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

Yuqin Song[1], Junyuan Qi[2], Wei Xu[3], Jianfeng Zhou[4], Dengju Li[4], Jianyong Li[3], Lugui Qiu[2], Jun Zhu[1*], Chenmu Du[5], Haiyi Guo[5], Lai Wang[5], Jane Huang[5], William Novotny[5], Shibao Feng[5]
*Corresponding Author

[1] Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China
[2] Chinese Academy of Medical Sciences, Blood Diseases Hospital (Institute of Hematology), Tianjin, China
[3] Jiangsu Province Hospital, Nanjing, Jiangsu, China
[4] Department of Hematology, Tongji Hospital, affiliated Huazhong University of Science and Technology, Wuhan, Hubei, China
[5] BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA

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 long-term results of a Phase 1 trial of BGB-3111 in Chinese patients.

Method: This study was designed to investigate the safety, tolerability, pharmacokinetic, pharmacodynamics and preliminary antitumor activity 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.

The study was conducted in 2 parts: the first part was the safety assessment of doses （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) were graded 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; Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines 2008 ; Response assessment in Waldenstro¨m macroglobulinaemia: update from the VIth International Workshop 2013).

Result: As of the data cutoff date on15 Jun 2018, 44 Chinese pts have been enrolled and received Zanubrutinib treatment. The study is ongoing. In Part I, a total of 21 patients were treated with zanubrutinib and consisted of the following histological subtypes: CLL/SLL (n=9, 42.9%), NHL (not including CLL/SLL or WM subtypes) (n=10,47.6%), and WM (n=2,9.5%). 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, 12(57.1%) patients, in which 6 in the 160 mg twice a day dose group and 6 in the 320 mg once a day dose group, remained on treatment. Reasons for discontinuation of zanubrutinib included disease progression(n=7), adverse event (n=1) and protocol deviation (n = 1). In Part II, a total of 23 patients were treated with zanubrutinib and consisted of the following histological subtypes: FL (n=20, 87.0%) and MZL (n=3,13.0%). 9 (39.1%) patients remained on treatment with 14 patients (60.9%) discontinuing zanubrutinib for the following reasons: disease progression (n = 11), AE (n = 1), investigator's discretion (n = 1), and "other" reasons (n = 1). The median follow-up was 9.5 months overall, with 21.1 months for the Part I 160 mg BID cohort, 20.9 months for the Part I 320 mg QD cohort, and 7.7 months for the Part II cohort. 43 (97.7%) patients reported ≥ 1 Treatment emergent adverse event (TEAE). The most commonly reported TEAEs by system organ class was Investigations (37 [84.1%] patients), with neutrophil count decreased (22 [50.0%] patients) as the most commonly reported TEAE, followed by WBC count decreased (11 [25.0%] patients) and platelet count decreased (10 [22.7%] patients). Other commonly reported TEAEs ≥ 20% included anaemia (14 [31.8%] patients), upper respiratory tract infection (11 [25.0%] patients), rash (10 [22.7%] patients), hyperuricemia (9 [20.5%] patients), and haematuria (9 [20.5%] patients). No DLT or death occurred during DLT evaluation period.

A total of 23 (52.3%) patients experienced at least 1 Grade 3 or higher TEAE. The most frequently reported Grade 3 or above TEAE was neutrophil count decreased (11/44; 25%). Six patients experienced SAEs, which included Grade 4 toxic epidermal necrolysis (1 patient), Grade 4 neutropenia (1 patient), Grade 3 febrile neutropenia and Grade 4 platelet count decreased (1 patient), Grade 2 ascites, Grade 3 pleural infection, and Grade 3 lung infection (1 patient), induced abortion (1 patient), and Grade 3 anaemia and Grade 3 fatigue (1 patient). As of the data cutoff date, 4 deaths were reported due to disease progression or other reasons. No TEAEs leading to death were reported. There were no reports of major hemorrhage, atrial fibrillation/flutter, Grade 3 or higher hypertension, tumor lysis syndrome, or second primary malignancies.

For patients in Part I, the overall response rate (ORR, complete response [CR] or partial response [PR] or partial response with lymphocytosis [PR-L]) for 160mg twice daily cohort was 72.7% (8/11 patients) and 70.0% for the 320 mg daily

cohort (7/10 patients), with the CR rate of 27.3% and 10.0% respectively (3/11 and 1/10 patients). For Part II, the ORR was 30.4% (7/23 patients) and the CR rate was 4.3% (1 patient). Median time to response was 2.8 months for both Part I and Part II. Overall, 9 of 9 (100%) CLL/SLL patients, 1 of 2 (50%) WM patients, 1of 2 (50%) MCL patient, and 11 of 26 (42.3%) FL patients achieved overall response. None of the 5 MZL patients achieved overall response as of the data cut.

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.