A Phase 1 Study With the Novel B-Cell Lymphoma 2 (Bcl-2) Inhibitor BGB-11417 As Monotherapy or in Combination with Zanubrutinib (ZANU) in Patients (Pts) With Non-Hodgkin Lymphoma (NHL) or Waldenström macroglobulinemia (WM): Preliminary Data

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Background/introduction: The Bcl-2 inhibitor venetoclax has exhibited activity in pts with NHL in monotherapy (*Clin Cancer Res* 2021;27:4690-5) and in combination regimens (*Blood* 2019;133;1964-7). BGB-11417 is a highly selective Bcl-2 inhibitor with potency >10 times that of venetoclax in biochemical assays. BGB-11417 has favorable pharmacokinetics and a broad therapeutic index that may result in an improved safety profile. 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 pts with NHL (EHA 2022. Abstract P687).

The combination of Bcl-2 and Bruton tyrosine kinase (BTK) inhibitors is tolerable with synergistic activity in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL) (*J Clin Oncol* 2019;37:2722-9; *N Engl J Med* 2019; 380:2095-103; ASH 2020 Abstract S158; *N Engl J Med* 2018;378:1211-23). ZANU is a next-generation BTK inhibitor with favorable activity and safety profiles in pts with CLL/SLL (EHA 2021 Abstract LB1900) and WM (*Blood*. 2020;136(18):2038-2050) with FDA approval for treatment in MCL, marginal zone lymphoma (MZL), and WM. BGB-11417-101 is an ongoing first-in-human phase 1/1b dose-escalation/expansion study (NCT04277637). Data from separate cohorts of MCL, WM and combined NHL (Follicular lymphoma [FL], diffuse large B cell lymphoma [DLBCL], MZL, transformed FL) are presented here.

Methods: In the monotherapy cohorts, pts received BGB-11417 (40, 80, 160, 320, or 640 mg QD) with a ramp-up to the intended dose. In combination cohorts, pts received ZANU (320 mg QD or 160 mg twice daily) 8-12 weeks before BGB-11417. Dose-limiting toxicity for each dose cohort was evaluated by a Bayesian logistic regression model during dose ramp-up through day 21 at the intended dose. Responses were assessed per Lugano criteria. Adverse events (AEs) were reported per Common Terminology Criteria for AEs v5.0, and tumor lysis syndrome (TLS) was assessed per Howard (2011) criteria.

Results: As of May 15 2022, 45 pts with NHL, WM, or MCL received BGB-11417 (34 monotherapy; 11 combination). Monotherapy pts (n=28 NHL [n=18 DLBCL, n=6 FL, n=4 MZL]; n=6 WM) received BGB-11417 doses ≤640 mg. Combination pts (n=11 MCL) received ZANU, and 9 (82%) had also received BGB-11417 doses ≤160 mg (data include 2 pts who are still in the pretreatment phase with ZANU). Dose escalation to 640 mg was completed for NHL monotherapy; all planned doses were tested, with no MTD reached. Dose escalation is ongoing for monotherapy in WM and combination therapy in MCL cohorts.

Median follow-up was 6.5 months (range 0.4-25.3) for monotherapy and 4.8 months (range 0.4-8.9) for combination therapy.

Treatment-emergent AEs (TEAEs) across all dose levels are listed in the **Table**. For monotherapy, the most common TEAEs (≥20%) were nausea (38%), fatigue (24%), constipation, diarrhea and dizziness (21% each); the most common grade ≥3 TEAE was neutropenia (12%). For combination therapy, the most common TEAEs were contusion and neutropenia; grade ≥3 AEs were infrequent. Twenty-five monotherapy pts (22 disease progression [PD]; 1 AE; 2 other reasons) and 2 combination therapy pts (PD) discontinued treatment. No TEAEs leading to death and no TLS were reported to date.

Amongst combined NHL cohorts, 23 pts reached the first response assessment time point, but most were treated below the recommended phase 2 dose (RP2D). Of these pts, 3 responded (n=2 DLBCL, n=1 MZL) including 1 complete response (DLBCL), and notable reductions in the sum of the product of perpendicular diameters (SPD) were seen (**Figure**). In the MCL combination cohort, 6 of 11 (55%) pts responded. In the monotherapy WM cohort, 1 of 4 evaluable pts exhibited minor response at the first dose level tested (80 mg); hemoglobin count increases of more than 20 g/L were seen in 3 of 6 treated pts and all remain on treatment.

Conclusion: These initial data show an encouraging safety profile and preliminary evidence of efficacy for BGB-11417 in NHL, MCL, and WM cohorts. No MTD was reached even at the highest dose level of 640 mg QD. All low-grade TEAEs and grade ≥3 neutropenia were manageable. The response data includes NHL patients mostly treated at doses below the RP2D; longer follow-up of BGB-11417 monotherapy and combination therapy at the RP2D is needed. Monotherapy MCL data are forthcoming.

