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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Introduction: BGB-11417, a potent and highly selective BCL2 inhibitor, had superior antitumor activity vs venetoclax (approved BCL2 inhibitor) in human acute lymphoblastic leukemia, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma xenograft models. BGB-11417 had a favorable PK profile with excellent bioavailability and BCL2 selectivity at <1 nM. Toxicology studies showed a broad therapeutic index and tolerable safety profile. Zanubrutinib (zanu), a next-generation BTK inhibitor with excellent activity and favorable toxicity in pts with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and MCL, is approved for MCL, R/R marginal zone lymphoma, and Waldenström's macroglobulinemia (WM). Combining BCL2+BTK inhibitors is tolerable with synergistic activity in CLL and MCL.

Methods: BGB-11417-101 (NCT04277637), a phase 1, open-label, multicenter, dose-escalation/expansion study, examined BGB-11417 +/- zanu in non-Hodgkin lymphoma (NHL) or CLL/SLL. For dose escalation, pts with R/R B-cell malignancies were enrolled in 1 of 5 BGB-11417 dose cohorts (40, 80, 160, 320, or 640 mg QD). All pts used a ramp-up to intended target dose that varied by disease. Pts in the combination arm received zanu 320

mg daily starting 8-12 wks before BGB-11417 introduction. Adverse events (AEs) were reported per Common Terminology Criteria for AEs v5.0. Dose-limiting toxicity (DLT) was assessed from ramp-up through day 21 at intended daily dose; Bayesian logistic regression determined the maximum tolerated dose.

Results: As of 24 May 2021 (data cutoff) 19 pts were treated; 14 with monotherapy (NHL: n=11; CLL/SLL: n=3) and 5 with combination (all CLL; 3 on zanu pretreatment; 2 started combination). All pts (median age, 72 y) were R/R (median of 2 prior regimens); median follow-up was 1.9 mo. No DLTs were seen in pts with NHL receiving BGB-11417 alone (n=11) up to 160 mg. Reported AEs across all doses are shown in Table 1. Five pts (all NHL) discontinued treatment (disease progression, n=4 [2 at 40 mg, 2 at 80 mg]; lack of efficacy, n=1 [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-mo restaging in pts with CLL/SLL had 1 one partial response (monotherapy) at the first dose level tested. All pts with CLL/SLL completing ramp-up (n=2, both monotherapy) normalized absolute lymphocyte count (ALC). Marked decreases in ALC occurred at doses as low as 1 mg (Fig 1).

Conclusions: Preliminary results suggest BGB-11417 is tolerable in R/R NHL at the tested dose levels. Updated safety and efficacy data of BGB-11417+/-zanu in CLL/SLL and NHL will be presented; evaluation of 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 edema	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

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

Fig 1. Absolute lymphocyte count in pts with CLL