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)

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ABSTRACT

Background: Up to 50% of patients (pts) with DLBCL experience R/R disease, which is associated with a poor prognosis. The pursuit of effective chemotherapy-free treatment options for R/R DLBCL is longstanding; despite recent treatment advances, a need remains for novel, easily-administered treatment options. 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 1, open-label, dose-escalation/expansion study of zanu+len in Chinese pts with R/R DLBCL. Preliminary study results for the dose-escalation part detailing the recommended dose for expansion, and results for interim analysis of the study have been previously presented.

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

Methods: Pts with R/R DLBCL who were ineligible for high-dose therapy/stem cell transplant and had received ≥1 prior line of systemic therapy were enrolled. Pts received zanu 160 mg twice daily (BID) + escalating doses of len once daily (QD; with target doses of 15, 20, or 25 mg in each cohort) on days 1-21 of each 28-day cycle in part 1 and the recommended phase 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 (COO) assay (ABC vs GCB vs unclassified).

Results: As of March 28, 2024, 66 pts were enrolled and treated with zanu+len (part 1: 15 mg, n=6; 20 mg, n=10; 25 mg, n=11; part 2: 25 mg, n=39). Median age was 59 y (range, 23-85), 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 in part 1; RP2D of len was 25 mg. Grade ≥3 treatment-emergent adverse events (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 death in 2 pts (3%; cardiopulmonary failure, n=1; pneumonia, n=1; neither considered related to study tx).

Overall, the ORR was 50%, with 35% achieving a complete response (CR). In 50 pts who received len at RP2D, the ORR was 58% and 42% achieved CR. At RP2D, the ORR by IHC subtype was 50% in GCB disease and 62% in non-GCB; CR rates were 50% and 38%, respectively. The ORR at RP2D by GEP subtype was 69% in ABC disease and 45% in GCB; CR rates were 46% and 45%, respectively. At RP2D, the 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%).

Summary/Conclusion: The BGB-3111-110 results demonstrated that the RP2D (zanu 160 mg BID + len 25 mg QD) had a manageable safety profile 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 therapeutic option for R/R DLBCL. Further molecular analysis is ongoing.