A Phase 1 Study With the Novel B-Cell Lymphoma 2 (Bcl-2) Inhibitor BGB-11417 as Monotherapy or in Combination With Zanubrutinib in Patients With B-Cell Malignancies: Preliminary Data

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Abstract:

Introduction: BCL2 is aberrantly expressed in many hematologic malignancies and promotes tumorigenesis.

Objective: BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study evaluating safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose of oral BGB-11417, a potent, highly selective Bcl-2 inhibitor, alone or in combination with zanubrutinib, a BTK inhibitor, in patients with relapsed/refractory (R/R) B-cell malignancies.

Materials and Methods: BGB-11417 (40, 80, 160, 320, or 640 mg QD, with a weekly or daily ramp-up to the target dose) was given as monotherapy or combined with zanubrutinib (320mg QD or 160mg BID) 8-12 weeks before BGB-11417. Dose-limiting toxicity was evaluated by Bayesian logistic regression. Adverse events (AEs) were reported per CTCAE v5.0.

Results: As of 17Dec2021, 58 patients received BGB-11417 as monotherapy (n=32) or in combination with zanubrutinib (n=26). Of patients receiving monotherapy, 26 with non-Hodgkin lymphoma (NHL; 17 DLBCL, 6 follicular lymphoma, 3 marginal zone lymphoma) received ≤640mg and 6 with CLL/SLL received ≤160mg; for those receiving combination treatment, 19 with R/R CLL/SLL received BGB-11417 ≤160mg and 7 with R/R MCL received ≤80mg. MTD has not been reached. Median follow-up was 3.9 months (range=0.1-20.4 months). Two grade ≥3 AEs (neutropenia: n=1, autoimmune hemolytic anemia: n=1) occurred in combination cohorts. 20 patients discontinued treatment (disease progression: n=17; AE: n=1; other: n=2). One high-risk patient with CLL in the monotherapy cohort had laboratory tumor lysis syndrome (<2%) that resolved without intervention. Early data show that most patients had a reduction in sum of product of perpendicular diameters; 2 patients with NHL in the monotherapy cohort had responses (complete response: n=1). Patients with CLL/SLL had notable reductions in absolute lymphocyte counts at doses ≥1mg; 2 responses (≥partial response) occurred with monotherapy and 12 with combination therapy (≥partial response + lymphocytosis).

Conclusion: Preliminary findings suggest BGB-11417 has promising efficacy and is tolerable at ≤640mg as monotherapy and ≤160mg combined with zanubrutinib. Dose escalation continues as MTD has not been reached. Enrollment is ongoing and data for patients with Waldenström macroglobulinemia and treatment-naïve CLL/SLL are forthcoming.