Final analysis of a phase 1 study of zanubrutinib plus lenalidomide in patients with relapsed/refractory diffuse large b-cell lymphoma

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Introduction: Outcomes in patients with diffuse large B-cell lymphoma (DLBCL) have improved with recent advances in treatment; however, approximately one-third of patients still experience relapsed/refractory (R/R) disease after an initial response. The activated B-cell–like (ABC) DLBCL subtype, which is more common in Asia than in Western countries, has historically demonstrated inferior outcomes to chemoimmunotherapy compared with germinal B-cell–like (GCB) subtypes. Lenalidomide is commonly used to treat R/R DLBCL. In preclinical studies, lenalidomide has been shown to induce cytotoxicity in ABC DLBCL cells by inhibiting NF-κB signaling and a synergistic effect is seen when B-cell receptor signaling is inhibited by the BTK inhibitor ibrutinib. Thus, combining lenalidomide with a BTK inhibitor may represent a novel therapeutic option for ABC DLBCL. Zanubrutinib is a next-generation, selective BTK inhibitor designed to maximize BTK occupancy and minimize off-target binding. Preliminary results of the phase 1, open-label, dose-escalation/expansion BGB-3111-110 study (NCT04436107) demonstrated the efficacy and safety of zanubrutinib plus

lenalidomide in Chinese patients with R/R DLBCL. Here, final data from the BGB-3111-110 study are presented.

Methods: Patients with R/R DLBCL ineligible for high-dose therapy/stem cell transplant who had received ≥1 prior line of systemic therapy were enrolled. Patients received zanubrutinib 160 mg twice daily plus escalating doses of lenalidomide once daily (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 lenalidomide (25 mg) in part 2, until disease progression or unacceptable toxicity. 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. Immunohistochemistry (IHC) was used to identify GCB and non-GCB phenotypes. Gene expression profiling (GEP) by HTG EdgeSeq DLBCL cell-of-origin (COO) assay was used to determine ABC, GCB, and unclassified subtypes.

Results: As of March 28, 2024, 66 patients were enrolled and treated with zanubrutinib plus lenalidomide (part 1: 15 mg, n=6; 20 mg, n=10; 25 mg, n=11; part 2: 25 mg, n=39). Median age was 59 years (range, 23-85 years), 83% had stage III/IV disease, and 42% had refractory disease. Per IHC, 65% had non-GCB disease; 67% had ABC disease per GEP. Patients had a median of 1.5 prior lines of therapy (range, 1-5).

With a median follow-up of 16.5 months (range, 0.5-41.6 months) across all dose groups, the median exposure time to zanubrutinib and lenalidomide was 4.9 months. No dose-limiting toxicities occurred in part 1 and the RP2D of lenalidomide was determined to be 25 mg. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 74% of patients; the most common TEAEs were neutrophil count decreased (58%), white blood cell count decreased (29%), and lymphocyte count decreased (20%). TEAEs led to treatment discontinuation in 7 patients (11%) and death in 2 patients (3%; cardiopulmonary failure, n=1; pneumonia, n=1; neither considered related to study treatment).

Across all dose groups, the ORR was 50%, with 35% achieving a complete response (CR). In 50 patients who received lenalidomide at RP2D, the ORR was 58%, and 42% achieved CR. At the RP2D, the ORR by COO subtype by IHC was 50% in GCB disease

and 62% in non-GCB disease; CR rates were 50% and 38%, respectively. The ORR at the RP2D by COO subtype by GEP was 69% in ABC disease and 45% in GCB disease; CR rates were 46% and 45%, respectively. At the RP2D, the median time to response was 2.8 months, median duration of response was 14.9 months (95% CI, 5.5-NE months), and median progression-free survival (PFS) was 5.5 months (95% CI, 2.9-11.1 months), with a 12-month event-free rate of 34% (95% CI, 21%-48%).

Conclusions: The results of the BGB-3111-110 study demonstrated that the RP2D of zanubrutinib 160 mg twice daily plus lenalidomide 25 mg once daily had a manageable safety profile and promising efficacy in patients with R/R DLBCL. Similar efficacy was observed across DLBCL subtypes; ORR was numerically higher in the ABC subtype. Further molecular analysis is ongoing.