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

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Introduction: Effective therapies for R/R DLBCL are limited in China, especially for patients (pts) who are ineligible for high-dose therapy/stem cell transplantation (HDT/SCT). Preclinical data suggest synergy of len and zanu, a potent and selective Bruton tyrosine kinase inhibitor approved for various B-cell malignancies (Guo et al. *J Med Chem* 2019). Here, we present the interim analysis of an ongoing phase 1, open-label, dose-escalation/expansion study of zanu + len in R/R DLBCL in China (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 the 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; and median number of prior systemic therapies was 1 (range, 1-5).

Median exposure to zanu and len was 3.9 months (range, 0.4-24.9), median follow-up was 6.6 months (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-like 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-month event-free rate was 59% (95% CI: 23.8, 82.8). The 9-month progression-free survival rate was 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 patient (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 assessed as unrelated to treatment.

Conclusions: Zanu 160 mg + 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.