A Phase 1 Study With the Novel Bcl-2 Inhibitor BGB-11417 as Monotherapy or in Combination With Zanubrutinib in Patients With B-Cell Malignancies: Preliminary Data

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INTRODUCTION

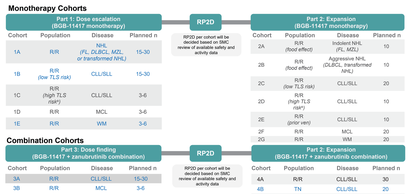
- BGB-11417 is a B-cell lymphoma 2 (Bcl-2) inhibitor
  - BCL2 is a key regulator of apoptosis, aberrantly expressed in many hematologic malignancies[1]
  - The currently approved Bcl-2 inhibitor, venetoclax, has been shown to be safe and effective and is approved for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and acute myeloid leukemia[2]
  - Treatment with venetoclax can be limited by common gastrointestinal toxicities, neutropenia, and the emergence of specific BCL2 mutations around the BH3-binding groove, resulting in resistance[3,4]
- BGB-11417 was developed as a potent and highly selective inhibitor of Bcl-2[5]
  - Antitumor activity of BGB-11417 appeared to be more potent than venetoclax in human acute lymphoblastic leukemia, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) in xenograft mouse models[5]
  - BGB-11417 has a favorable pharmacokinetic (PK) profile with excellent bioavailability and selectivity for Bcl-2 at a concentration of <1 nM[5]
  - Toxicology studies (data on file) have shown BGB-11417 to have a broad therapeutic index and tolerable safety profile
- The combination of venetoclax and the Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, is tolerable and provides synergistic activity in patients with CLL[6-8] or MCL[9]
- Zanubrutinib is a next-generation BTK inhibitor that elicited excellent activity and favorable toxicity in patients with CLL/SLL[10] or MCL.[11] It is currently approved for the treatment of MCL, marginal zone lymphoma (MZL), and Waldenström macroglobulinemia (WM)[12]
  - Early safety data show that combining zanubrutinib with venetoclax in patients with treatment-naive (TN) CLL/SLL appears to be tolerable.[13] Additionally, promising safety and efficacy were seen with the combination of zanubrutinib, obinutuzumab, and venetoclax in patients with CLL[14] or MCL.[15]
- Here, we report preliminary results of the BGB-11417-101 trial (NCT04277637) in patients with non-Hodgkin lymphoma (NHL), WM, or CLL/SLL treated with BGB-11417 monotherapy or BGB-11417 in combination with zanubrutinib

METHODS

Study Design

- BGB-11417-101 is a first-in-human, phase 1, open-label, multicenter, dose-escalation and -expansion study
- Disease-specific dose escalation cohorts are followed by the corresponding expansion cohorts
  - BGB-11417 monotherapy cohorts (parts 1 and 2)
  - BGB-11417 in combination with zanubrutinib cohorts (parts 3 and 4)
- Eligible patients include those with various B-cell malignancies (varies by cohort; **Figure 1**)
- Dose escalation investigates up to 5 potential dose levels of BGB-11417 (40, 80, 160, 320, or 640 mg once daily [QD]) before establishing the recommended phase 2 dose (RP2D)
  - Patients in the combination therapy cohorts received zanubrutinib 320 mg QD beginning 8-12 weeks before BGB-11417 was introduced
- Adverse events (AEs) are reported per Common Terminology Criteria for Adverse Events v5.0 (International Workshop for CLL [iwCLL] for select hematologic toxicities for patients with CLL)
- Response to treatment was assessed by Lugano classification[16] for patients with NHL, iwCLL guidelines[17] for patients with CLL, and Owen criteria for patients with WM[18]

Figure 1. Study Schema

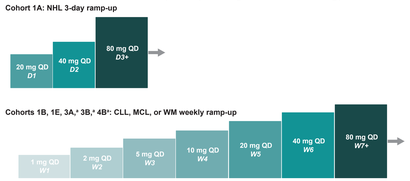


Blue text indicates cohorts presented in this poster. *High TLS risk defined as the presence of any lymph node ≥10 cm or the presence of any lymph node ≥5 cm with concurrent absolute lymphocyte count ≥25×10⁹/L.
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SMC, safety monitoring committee; TLS, tumor lysis syndrome; TN, treatment naive; ven, venetoclax; WM, Waldenström macroglobulinemia.

Dose Escalation

- For dose-escalation cohorts, patients were enrolled in 1 of 5 planned oral BGB-11417 dose levels in cohorts of at least 3 patients (**Figure 2**)
  - Planned daily dose levels: 40 mg, 80 mg, 160 mg, 320 mg, and 640 mg
- Dose-limiting toxicities (DLTs) assessed from ramp-up through day 21 at the intended daily dose, and evaluated by bayesian logistic regression model, were used to determine the maximum tolerated dose (MTD)

Figure 2. Ramp-Up Schemas (Example Target Dose of 80 mg)



[a]Combination cohorts began zanubrutinib treatment 8-12 weeks before and during BGB-11417 ramp-up.
D, day; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; QD, once daily; W, week; WM, Waldenström macroglobulinemia.

