Preliminary Safety and Efficacy Data from Patients (Pts) With Relapsed/Refractory (R/R) B-cell Malignancies Treated with the Novel B-cell Lymphoma 2 (BCL2) Inhibitor BGB-11417 in Monotherapy or in Combination with Zanubrutinib

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Background: BCL2, a key regulator of apoptosis, is aberrantly expressed in many hematologic malignancies, which can lead to pathologic cancer cell survival. BCL2 inhibitors have been shown to be safe and effective, resulting in their approval for the treatment of pts with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and acute myeloid leukemia. Treatment with the currently approved BCL2 inhibitor, venetoclax, can be limited by common gastrointestinal toxicities, neutropenia, and the emergence of specific BCL2 mutations around the BH3-binding groove causing resistance. BGB-11417 was developed as a potent and highly selective inhibitor of BCL2. It has shown antitumor activity superior to venetoclax in human acute lymphoblastic leukemia, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) xenograft models (Hu, AACR 3077). BGB-11417 also has a favorable pharmacokinetic profile with excellent bioavailability and selectivity for BCL2 at concentration <1nM. Toxicology studies have shown a broad therapeutic index and tolerable safety profile.

The combination of a BCL2 inhibitor and a BTK inhibitor is tolerable with synergistic activity in CLL and MCL pts (Hillmen, *J Clin Oncol* 2019;37(30):2722-9; Jain, *N Engl J Med* 2019;30;380(22):2095-103; Siddiqi, ASH 2020 S158; Tam, *N Engl J Med* 2018; 378:1211-23). Zanubrutinib is a next-generation BTK inhibitor that has shown excellent activity and favorable toxicity in pts with CLL/SLL (Hillmen, EHA 2021 LB1900) and MCL (Tam, *Blood Adv* 2021;5(12):2577-85); with approval for treatment in MCL. Here we report preliminary results of the BGB-11417-101 trial (NCT04277637) in pts with non-Hodgkin lymphoma (NHL) or CLL/SLL treated with BGB-11417 monotherapy or in combination with zanubrutinib.

Methods: BGB-11417-101 is a phase 1, open label, multicenter, dose-escalation and expansion study. Pts with NHL or CLL/SLL are treated with BGB-11417 as monotherapy or in combination with

zanubrutinib. For dose escalation, pts with R/R B-cell malignancies are enrolled in 1 of 5 potential dose levels of BGB-11417 (40, 80, 160, 320, or 640 mg once daily). All pts utilize a ramp-up to intended target dose that varies by disease type. Pts in the combination therapy arm receive zanubrutinib 320 mg daily beginning 8-12 weeks before BGB-11417 is introduced. Adverse events (AEs) are reported per Common Terminology Criteria for AEs v5.0. Dose-limiting toxicity (DLT; assessed from ramp-up through day 21 at intended daily dose), evaluated by Bayesian logistic regression model, will be used to determine the maximum tolerated dose (MTD).

Results: As of 24 May 2021 (data cutoff) 19 pts had been treated; 14 pts with monotherapy (NHL: n=11; CLL/SLL: n=3) and 5 pts with combination (all CLL; 3 pts were still on zanubrutinib pretreatment; 2 had started combination treatment). Median age was 72 y (range, 50–86); median follow-up was 1.9 mo (range, 0.7–12.4); all pts were R/R with a median of 2 prior regimens (range, 1–4). No DLTs were observed in pts with NHL receiving BGB-11417 monotherapy (n=11) up to the 160 mg dose level. AEs across all dose levels occurring in ≥2 pts (monotherapy) or ≥1 pt (combination) are listed in **Table 1**. A total of 5 pts discontinued treatment (all NHL) due to disease progression (n=4; 2 at 40 mg, 2 at 80 mg) or lack of efficacy (n=1 at 40 mg). No pt discontinued due to AEs. Laboratory tumor lysis syndrome was observed in 1 pt with CLL and high tumor burden (resolved with no sequelae). Initial efficacy after 3-month restaging in pts with CLL/SLL demonstrated 1 partial response (monotherapy arm) at the first dose level tested. All pts with CLL/SLL who have completed ramp-up (n=2, both monotherapy) normalized absolute lymphocyte count (ALC). Marked decreases in ALC were observed in pts with CLL at doses as low as 1 mg (**Figure 1**).

Conclusion: Preliminary results suggest that BGB-11417 monotherapy is tolerable in pts with R/R NHL at the tested dose levels. Further assessment of safety and efficacy of BGB-11417 +/- zanubrutinib in CLL/SLL and NHL will be presented at the meeting, and evaluation in patients with treatment naïve CLL/SLL, R/R MCL, and R/R WM is planned.

Table 1.

BGB-11417 Monotherapy (n=14)		
Adverse Events (≥2 pts), n (%)	**All Grade**	**Grade ≥3**
Nausea	7 (50)	0
AST increased	3 (21.4)	1 (7.1)
Constipation	3 (21.4)	0
Diarrhea	3 (21.4)	0
Dizziness	3 (21.4)	0
Neutrophil count decreased + neutropenia	3 (21.4)	3 (21.4)
ALT increased	2 (14.3)	1
Anemia	2 (14.3)	0
Dyspnea	2 (14.3)	0
Hypokalemia	2 (14.3)	1 (7.1)
Musculoskeletal chest pain	2 (14.3)	0
Peripheral oedema	2 (14.3)	0
Pyrexia	2 (14.3)	1 (7.1)
Vomiting	2 (14.3)	0
BGB-11417 + Zanubrutinib (n=5)		

Adverse Events (≥1 pt), n (%)	All Grade	Grade ≥3
Back Pain	1 (20)	0
Cellulitis	1 (20)	0
Constipation	1 (20)	0
GGT increased	1 (20)	0
Headache	1 (20)	0
Nausea	1 (20)	0
Petechiae	1 (20)	0
Rash maculo-papular	1 (20)	0
Vision blurred	1 (20)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Figure 1. Absolute lymphocyte count