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 CLL/SLL: Preliminary data

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ABSTRACT

Objectives: The effectiveness of Bcl-2 inhibitors as a treatment for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) was established with the approval of venetoclax for patients with CLL/SLL across all lines of therapy. However, related adverse events (AEs) and the emergence of *BCL2* mutations resulting in resistance can limit the utility of venetoclax. BGB-11417 is a highly selective Bcl-2 inhibitor with a potency >10 times that of venetoclax in biochemical assays. BGB-11417 monotherapy is tolerable, with no maximum tolerated dose (MTD) reached after dose escalation through all planned doses to 640 mg once daily (QD) in patients with non-Hodgkin lymphoma (EHA 2022. Abstract P687). The combination of Bcl-2 and Bruton tyrosine kinase (BTK) inhibitors is tolerable, with synergistic activity in CLL and mantle cell lymphoma (*J Clin Oncol.* 2019;37:2722-2729; *N Engl J Med.* 2019;380:2095-2103; EHA 2020. Abstract S158; *N Engl J Med.* 2018;378:1211-1223). Zanubrutinib, a next-generation BTK inhibitor, has shown favorable activity and safety in patients with CLL/SLL (EHA 2021. Abstract LB1900) and Waldenström macroglobulinemia (*Blood*. 2020;136[18]:2038-2050). BGB-11417-101 is an ongoing first-in-human, phase 1/1b, dose-escalation/expansion study (NCT04277637). Patients with various B-cell malignancies were enrolled; data from CLL/SLL cohorts are presented here.

Methods: In separate monotherapy and combination therapy cohorts, patients received escalating doses of BGB-11417 (40, 80, 160, 320, or 640 mg QD) with a ramp-up to the intended target dose to minimize risk of tumor lysis syndrome (TLS). In combination therapy cohorts, patients received zanubrutinib (320 mg QD or 160 mg twice daily) beginning 8 to 12 weeks before BGB-11417 treatment. Dose-limiting toxicity in each cohort was evaluated by a Bayesian logistic regression model during dose ramp-up through day 21 at the intended dose. AEs were reported per Common Terminology Criteria for Adverse Events v5.0. Minimal residual disease (MRD) was assessed by a European Research Initiative on CLL flow cytometry assay.

Results: As of May 15, 2022, 50 patients with CLL received treatment: 6 monotherapy (all relapsed/refractory [R/R]) and 44 combination (R/R, 22; treatment naive [TN], 22). The monotherapy CLL cohort received BGB-11417 doses up to 160 mg. Based on emerging safety data from other cohorts, patients with R/R CLL in combination cohorts received BGB-11417 up to 640 mg, and patients with TN CLL received up to 320 mg (data include 8 patients receiving zanubrutinib pretreatment not yet treated with BGB-11417). MTD has not yet been reached in any CLL cohort, with dose escalation ongoing. Median follow-up was 11.5 months (range, 8.5-18.3) for monotherapy and 5.8 months (range, 0.2-10.5) for combination. Treatment-emergent AEs (TEAEs) across all doses are listed in the **Table**. With monotherapy, cytopenias were the most common TEAEs (≥50%), with

33% grade ≥3. With combination therapy, contusion, neutropenia, and low-grade gastrointestinal toxicity were the most common TEAEs (≥22.7%); neutropenia was the most common grade ≥3 TEAE (n=5; 11.4%). No patients discontinued monotherapy, and 1 discontinued combination treatment (disease progression; Richter transformation). Only 1 patient with high-risk CLL receiving monotherapy had laboratory TLS that resolved without intervention (overall laboratory TLS, ≤2%). No clinical TLS was reported. Diarrhea was mostly grade 1, and grade ≥3 was not seen. Although efficacy data are early, most patients with CLL/SLL had notable reductions in absolute lymphocyte count (ALC), with responses seen at doses as low as 1 mg (**Figure**), consistent with improved potency of BGB-11417 vs venetoclax. Four responses (partial response [PR] or better, 66%) and 32 responses (PR with lymphocytosis or better, 72.7%) were observed with mono- and combination therapy, respectively. MRD data are early; among 4 MRD-evaluable patients at 160 mg, 3 (monotherapy, n=2; combination, n=1) had a peripheral blood CLL count of $<10^{-4}$ at 24 weeks after BGB-11417 initiation.

