

Preliminary results from a phase 1/1b first-in-human study of BGB-21447, a next-generation BCL2 inhibitor, in patients with B-cell non-Hodgkin lymphoma

Authors: Fei Li,¹ Stephen S. Opat,² Dengju Li,³ Keshu Zhou,⁴ Peng Liu,⁵ Wei Yang,⁶ Chan Y. Cheah,^{7,8} Tingyu Wang,^{9,10} Yu Yang,¹¹ Caixia Li,¹² Hongmei Jing,¹³ Henry Ngu,¹⁴ Lipeng Chen,¹⁵ Ting Deng,¹⁵ Fangjie Xie,¹⁵ Naisargee Shah,¹⁶ Zhao Xu,¹⁷ Richard Delarue,¹⁸ Jianyong Li¹⁹

Affiliations: ¹The First Affiliated Hospital of Nanchang University, Nanchang, China; ²Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; ³Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; ⁴Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; ⁵Affiliated Zhongshan Hospital of Fudan University, Shanghai, China; ⁶Shengjing Hospital of China Medical University, Shenyang, China; ⁷Sir Charles Gairdner Hospital, Nedlands, WA, Australia; ⁸Medical School, University of Western Australia, Crawley, WA, Australia; ⁹National Clinical Research Center for Hematological Disorders, State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Diseases Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; ¹⁰Tianjin Institutes of Health Science, Tianjin, China; ¹¹Fujian Cancer Hospital, Fuzhou, Fujian, China; ¹²The First Affiliated Hospital of Soochow University, Suzhou, China; ¹³Peking University Third Hospital, Beijing, China; ¹⁴Auckland City Hospital, Auckland, New Zealand; ¹⁵BeOne Medicines Ltd, Beijing, China; ¹⁶BeOne Medicines Ltd, San Carlos, CA, USA; ¹⁷BeOne Medicines Ltd, Shanghai, China; ¹⁸BeOne Medicines Ltd, Basel, Switzerland; ¹⁹The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China

Introduction: B-cell lymphoma 2 (BCL2)–mediated resistance to the intrinsic apoptosis pathway is a key factor in the pathogenesis and chemoresistance of hematologic malignancies. BGB-21447 is a novel, orally bioavailable BH3 mimetic that was designed to be a highly potent inhibitor of both wild-type and mutant BCL2. BGB-21447-101 (NCT05828589) is a first-in-human phase 1/1b study of BGB-21447 in patients with B-cell malignancies. Presented here are preliminary safety data and antitumor activity in all dose-limiting toxicity (DLT)–evaluable patients with B-cell non-Hodgkin lymphoma (B-NHL) treated with BGB-21447 monotherapy under fasted status in part 1 (dose finding).

Methods: BGB-21447-101 is an ongoing, global, open-label, dose-escalation and dose-optimization study to evaluate BGB-21447 in adults with mature B-cell malignancies. Eligible patients have a confirmed diagnosis with a relapsed/refractory B-cell malignancy (ie, diffuse large B-cell lymphoma [DLBCL], follicular lymphoma [FL], or marginal zone lymphoma [MZL]), transformed B-NHL, or Richter transformation to DLBCL. Key exclusion criteria include prior malignancy other than the disease under study within 2 years, known central nervous system involvement, autologous stem cell transplant or chimeric antigen receptor T-cell (CAR-T) therapy within 3 months, and prior allogeneic stem cell transplant. In the dose-escalation stage, BGB-21447 is administered orally at planned dose levels ranging from 10 mg to 320 mg using a ramp-up strategy. The primary study objectives are to evaluate the safety/tolerability and determine the recommended phase 2 dose of BGB-21447 monotherapy. Treatment-emergent adverse events (TEAEs) are graded per NCI-CTCAE v5.0. DLTs are

assessed from the first dose to day 21 of BGB-21447 treatment at the target dose. Tumor lysis syndrome (TLS) is assessed according to Howard 2011 criteria.

Results: As of May 16, 2025, 44 patients with B-NHL had been enrolled in the dose-escalation cohort and received BGB-21447 at target doses ranging from 10 mg to 320 mg. The median age of study patients was 58 years (range, 32-81 years), 56.8% of patients (n=25) were male, 88.6% (n=39) were Asian, and 11.4% were White. Sixteen patients (36.4%) had FL and 12 (27.3%) had DLBCL. Across indications, patients had a median of 3 (range, 0-7) lines of therapy; 63.6% of patients (n=28) had received ≥ 3 prior lines, 11.4% (n=5) had prior CAR-T therapy, and 4.5% (n=2) had prior bispecific or trispecific antibodies. The median study follow-up was 6.4 months (range, 0.8-22.9 months), and median treatment duration was 2.6 months (range, 0.2-22.5 months). Any-grade TEAEs occurred in 93.2% of patients (n=41; treatment-related, 79.5%) and grade ≥ 3 TEAEs were seen in 59.1% of patients (n=26; treatment-related, 40.9%). TEAEs occurring in $>20\%$ of patients were leukopenia (56.8%; grade ≥ 3 , 20.5%), neutropenia (50.0%; grade ≥ 3 , 27.3%), lymphopenia (36.4%; grade ≥ 3 , 18.2%), anemia (31.8%, grade ≥ 3 , 4.5%), thrombocytopenia (29.5%; grade ≥ 3 , 6.8%), and hypokalemia (22.7%, grade ≥ 3 , 2.3%). During BGB-21447 treatment, 29.5% of patients (n=13) received G-CSF and 9.1% of patients (n=4) received thrombopoietin. Two patients (4.5%) had TEAEs that led to treatment discontinuation. One patient had laboratory TLS that resolved within 3 days with no sequelae; no clinical TLS was observed. In evaluable patients, overall response rates (ORRs) were 38.1% (8/21) in FL/MZL and 33.3% (4/12) in DLBCL, with complete response rates of 14.3% (3/21) in FL/MZL and 16.7% (2/12) for DLBCL. The median time to first response was 2.8 months in FL/MZL and 4.1 months in DLBCL. Marked pharmacodynamic effects were observed following BGB-21447 treatment, as demonstrated by dissociation of the BCL2:BIM complex and decreases in B-cell count in peripheral blood.

Conclusions: Initial first-in-human data demonstrate that BGB-21447 is well tolerated in heavily pretreated patients with B-NHL. The safety profile is as expected; as with other BCL2 inhibitors, hematologic toxicities are the most common all-grade and grade ≥ 3 TEAEs observed. Antitumor activity is encouraging, with ORRs of 38% and 33% observed in patients with FL/MZL and DLBCL, respectively. Enrollment in BGB-21447-101 is ongoing.