Zanubrutinib, a Highly Specific BTK Inhibitor in Chinese Patients with Relapsed/ Refractory B-cell Malignancies: Initial Report of a Phase 1 Trial in China.

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Introduction: Bruton's tyrosine kinase (BTK) inhibitors have been demonstrated to be highly active in a variety of B cell malignancies, including Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/ SLL), Mantle Cell Lymphoma (MCL), and Waldenström's macroglobulinemia (WM). Zanubrutinib (BGB-3111) is a potent, specific and irreversible BTK inhibitor, which has favorable safety profile and deep response. We report here the initial findings of a Phase 1 trial of BGB-3111 in Chinese.

Method: This study was designed to investigate the safety, tolerability, pharmacokinetic, and pharmacodynamics of zanubrutinib in Chinese patients with B-cell malignancies, and to determine the (Recommended Phase 2 Dose) RP2D that was proposed in phase 2 study in China. Based on the results, dose expansion studies will be performed in patients with indolent lymphoma, including FL and MZL. The study was conducted in 2 parts: the first part was the safety assessment of dose (320mg once daily or 160mg twice daily), and the second part was the dose expansion (use the recommended dose, 160mg twice daily). Adverse events (AE) are reported per CTCAE v4.03, responses per standard criteria according to histology Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification 2014; International Workshop Group on CLL (IWCLL) response criteria for CLL 2013; Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop 2013).

Result: As of the data cutoff date as14 Dec 2017, 44 Chinese pts have been enrolled and received Zanubrutinib treatment. In Part I, a total of 21 patients were treated with zanubrutinib and consisted of the following histological subtypes: CLL/SLL (n=9), NHL (not including CLL/SLL or WM subtypes) (n=10), and WM (n=2). Of these, 11 patients were treated with zanubrutinib 160 mg twice a day and 10 patients were treated with

zanubrutinib 320 once a day. As of the data cutoff date, 8 patients in the 160 mg twice a day dose group and 7 patients in the 320 mg once a day dose group remained on treatment. Reasons for discontinuation of zanubrutinib included progressive disease (n=5) and adverse event (n=1). In Part II, a total of 23 patients were treated with zanubrutinib and consisted of the following histological subtypes: FL (n=20) and MZL (n=3). Twenty (87.0%) patients remained on treatment with 3 patients in the FL group discontinuing zanubrutinib for the following reasons: progressive disease (n=2) and "other" reasons (n=1). Most patients in Part I had been treated for more than 48 weeks. The median efficacy follow-up was 48.3 and 48.1 weeks for Part I patients in the 160 mg BID cohort and 320 mg QD cohort, respectively. By the cutoff date of this report, patients in Part II hasn't had their first post-baseline disease assessment, defined as tumor assessment after 12 weeks of study drug treatment. This report includes the efficacy data from Part I and safety data from both Part I and Part II. 41 (93.2%) patients reported ≥ 1 Treatment emergent adverse event (TEAE). The most commonly reported (≥ 20%) TEAEs occurred in the Investigations system organ class (35/44; 79.5%) with neutrophil count decreased (20/44; 45.5%) as the most commonly reported related TEAE overall. Other commonly reported related TEAEs in this system organ class included platelet count decreased (9/44; 20.5%) and white blood cell count decreased (9/44; 20.5%). A total of 17 (38.6%) patients experienced at least 1 Grade 3 or higher TEAE. The most frequently reported Grade 3 or above TEAE was neutrophil count decreased (9/44; 20.5%). Four patients experienced severe TEAEs that were reported as SAEs, which included toxic epidermal necrolysis (1 patient), Grade 4 worsening of neutrophil count decreased (1 patient), Grade 3 febrile neutropenia and Grade 4 platelet count decreased (1 patient), and Grade 2 ascites, Grade 2 pleural effusion, Grade 3 pleural infection, and Grade 3 lung infection (1 patient). There were no reports of major hemorrhage, atrial fibrillation/flutter, hypertension, tumor lysis syndrome, or second primary malignancies.

For patients in Part I (160 mg twice daily), the overall response rate (ORR, complete response [CR] or partial response [PR] or partial response with lymphocytosis [PR-L]) was 72.7% (8/11 patients) and 70.0% for the 320 mg daily cohort (7/10 patients), with the complete response rate (CRR) of 9.1% and 10.0% respectively (1/11 and 1/10 patients; both in patients with NHL).

Conclusion: Zanubrutinib was generally well tolerated in Chinese patients with B-cell malignancies. The study also showed the preliminary antitumor activity. Currently, a number of Phase 2 and 3 clinical trials are being conducted globally including China, to further investigate the role of zanubrutinib in the treatment of B-cell malignancies.