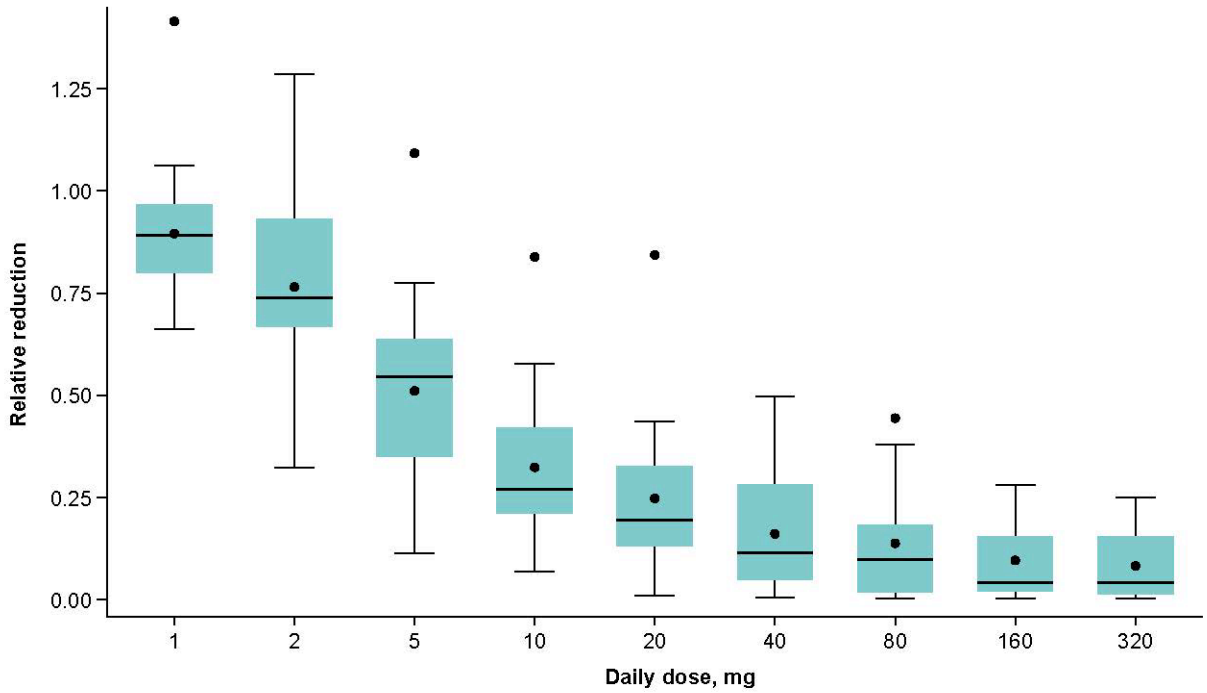
Conclusions: These preliminary data show that BGB-11417, alone or in combination with zanubrutinib, was well tolerated in most patients. Grade ≥3 neutropenia was uncommon and manageable. Efficacy is supported by the rapid reduction in ALC during ramp-up, and early response data are promising. TLS rates are low; the prophylactic measures and ramp-up schedule seem to adequately mitigate TLS across all dose levels tested. Mature MRD data are forthcoming, and venetoclax-treated CLL/SLL cohorts will soon be open for enrollment.

Table. Summary of Treatment-Emergent Adverse Events

BGB-11417 monotherapy (R/R CLL; n=6)		
TEAEs (≥2 patients), n (%)	**All grade**	**Grade ≥3**
Thrombocytopenia (includes platelet count decreased)	4 (66.7)	2 (33.3)
Neutropenia (includes neutrophil count decreased)	3 (50)	2 (33.3)
Arthralgia	2 (33.3)	0
Contusion	2 (33.3)	0
Diarrhea	2 (33.3)	0
Musculoskeletal chest pain	2 (33.3)	0
Nausea	2 (33.3)	0
Edema peripheral	2 (33.3)	0
Pyrexia	2 (33.3)	1 (16.7)
BGB-11417 + Zanubrutinib combination (CLL; n=44)		
TEAEs (≥3 patients), n (%)	**All grade**	**Grade ≥3**
Contusion	13 (29.5)	0
Neutropenia (includes neutrophil count decreased)	10 (22.7)	5 (11.4)
Diarrhea	10 (22.7)	0
Nausea	10 (22.7)	0
COVID-19	9 (20.5)	1 (2.27)
Fatigue	9 (20.5)	0
Headache	8 (18.2)	0
Constipation	7 (15.9)	0
Arthralgia	6 (13.6)	0
Petechiae	6 (13.6)	0
Back pain	4 (9.1)	0
Immunization reaction	4 (9.1)	0
Thrombocytopenia (includes platelet count decreased)	4 (9.1)	0
Abdominal pain	3 (6.8)	1 (2.27)
Epistaxis	3 (6.8)	0
Seasonal allergy	3 (6.8)	0

CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

Figure. Reduction in Absolute Lymphocyte Count per Ramp-Up Dose Level With BGB-11417 + Zanubrutinib Combination Therapy in Patients With CLL



CLL, chronic lymphocytic leukemia.