ZANUBRUTINIB + OBINUTUZUMAB (ZO) VS OBINUTUZUMAB (O) MONOTHERAPY IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): PRIMARY ANALYSIS OF THE PHASE 2 RANDOMIZED ROSEWOOD TRIAL

Pier Luigi Zinzani,[1] Jiří Mayer,[2] Rebecca Auer,[3] Fontanet Bijou,[4] Ana C. de Oliveira,[5] Qingyuan Zhang,[6] Christopher R. Flowers,[7] Michele Merli,[8] Krimo Bouabdallah,[9] Peter S. Ganly,[10] Yuqin Song,[11] Huilai Zhang,[12] Roderick Johnson,[13] Alejandro Martín García-Sancho,[14] Mariano Provencio,[15] Marek Trněný,[16] Sam Yuen,[17] Herve Tilly,[18] Edwin Kingsley,[19] Gayane Tuyman,[20] Sarit E. Assouline,[21] Elena Ivanova,[22] Pil Kim,[23] Jane Huang,[24] Richard Delarue,[22] Judith Trotman[24,25]

[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]St. Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom; [4]Institut Bergonié, Bordeaux, France; [5]Institut Catala d'Oncologia (ICO) Hospital Duran I Reynals, Hospital, Barcelana, Spain; [6]Harbin Medical University Cancer Hospital, Harbin, China; [7]Department of Lymphoma/Myeloma, MD Anderson Cancer Center, Houston, TX, USA; [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]Beijing Cancer Hospital, Beijing, China; [12]Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [13]St. James's University Hospital Trust, Leeds, United Kingdom; [14]Hospital Universitario de Salamanca, Salamanca, Spain; [15]Hospital Universitario Puerta de Hierro — Majadahonda, Madrid, Spain; [16]Vseobecna fakultní nemocnice v Praze, Prague, Czech Republic; [17]Calvary Mater Newcastle, Waratah, New South Wales, Australia; [18]Centre Henri-Becquerel, Rouen, France; [19]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [20]Department of Chemotherapy of Hemoblastosis, Blokhin Russian Cancer Research Center, Moscow, Russian Federation; [21]Jewish General Hospital, Montreal, Canada; [22]BeiGene Switzerland GmbH, Basel, Switzerland; [23]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [24]Concord Repatriation General Hospital, Concord, New South Wales, Australia; [25]Department of Haemotology, University of Sydney, Concord, New South Wales, Australia

Objectives: 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. To present a primary analysis of ROSEWOOD (BGB-3111-212; NCT03332017), 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 or no response within 12 months 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. All pts gave informed consent.

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 therapy was 54%, 32%, and 35% with ZO and 50%, 40%, and 42% 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 (ZO; NE) 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 adverse events (AEs) with incidence >10% 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 hemorrhage 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.