Table: Summary of Treatment-Emergent Adverse Events

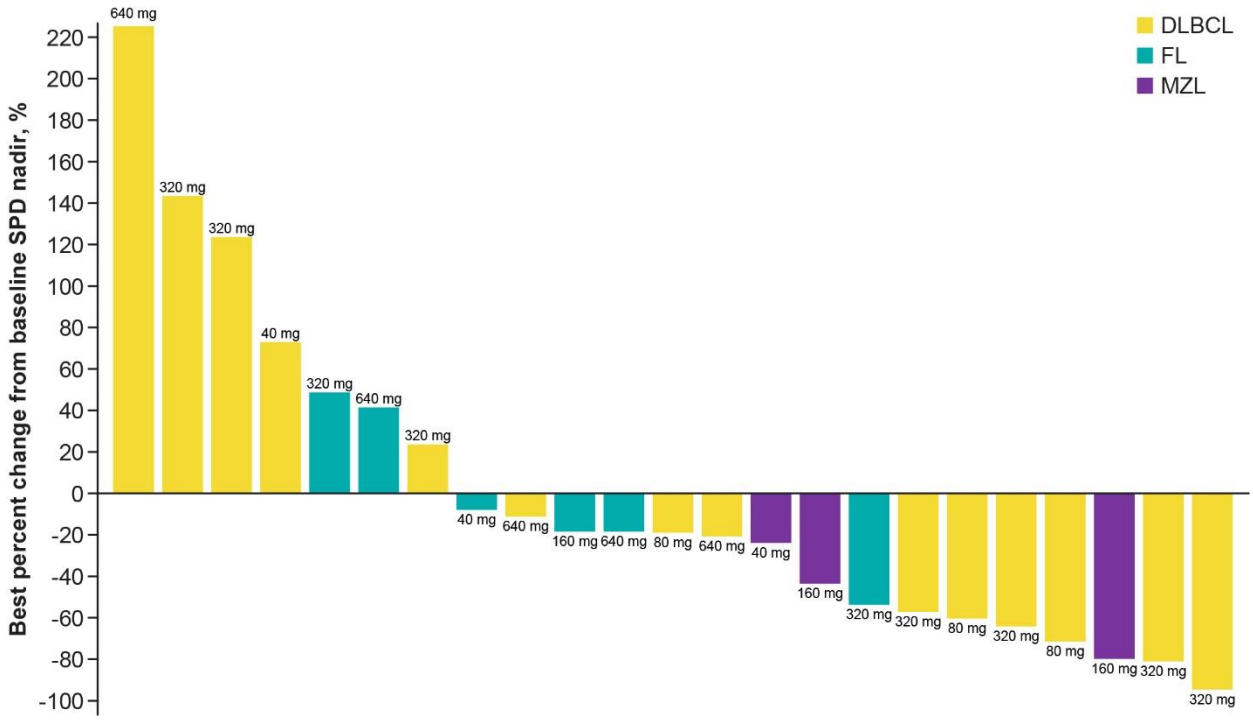
BGB-11417 monotherapy (R/R NHL + WM; n=34)		
TEAEs (≥3 patients), n (%)	**All grade**	**Grade ≥3**
Nausea	13 (38.2)	0
Fatigue	8 (23.5)	0
Constipation	7 (20.6)	0
Diarrhea	7 (20.6)	0
Dizziness	7 (20.6)	0
Fall	6 (17.6)	2 (5.9)
Headache	6 (17.6)	0
Neutropenia (includes neutrophil count decreased)	5 (14.7)	4 (11.8)
Pyrexia	5 (14.7)	0
Abdominal pain	4 (11.8)	2 (5.9)
Anemia	4 (11.8)	1 (2.9)
Urinary tract infection	4 (11.8)	0
Vomiting	4 (11.8)	0
Arthralgia	3 (8.8)	1 (2.9)
Aspartate aminotransferase increased	3 (8.8)	1 (2.9)
Back pain	3 (8.8)	1 (2.9)
Dyspnea	3 (8.8)	0
Hypotension	3 (8.8)	0
Lethargy	3 (8.8)	0
Oedema peripheral	3 (8.8)	0
Cough	3 (8.8)	0

BGB-11417+ZANU combination (R/R MCL; n=11[*])		
TEAEs (≥2 patients), n (%)	**All grade**	**Grade ≥3**
Contusion	3 (27.3)	0
Neutropenia (includes neutrophil count decreased)	3 (27.3)	1 (9.1)
Herpes zoster	2 (18.2)	0
Lethargy	2 (18.2)	0
Nausea	2 (18.2)	0
Thrombocytopenia (includes platelet count decreased)	2 (18.2)	1 (9.1)

[*]Two patients had not yet received BGB-11417 at the time of analysis.

MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; TEAEs, treatment-emergent adverse events; WM, Waldenström macroglobulinemia.

Figure: Percent Change From Baseline in SPD Among Efficacy Evaluable Patients With NHL (DLBCL, FL, or MZL)



Note: WM and MCL are treated in separate cohorts and are not included in this figure.
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; SPD, sum of product of perpendicular diameters.