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

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

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, BeiGene (Beijing) Co, Ltd, and BeiGene USA, Inc, Shanghai, China; Beijing, China; San Mateo, CA, USA, [11] Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China.

ABSTRACT

Objective: Effective therapies for R/R DLBCL are limited in China, especially for patients ineligible for high-dose therapy/stem cell transplant (HDT/SCT). Preclinical data suggest synergy of lenalidomide with zanubrutinib, a potent and selective Bruton tyrosine kinase inhibitor approved for various B-cell malignancies. Here, we present interim analysis results of an ongoing phase 1, open-label, dose-escalation/expansion study of zanubrutinib plus lenalidomide in R/R DLBCL (NCT04436107).

Methods: Patients with R/R DLBCL ineligible for HDT/SCT who had received ≥1 prior line of adequate systemic therapy were enrolled. In the dose-escalation phase (part 1), lenalidomide 15 mg, 20 mg, or 25 mg was administered orally once daily on days 1 to 21 of each 28-day cycle. In the dose-expansion phase (part 2), lenalidomide 25 mg was administered orally once daily on days 1 to 21 of each 28-day cycle. Zanubrutinib 160 mg was given orally twice daily continuously in parts 1 and 2. Primary endpoints were safety and recommended phase 2 dose (RP2D) of lenalidomide (part 1) and overall response rate (ORR) by investigator based on Lugano classification (part 2). Interim analysis was performed when the 19th patient in part 2 completed the first tumor assessment. Patients who received lenalidomide 25 mg (RP2D) were pooled and analyzed separately.

Results: As of November 8, 2022, 46 patients were treated and included in the interim analysis (27 in part 1; 19 in part 2; 30 at RP2D). The median age was 60 years (range, 29-82 years), 83% had stage III/IV disease, 37% had refractory disease, and 70% had non–germinal center B-cell (non-GCB) disease. The median number of prior systemic therapies was 1 (range, 1-5). The median exposure to zanubrutinib and lenalidomide was 3.9 months (range, 0.4-24.9 months), and median follow-up was 6.6 months (range, 0.5-25.5 months). The ORR was 46% overall (95% CI, 30.9%-61.0%; complete response [CR], 24%) and 57% at RP2D (95% CI, 37.4%-74.5%; CR, 30%). At RP2D, the ORR was 61% (95% CI, 38.5%-80.3%; CR, 35%) in patients with non-GCB disease and 50% (95% CI, 11.8%-88.2%; CR, 17%) in patients with GCB disease. At RP2D, the median duration of response was not reached, and the 6-month event-free rate was 59% (95% CI, 23.8%-82.8%). Median progression-free survival was 5.5 months (95% CI, 2.8 months to not estimable), with a 9-month event-free rate of 37% (95% CI, 17.6%-57.4%).

All 46 patients experienced ≥1 treatment-emergent adverse event (TEAE). At RP2D, grade ≥3 TEAEs occurred in 60% of patients, most commonly neutrophil count decreased (43%), white blood cell count decreased (23%), and pneumonia (13%). One patient (2%) had febrile neutropenia (grade 3) but recovered within 2 days. TEAEs led to discontinuation of both lenalidomide and zanubrutinib in 2 patients (cardiopulmonary failure unrelated to treatment [part 1, lenalidomide 20 mg], pulmonary embolism [part 1, lenalidomide 25 mg]) and discontinuation of lenalidomide in 2 patients (platelet count decreased [part 1, lenalidomide 20 mg], rash [part 2]). Two TEAEs leading to death were reported but were unrelated to treatment.

Conclusion: The zanubrutinib 160 mg plus lenalidomide 25 mg combination showed an acceptable safety profile with promising efficacy. Further evaluation of the combination in a larger sample size is planned in future analysis.