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

Authors: Huilai Zhang, MD, PhD[1]; Ying Cheng, MD[2]; Haiyang Yang, MD, PhD [3]; Liling Zhang, MD[4]; Liqun Zou, MD, PhD[5]; Ye Guo, MD[6]; Junning Cao, MD[7]; Huiqiang Huang, MD, PhD[8]; Zhao Wang, MD[9]; Sha Huang, MD[10]; Zhiyu Liang, MD[10]; Jiaoyan Lyu, PhD[10]; Yiqian Fang, PhD[10]; Aileen Cohen, MD, PhD[10]; Keshu Zhou, MD[12]

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

Background: Effective therapies for R/R DLBCL are limited in China, especially for pts ineligible for high-dose therapy/stem cell transplantation (HDT/SCT). Preclinical data suggest synergy of len with zanu, 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 zanu + len in R/R DLBCL (NCT04436107).

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

Results: As of November 8, 2022, 46 pts were treated and included in interim analysis (27 in part 1; 19 in part 2; 30 at RP2D). Median age was 60 years (range, 29-82), 83% had stage III-IV disease, 37% had refractory disease, 70% had non-germinal center B-cell (non-GCB) like disease; median number of prior systemic therapies was 1 (range, 1-5).

Median exposure to zanu and len was 3.9 months (mo) (range 0.4-24.9), median follow-up was 6.6 mo (range 0.5-25.5). 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, ORR was 61% (95% CI: 38.5-80.3; CR: 35%) for pts with non-GCB disease and 50.0% (95% CI: 11.8-88.2; CR: 17%) for GCB. At RP2D, median duration of response was not reached and 6-mo event-free rate was 59% (95% CI: 23.8-

82.8). Median progression-free survival was 5.5 mo (95% CI: 2.8-not estimable) with a 9-mo event-free rate of 37% (95% CI: 17.6-57.4).

Overall, 46 (100%) pts experienced ≥1 treatment-emergent adverse event (TEAE). At RP2D, grade ≥3 TEAEs occurred in 60% of pts, most commonly neutrophil count decreased (43%), white blood cell count decreased (23%), and pneumonia (13%). One pt (2%) had febrile neutropenia (grade 3) but recovered within 2 days. TEAEs led to discontinuation of both len and zanu in 2 pts (cardiopulmonary failure unrelated to treatment [part 1, len 20 mg], pulmonary embolism [part 1, len 25 mg]) and discontinuation of len in 2 pts (platelet count decreased [part 1, len 20 mg], rash [part 2]). Two TEAEs leading to death were reported, unrelated to treatment.

Conclusions: Zanu 160 mg plus len 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.