEAEs) led to treatment discontinuation in 21.7% and 12.7% and death in 10.5% and 9.9% of patients in the ZO and O arms, respectively. The most common TEAEs in the ZO arm were thrombocytopenia (21.7%), COVID-19, diarrhea, and pneumonia (each 20.3%); the most common TEAEs in the O arm were pyrexia (19.7%), diarrhea (18.3%), nausea, and neutropenia (both 16.9%). Exposure-adjusted incidence rates (persons per 100 person-months) for select TEAEs of interest in the ZO vs O arms were 0.14 vs 0.13 for atrial fibrillation/flutter, 0.07 vs 0.25 for major hemorrhage, 0.28 vs 0.53 for hypertension, and 5.86 vs 5.69 for infection.

**Conclusions:** The final analysis of ROSEWOOD confirmed the favorable risk-benefit profile of ZO in patients with R/R FL. The ORR and CR rate with ZO improved over time, responses remained durable, and the PFS benefit over O was sustained. ZO had a manageable safety profile with no new safety signals observed. To further evaluate ZO in patients with R/R FL with ≥1 prior line of therapy, the phase 3 MAHOGANY study (NCT05100862) comparing ZO vs lenalidomide + rituximab is ongoing.