Safety data 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

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ABSTRACT

Objectives: 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, next-generation BH3 mimetic that was designed to be a highly potent inhibitor of both wild-type and mutant BCL2, which is also active against BCL-xL. BGB-21447-101 (NCT05828589) is a phase 1/1b study of BGB-21447 in patients with B-cell malignancies. The objective of the analysis presented here was to assess preliminary safety data from patients with B-cell non-Hodgkin lymphoma (B-NHL) who received BGB-21447 monotherapy in the dose-escalation portion of BGB-21447-101.

Methods: BGB-21447-101 (NCT05828589) is an ongoing, global, first-in-human, open-label, dose-escalation and dose-optimization study to evaluate BGB-21447 in adult patients with mature B-cell malignancies. Key inclusion criteria include a confirmed diagnosis with a relapsed/refractory (R/R) B-cell malignancy (ie, diffuse large B-cell lymphoma [DLBCL], follicular lymphoma [FL], or marginal zone lymphoma), transformed B-NHL, or Richter transformation to DLBCL, and measurable disease. 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 therapy within 3 months, and prior allogeneic stem cell transplant. In the dose-escalation part of the study, BGB-21447 is administered orally at 1 of the 7 planned dose levels, using a ramp-up to the target dose. The primary study objectives are to evaluate safety/tolerability and determine maximum tolerated dose and recommended phase 2 dose of BGB-21447 monotherapy. Treatment-emergent adverse events (TEAEs) are graded per Common Terminology Criteria for Adverse Events v5.0. Dose-limiting toxicities 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 March 7, 2025, 40 patients with B-NHL had been enrolled and received BGB-21447. Overall, the median age was 56.5 years (range, 32-78 years), and 57.5% of patients (n=23) were male. FL was the most common disease type (n=16; 40.0%), followed by DLBCL (n=11; 27.5%). Across all indications, patients had a median of 3 (range, 0-7) lines of therapy and 65.0% (n=26) of patients had ≥3 prior lines. The median study follow-up was 5.9 months (range, 0.3-20.6 months), and median treatment duration was 2.6 months (range, 0.2-20 months). In total, 97.5% (n=39) of patients experienced all-grade TEAEs, 52.5% (n=21) had grade ≥3 TEAEs, and 27.5% (n=11) had serious TEAEs. Nineteen patients (47.5%) discontinued treatment due to disease progression (n=15), consent withdrawal (n=3), or TEAE (blood creatine phosphokinase increased; n=1). The most common TEAEs were hematologic toxicities, including white blood cell count decreased (60.0%; grade ≥3, 17.5%), neutrophil count decreased (45.0%; grade ≥3, 22.5%), and lymphocyte count decreased (35.0%; grade ≥3, 17.5%). No febrile neutropenia was observed, and no patients required BGB-21447 dose reductions due to hematologic TEAEs. One patient had laboratory TLS that resolved within 3 days with no sequelae. No clinical TLS was observed.

Conclusions: Preliminary results from this first-in-human study demonstrate that BGB-21447 is well tolerated in patients with heavily-pretreated B-NHL. Hematologic toxicities were the most frequently observed all-grade and grade ≥3 TEAEs, which is consistent with the safety profile of other BCL2 inhibitors. Given the limited number of patients and shorter follow-up, further safety evaluation and longer follow-up are warranted. Enrollment in the BGB-21447-101 study is ongoing.