Dose Ramp-Up

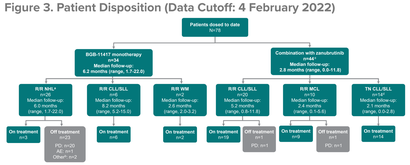
- To protect against potential tumor lysis syndrome (TLS), all patients received a dose ramp-up to the target dose level (**Figure 2**)
  - Patients with NHL (excluding MCL) received a ramp-up over 3 days, with daily dose increases (day 1, 25% of target dose; day 2, 50%) before reaching the target daily dose (day 3+, 100%)
  - Patients with CLL/SLL, MCL, or WM received a longer ramp-up over several weeks, with weekly dose increases (beginning with 1 mg QD, then doubling the dose weekly until the target dose was reached)
- Other TLS prophylaxis included
  - Hydration: oral or intravenous 1.5-2 L/day from ≥1 day before until ≥1 day after each new dose level
  - Antihyperuricemics (allopurinol; rasburicase as needed): from ≥2 days before first dose until 1 week after reaching final target dose level
  - Hospitalization for observation at select ramp-up visits: TLS laboratory results and PK monitored frequently at select time points

RESULTS

Disposition and Baseline

- As of the data cutoff (4 February 2022), cohorts 1A, 1B, 1E, 3A, 3B, and 4B treated patients with the study drug (blue text; **Figures 1** and **3**)

Figure 3. Patient Disposition (Data Cutoff: 4 February 2022)



*FL (n=6), DLBCL (n=17), MZL (n=3). †Includes "other" or "physician decision." ‡n=20 still in zanubrutinib pretreatment phase.
[a]Expansion cohort at 160 mg QD.
AE, adverse event; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; QD, once daily; R/R, relapsed/refractory; TN, treatment-naive; WM, Waldenström macroglobulinemia.

Table 1. Patient and Disease Characteristics

Characteristic	BGB-11417 monotherapy (n=34)	BGB-11417 + zanubrutinib combination (n=44)	All patients (N=78)
Age, median (range), years	72 (55-86)	61 (36-84)	65 (36-86)
ECOG PS, n (%)			
Unknown	1 (2.9)	1 (2.3)	2 (2.6)
0	14 (41.2)	27 (61.4)	41 (52.6)
1	16 (47.1)	15 (34.1)	31 (39.7)
2	3 (8.8)	1 (2.3)	4 (5.1)
Disease types, n (%)			
CLL	6 (17.6)	34 (77.3)	40 (51.3)
R/R DLBCL	17 (50)	N/A	17 (21.8)
R/R FL	6 (17.6)	N/A	6 (7.7)
R/R MZL	3 (8.8)	N/A	3 (3.8)
MCL	0	10 (22.7)	10 (12.8)
WM	2 (5.9)	N/A	2 (2.6)
TN, n (%)	0	14 (31.8)	14 (17.9)
R/R, n (%)	34 (100.0)	30 (68.2)	64 (82.1)
Prior lines of therapy, median (range)	2 (1-6)	1 (1-2)	1 (0-6)
Time from end of most recent systemic therapy to first dose, median (range), months	5.3 (0-49.7)	43.4 (1.6-194.4)	10.8 (0-194.4)

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory; TN, treatment naive; WM, Waldenström macroglobulinemia.

Table 2. Overall Adverse Events

AEs, n (%)	BGB-11417 monotherapy (n=34[a])	BGB-11417 + zanubrutinib combination (n=44[a,b])	All patients (N=78)
Any AEs	32 (94.1)	34 (77.3)	66 (84.6)
Grade ≥3 AEs	14 (41.2)	7 (15.9)	21 (26.9)
Serious AEs	11 (32.4)	5 (11.4)	16 (20.5)
Leading to death	2[c] (5.9)	1 (2.3)[d]	3 (3.8)
Leading to hold of BGB-11417	5[f] (14.7)	1[g] (2.3)	6 (7.7)
Leading to dose reduction of BGB-11417	0	0	0
Leading to discontinuation of BGB-11417	1[h] (2.9)	0	1 (1.3)

[a]All patients have relapsed/refractory disease. [b]Includes 20 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. [c]Includes 14 patients who are treatment naive. [d]Neither related to study drug; 1 death secondary to disease progression and 1 gastrointestinal hemorrhage subsequent to bowel surgery. [e]Cardiac arrest, not related to study drug. [f]Thrombocytopenia, hemoptysis and pyrexia; ALT, AST, and GGT levels increased; neutropenia, pyrexia, and febrile neutropenia; small intestinal obstruction; neutropenia. [g]Dose withheld due to COVID-19 infection. [h]Gastrointestinal hemorrhage subsequent to bowel surgery.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease of 2019; GGT, gamma-glutamyl transferase.

