Primary analysis results of novel BCL2 inhibitor sonrotoclax (BGB-11417) monotherapy in patients with relapsed/refractory b-cell malignancies

Authors: Caixia Li,[1] Jia Wei,[2] Keshu Zhou,[3] Peng Liu,[4] He Huang,[5] Fei Li,[6] Hui Zhou,[7] Qingqing Cai,[8] Shenmiao Yang,[9] Yujun Dong,[10] Zhiyu Liang,[11] Sudong Zhang,[11] Zaixing Shi,[11] Remus Vezan,[12] Depei Wu[1]

Affiliations: [1]The First Affiliated Hospital of Soochow University, Suzhou, China; [2]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [4]Affiliated Zhongshan Hospital of Fudan University, Shanghai, China; [5]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [6]The First Affiliated Hospital of Nanchang University, Nanchang, China; [7]Hunan Cancer Hospital, Changsha, China; [8]Sun Yat-sen University Cancer Center, Guangzhou, China; [9]Peking University People's Hospital, Beijing, China; [10]Peking University First Hospital, Beijing, China; [11]BeOne Medicines Ltd, Shanghai, China; [12]BeOne Medicines Ltd, San Carlos, CA, USA

ABSTRACT

Objective: The first-generation B-cell lymphoma 2 (BCL2) inhibitor venetoclax is an effective treatment for patients with B-cell malignancies; however, its clinical use can be limited by toxicity. Sonrotoclax, a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax. BGB-11417-102 (NCT04883957) is an open-label, phase 1 study of sonrotoclax monotherapy in patients with B-cell malignancies in China. Presented here are results on the safety and efficacy of sonrotoclax in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and R/R non-Hodgkin lymphoma (NHL) in BGB-11417-102.

Methods: Patients with R/R CLL/SLL or NHL (≥1 prior line of therapy) received sonrotoclax with a ramp-up to the target dose (80, 160, 320, or 640 mg once daily) to mitigate potential tumor lysis syndrome (TLS) risk. Dose-limiting toxicities (DLTs) were assessed during ramp-up and through day 21 at the target dose. Primary endpoints were safety per Common Terminology Criteria for Adverse Events v5.0 or the Grading Scale for Hematologic Toxicity in CLL Studies, recommended phase 2 dose (RP2D), and maximum tolerated dose (MTD). Overall response rate (ORR) per Lugano 2014 criteria (or International Workshop on CLL 2008 for CLL) was a secondary endpoint. Exploratory endpoints included duration of response (DOR), progression-free survival (PFS), and undetectable measurable residual disease (uMRD4).

Results: As of August 23, 2024, 64 patients (CLL/SLL, n=29; diffuse large B-cell lymphoma [DLBCL], n=21; follicular lymphoma, n=7; marginal zone lymphoma, n=4; transformed B-cell NHL, n=3) were treated with sonrotoclax once daily (target dose: 80 mg, n=9; 160 mg, n=12; 320 mg, n=21; 640 mg, n=22). Median age was 61 years (range, 31-84 years); 54.7% were male. Patients had a median of 2 prior lines of therapy (range, 1-7). Median study follow-up was 23.4 months (range, 1.5-35.7 months). MTD was not reached up to 640 mg once daily; RP2D was 320 mg once daily. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 62.5% of patients (n=40); the most common were neutrophil count decreased (37.5%), platelet count decreased (23.4%), and white blood cell count decreased (21.9%). No cases of TLS were reported. TEAEs led to dose interruption in 31.3% of patients, dose reduction in 4.7%, and treatment discontinuation in 4.7%. TEAEs led to death in four patients (6.3%). Across dose levels, the ORR was 72.4% (21/29) in patients with R/R CLL/SLL and 20.0% (7/35) across other R/R NHL subtypes, with complete response rates of 31.0% (9/29) and 8.6% (3/35), respectively; the median DOR was 22.2 and 21.9 months, respectively. In patients with R/R CLL/SLL, the median PFS was 23.1 months, with a 12-month PFS rate of 68.6%. The best blood uMRD4 rate in patients with R/R CLL/SLL was 41.4% (12/29). Median time to uMRD4 was 7.4 months (range, 4.5-18.0 months).

Conclusion: Sonrotoclax monotherapy was well tolerated in patients with R/R NHL and CLL/SLL at doses up to 640 mg once daily, with no cases of TLS reported and low rates of discontinuation due to TEAEs. Patients with

R/R CLL/SLL had an ORR of 72% with deep responses (best blood uMRD4 rate of 41.4%, and 31% achieved a CR).