Title: Zanubrutinib monotherapy for patients with relapsed or refractory non-germinal center diffuse large B-cell lymphoma: results from a phase 2, single-arm, multicenter, study

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Background: The non-germinal center (non-GCB) subtype of diffuse large B-cell lymphoma (DLBCL) is associated with poor clinical outcomes. Inhibitors of Bruton's tyrosine kinase (BTK) have established therapeutic activity in mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenstrom macroglobulinemia and have shown modest activity in DLBCL. Zanubrutinib, a potent and selective BTK inhibitor, was evaluated in a phase 2 study in patients with relapsed or refractory (R/R) non-GCB DLBCL.

Methods: The BGB-3111-207 study (NCT03145064) is a multicenter, single arm, phase 2 study in patients with R/R non-GCB DLBCL who were ineligible for intensive chemotherapy and bone marrow transplantation. Subjects received zanubrutinib 160 mg by mouth twice daily until disease progression or unacceptable toxicity. The primary endpoint was the overall response rate (ORR) using the Lugano criteria. Secondary endpoints included progression free survival (PFS) and duration of response (DOR). Overall survival (OS) was the exploratory endpoint.

Results: Forty-one patients were enrolled at 11 sites in China between June 2017 and May 2018. Patients were 61% male, with a median age of 62 years. The median number of prior therapies was 2. International Prognostic Index risk was high-intermediate or high for 48.8% of patients, and 56.1% of patients had extranodal disease at study entry. As of the data cutoff date of May 24, 2019, four patients were continuing treatment and 37 patients had discontinued. With a median follow-up time of 6.8

months, the ORR was 29.3% and the complete response rate was 17.1%. The median DOR was 4.5 months, the median PFS was 2.8 months, and the median OS was 8.4 months. Adverse events (AEs) leading to treatment discontinuation were reported in four patients. Grade 3 or higher AEs were reported in 48.8% of patients. Major hemorrhage, atrial fibrillation and/or flutter, second primary malignancy, and tumor lysis syndrome were not observed.

Conclusions: In this study zanubrutinib demonstrated modest antitumor activity in non-GCB DLBCL, similar to other BTK inhibitors. The safety profile was tolerable and consistent with previous reports of zanubrutinib treatment. Future studies of zanubrutinib in R/R non-GCB DLBCL will focus on the development of mechanism-based treatment combinations and biomarker-driven patient selection.