Title: PHASE 1 STUDY WITH THE NOVEL B-CELL LYMPHOMA 2 (BCL-2) INHIBITOR BGB-11417 AS MONOTHERAPY OR IN COMBINATION WITH ZANUBRUTINIB FOR CLL/SLL: PRELIMINARY DATA

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ABSTRACT

Introduction: BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b, dose-escalation/expansion study of BGB-11417 (a highly selective Bcl-2 inhibitor) as monotherapy or in combination with zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor. Data from patients with CLL/SLL are presented.

Methods: Patients received BGB-11417 (40, 80, 160, 320, or 640 mg once daily [QD]) with a ramp-up to the intended target dose to mitigate tumor lysis syndrome (TLS). In combination cohorts, patients received zanubrutinib (320 mg QD or 160 mg twice daily) 8 to 12 weeks before BGB-11417. Dose-limiting toxicity was evaluated with a Bayesian logistic regression model during dose ramp-up through day 21. Minimal residual disease (MRD) was assessed by a European Research Initiative on CLL flow cytometry assay.

Results: As of 15May2022, 50 patients with CLL received treatment (tx): 6 had monotherapy (all relapsed/refractory [R/R]), and 44 had combination tx (R/R, n=22; tx naive [TN], n=22). The monotherapy cohort received BGB-11417 ≤160 mg, and the combination cohorts received BGB-11417 ≤640 mg (R/R CLL) or ≤320 mg (TN CLL; included 8 patients receiving zanubrutinib pre-tx and not yet treated with BGB-11417). Maximum tolerated dose had not been reached in any cohort, and dose escalation is ongoing. Median follow-up was 11.5 months (range, 8.5-18.3; monotherapy) and 5.8 months (range, 0.2-10.5; combination). Tx-emergent adverse events (TEAEs) are listed in the **Table**. With monotherapy, cytopenias were the most common TEAE (≥50%; grade ≥3, 33%). With combination tx, contusion, neutropenia, and low-grade gastrointestinal toxicity were the most common TEAEs (≥23%); neutropenia was the most common grade ≥3 TEAE (11%). One patient discontinued combination tx (disease progression; Richter transformation); none discontinued monotherapy. One monotherapy patient had laboratory TLS (overall, ≤2%) that resolved without intervention. No clinical TLS was reported. Most patients had reductions in absolute lymphocyte count (ALC), with responses seen at doses of ≥1 mg. 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: Preliminary data show that BGB-11417 ± zanubrutinib was well tolerated in most patients. Grade ≥3 neutropenia was uncommon and manageable, and TLS rates were low. Efficacy was supported by rapid ALC reduction during ramp-up. Enrollment for cohorts of venetoclax-treated patients with CLL/SLL will open soon.

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.