Final analysis of a phase 1 study of zanubrutinib (zanu) plus lenalidomide (len) in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)

Authors: Zheng Song,[1] Ying Cheng,[2] Haiyan Yang,[3] Liling Zhang,[4] Liqun Zou,[5] Ye Guo,[6] Junning Cao,[7] Huiqiang Huang,[8] Zhao Wang,[9] Sha Huang,[10] Yiqian Fang,[10] Jiaoyan Lyu,[11] Keshu Zhou,[12] Huilai Zhang[1]

Affiliations: [1]Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [2]Jilin Cancer Hospital, Changchun, China; [3]The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China; [4]Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [5]West China Hospital, Sichuan University, Chengdu, China; [6]Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China; [7]Fudan University Shanghai Cancer Center, Shanghai, China; [8]Sun Yat-sen University Cancer Center, Guangzhou, China; [9]Beijing Friendship Hospital, Capital Medical University, Beijing, China; [10]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [11]BeiGene (Beijing) Co, Ltd, Beijing, China; [12]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China

ABSTRACT

Introduction: Up to 50% of patients (pts) with DLBCL develop R/R disease, which has a poor prognosis. A need remains for effective, easily administered, chemotherapy-free treatment (tx) options for R/R DLBCL. Zanu is a next-generation, selective Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target binding. BGB-3111-110 (NCT04436107) is a phase (ph) 1, open-label, dose-escalation/expansion study of zanu+len in Chinese pts with R/R DLBCL. Preliminary data were previously presented.

Aims: To report final safety/efficacy data of zanu+len from BGB-3111-110.

Methods: Pts with DLBCL (≥1 prior line of systemic tx; ineligible for high-dose therapy/stem cell transplant) were enrolled. Pts received zanu 160 mg BID + len QD (escalating target doses: 15, 20, or 25 mg) on d1-21 of each 28-d cycle in part 1 and the recommended ph 2 dose (RP2D) of len 25 mg in part 2. Primary endpoints were safety per CTCAE v5.0, RP2D (part 1), and overall response rate (ORR) per Lugano 2014 criteria (part 2). Biomarker analysis was performed at baseline. DLBCL subtyping was done via immunohistochemistry (IHC) (GCB vs non-GCB) and gene expression profiling (GEP) by HTG EdgeSeq DLBCL cell-of-origin assay (ABC vs GCB vs unclassified).

Results: As of March 28, 2024, 66 pts were enrolled and then received zanu+len (15 mg, n=6; 20 mg, n=10; 25 mg, n=50); 83% had stage III/IV disease and 42% had refractory disease. Per IHC, 65% had non-GCB disease; 67% had ABC disease per GEP. Pts had a median of 1.5 prior lines of therapy (range, 1-5). Across all dose groups, median follow-up was 16.5 mo (range, 0.5-41.6) and median exposure time to zanu+len was 4.9 mo. No dose-limiting toxicities occurred; RP2D of len was 25 mg. Grade ≥3 tx-emergent AEs (TEAEs) occurred in 74% of pts; the most common TEAEs were neutrophil count decreased (58%), white blood cell count decreased (29%), and lymphocyte count decreased (20%). TEAEs led to tx discontinuation in 7 pts (11%) and 2 deaths (3%; cardiopulmonary failure, n=1; pneumonia, n=1; neither were tx-related). Overall, ORR was 50% and 35% achieved a complete response (CR). At RP2D (n=50), ORR was 58% and 42% achieved CR. The ORRs at RP2D by IHC subtype were 50% (GCB) and 62% (non-GCB); CR rates were 50% and 38%, respectively. The ORRs at RP2D by GEP subtype was 69% (ABC) and 45% (GCB); CR rates were 46% and 45%, respectively. At RP2D, median time to response was 2.8 mo, median duration of response was 14.9 mo (95% CI, 5.5-NE), and median

progression-free survival was 5.5 mo (95% CI, 2.9-11.1), with a 12-mo event-free rate of 34% (95% CI, 21-48).

Conclusions: These BGB-3111-110 results demonstrated that the RP2D of zanu 160 mg BID + len 25 mg QD had manageable safety and promising efficacy in pts with R/R DLBCL. Similar efficacy was observed across DLBCL subtypes. This study highlights the great potential of this oral combination as a convenient tx option for R/R DLBCL. Further molecular analysis is ongoing.