Zanubrutinib plus obinutuzumab vs obinutuzumab in patients with relapsed/refractory follicular lymphoma: Updated analysis of the ROSEWOOD study

Authors: Pier Luigi Zinzani,[1] Jiří Mayer,[2] Judith Trotman,[3] Fontanet Bijou,[4] Ana C. de Oliveira,[5] Yuqin Song,[6] Qingyuan Zhang,[7] Michele Merli,[8] Krimo Bouabdallah,[9] Peter S. Ganly,[10] Huilai Zhang,[11] Roderick Johnson,[12] Alejandro Martin Garcia-Sancho,[13] Mariano Provencio Pulla,[14] Marek Trněný,[15] Sam Yuen,[16] Sarit E. Assouline,[17] Rebecca Auer,[18] Elena Ivanova,[19] Pil Kim,[19] Adam Greenbaum,[19] Sha Huang,[19] Richard Delarue,[19] and Christopher R. Flowers[20]

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]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [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]St. James's University Hospital Trust, Leeds, United Kingdom; [13]Hospital Universitario de Salamanca, Salamanca, Spain; [14]Hospital Universitario Puerta de Hierro — Majadahonda, Madrid, Spain; [15]Vseobecna fakultní nemocnice v Praze, Prague, Czech Republic; [16]Calvary Mater Newcastle, Waratah, NSW, Australia; [17]Jewish General Hospital, Montreal, Canada; [18]St. Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom; [19]BeiGene (Shanghai) Co., Ltd. Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; and [20]Department of Lymphoma/Myeloma, MD Anderson Cancer Center, Houston, TX, USA

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

Methods: Pts with R/R FL (grade 1-3a) who received ≥2 lines of therapy including an anti-CD20 antibody and alkylating agent were randomized 2:1 to receive ZO or O. Zanubrutinib was given at 160 mg twice daily until 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), time to next treatment (TTNT), overall survival (OS), and safety.

Results: A total of 217 patients were randomized (145 for ZO; 72 for O). Median age was 64 years. Of the 217 pts, 114 (52.5%) had a high Follicular Lymphoma International Prognostic Index (FLIPI) score at screening and 123 (56.7%) pts had high tumor burden 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%) pts were refractory to rituximab; 214 (98.6%) patients received prior immunochemotherapy. Prior exposure to anticancer drugs included anthracyclines (80.6%), cyclophosphamide (94.0%), and bendamustine (54.8%). ORR was 69.0% (ZO) vs 45.8% (O) (P = 0.0012). Complete response rate was 39.3% (ZO) vs 19.4% (O); 18-month DOR rate was 69.3% (ZO) vs 41.9% (O); median PFS was 28.0 months (ZO) vs 10.4 months (O) (hazard ratio [HR], 0.50 [95% CI: 0.33, 0.75]; P = 0.0007). Median TTNT was not evaluable for ZO and 12.2 months for O (HR, 0.34 [95% CI: 0.22, 0.52]; P < 0.0001). Estimated OS rate at 24 months was 77.3% (ZO) and 71.4% (O), with median OS not reached (ZO) and 34.6 months (O). Nonhematologic treatment-emergent adverse events of any grade that occurred more frequently for ZO vs O (>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 on O. When adjusted for duration of treatment exposure, incidences of infection and cytopenia were similar, and incidence of all grades of hemorrhage was 2.4 (ZO) vs 1.3 (O) 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: ZO demonstrated meaningful activity and a manageable safety profile in patients with heavily pretreated R/R FL, representing a potential novel therapy.