A phase 1 study evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of Bcl-2 inhibitor BGB-11417 in adult patients with mature B-cell malignancies

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

Affiliations: *[1]The First Affiliated Hospital of Soochow University, Jiangsu, China; [2]Tongji Hospital of Tongji Medical College Huazhong University of Science and Technology, Wuhan, China; [3]HeNan Cancer Hospital, Zhengzhou, China; [4]Department of Hematology, Zhongshan Hospital, Fudan University, Shanghai, China; [5]Zhejiang University – The First Affiliated Hospital, Hangzhou, China; [6]The First Affiliated Hospital of Nanchang University, Nanchang, China; [7] Sun Yat-Sen University Cancer Center, Guangzhou, China; [8] Department of Hematology, Peking University First Hospital Beijing, China; [9]Peking University People's Hospital, Beijing, China; [10] Hunan Cancer Hospital, Changsha, China; [11] Shenzhen People's Hospital, Shenzhen, China; and [12]BeiGene (Shanghai) Co., Ltd., Shanghai, China*

ABSTRACT

Background

BGB-11417 is a potent and highly selective Bcl-2 inhibitor. Phase 1 study results showing high activity and good tolerability in patients (pts) with mature B-cell malignancies were previously reported (Abstract 2989, ASH 2022). We present here results of BGB-11417 monotherapy in B-cell malignancies with a longer follow up.

Methods

BGB-11417-102 (NCT04883957) is an ongoing, multicenter, phase 1, open-label, dose-finding study in China. Primary objectives: safety, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of BGB-11417 monotherapy for selected cohorts. Pts with relapsed/refractory (R/R) B-cell malignancies received escalating doses (80, 160, 320, or 640 mg once daily) with weekly or daily ramp-up to intended target dose. Dose-limiting toxicity (DLT) for each cohort was evaluated during ramp-up through day 21 at the intended dose. AEs were reported per CTCAE v5.0 (or Grading Scale for Hematologic Toxicity in chronic lymphocytic leukemia [CLL] Studies).

Results

As of 1 Oct 2022, 54 pts (34 R/R non-Hodgkin lymphoma [NHL; 20 diffuse large B-cell lymphoma, 7 follicular lymphoma, 4 marginal zone lymphoma, 3 transformed NHL], and 20 R/R CLL/small lymphocytic lymphoma [SLL]) received ≤640 mg/d. 640mg was the highest dose pre-defined in the study and MTD was not reached. Median (range) values: age, 61 y (31-84); prior lines of systemic therapy, 2 (1-7); follow-up duration, 6.6 m (0.2-13.0). Study discontinuation: 23 pts (22 NHL; 1 CLL/SLL); reasons: 18 progressive disease, 4 withdrew, 1 investigator decision.

Tx-emergent AEs (TEAEs): all grades, 92.6%; grade ≥3, 53.7%. Most common TEAE: all grades, white blood cell count decreased (48.1%); grade ≥3, neutropenia (25.9%). DLTs occurred in 3 patients at 80 mg/d or 160 mg/d; 14.8% had serious TEAEs and 14.8% had TEAEs leading to drug interruption. No pts had TEAEs leading to death/tx discontinuation or clinical tumor-lysis syndrome events. Of 39 pts available for tumor assessment (27 NHL; 12 CLL/SLL), 5 with NHL and 9 with CLL/SLL achieved responses (NHL: 3 partial responses [PR] at 160 mg/d, 1 PR at 320 mg/d, 1 complete response [CR] at 640 mg/d; CLL/SLL: 2 CR and 2 PR at 80 mg/d, 3 PR at 160 mg/d, 2 PR at 320 mg/d). Nine pts with R/R CLL/SLL (5 at 80mg/d, 4 at 160 mg/d) had minimum residual disease (MRD) assessment; 3 had undetectable MRD with CLL cell/total nucleated cells $<10^{-4}$ (uMRD4; 1 pt achieved blood and bone marrow aspirate uMRD4 after 4.5 months at 80 mg/d; 2 pts had blood uMRD4 after 7.1 months at 160 mg/d). The monotherapy RP2D for R/R CLL/SLL was 320 mg/d.

Conclusion

These results demonstrated that BGB-11417 monotherapy was well tolerated at all tested doses up to 640 mg/d, with no dose-dependent toxicity increase. BGB-11417 monotherapy showed promising initial efficacy results in R/R CLL/SLL, with pts achieving responses at lower dose levels.