Table 3. Dose-Limiting Toxicities in Dose-Escalation Cohorts

Cohort	40 mg*	80 mg	160 mg	320 mg	640 mg
	Monotherapy				
NHL (1A)	0/3	0/4	1/4	0/9	0/6
CLL (1B)	N/A	1/4	TBD	TBD	TBD
WM (1E)	N/A	TBD	TBD	TBD	TBD
	Combination				
CLL (3A)	0/4	0/3	0/3	TBD	TBD
MCL (3B)	N/A	0/3	TBD	TBD	TBD

*Not tested in cohorts 1B, 1E, and 3B because this dose had been cleared in other cohorts by the time these cohorts were open.
CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; TBD, to be determined; WM, Waldenström macroglobulinemia.

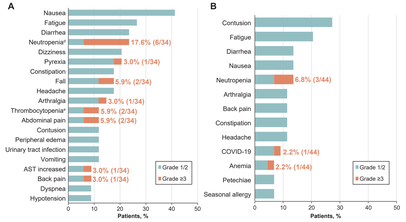
Monotherapy

- Dose escalation was completed for cohort 1A, with no MTD reached through 640 mg, and only 1 DLT of Grade 3 febrile neutropenia was seen at 160 mg
- Dose escalation continues for all other monotherapy dose-escalation cohorts
  - One DLT of Grade 4 neutropenia was seen in a patient with relapsed/refractory (R/R) CLL receiving BGB-11417 monotherapy at 80 mg (patient recovered and continued dosing)

Combination

- Dose escalation continues for all combination dose-escalation cohorts, with no DLTs yet up to 160 mg (CLL) or 80 mg (MCL)
- Cohort 4B, TN CLL expansion, was opened at 160 mg QD; owing to tolerability and promising activity seen during dose escalation, additional dose levels may potentially be expanded in the future

Figure 4. TEAEs Regardless of Causality in ≥3 Patients Receiving (A) Monotherapy (n=34[a]) or (B) Combination Therapy (n=44[b,c])



[a]All patients have relapsed/refractory disease. [b]Includes 20 patients who are are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. [c]Includes 14 patients who were treatment naive. *Neutropenia includes neutrophil count decreased and neutropenia. †Thrombocytopenia includes platelet count decreased and thrombocytopenia.
AST, aspartate aminotransferase; COVID-19, coronavirus disease of 2019; TEAE, treatment-emergent adverse event.

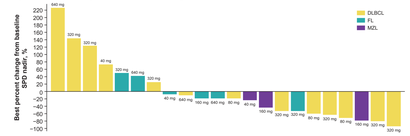
Bcl-2 Inhibitor Events of Interest

- One patient with CLL receiving monotherapy with high baseline TLS risk had a marked tumor flare on BTK inhibitor withdrawal and developed laboratory TLS in a late ramp-up
  - The patient experienced no sequelae from laboratory TLS and resolved by the next day; BGB-11417 did not need to be withheld
- Neutropenia was observed in 8 patients receiving monotherapy (n=6 Grade ≥3; n=5 received growth factor) and 6 patients receiving combination therapy (n=3 Grade ≥3; n=4 received growth factor). All cases resolved without the need for dose reduction

Early Efficacy

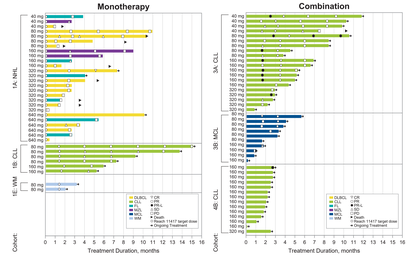
- Although dose escalation has not yet been completed for any cohort and the follow-up is limited, responses were observed at the preliminary dose levels (**Figures 5** and **6**)
- NHL (R/R monotherapy)
  - Significant reductions in the sum of product of perpendicular diameters (SPD) from baseline were seen in most patients (**Figure 5**)
  - Two of 20 patients (10%) have responded: 1 partial response (PR) at 160 mg and 1 complete response (CR) at 320 mg
- WM (R/R monotherapy)
  - Follow-up is limited: 1 of 2 patients (50%) have achieved a minor response at 80 mg
- MCL (R/R combination)
  - Five of 10 patients (50%) have achieved PR or better so far at either 80 or 160 mg, including 1 CR at each dose level
- CLL/SLL
  - Significant reduction in absolute lymphocyte count (ALC) was noted among all patients with CLL during ramp-up, with reduction in lymphocytes noted at dose levels as low as 1 mg (**Figure 7**)
  - R/R monotherapy
    - Four of 6 patients (67%) have achieved partial response with lymphocytosis (PR-L) or better so far at either 80 or 160 mg
  - Combination therapy
    - R/R: 16 of 20 patients (80%) have achieved PR-L or better across dose levels ranging between 40-320 mg
    - TN: follow-up is limited, with most patients still on zanubrutinib pretreatment

Figure 5. Change in SPD Among Patients With NHL



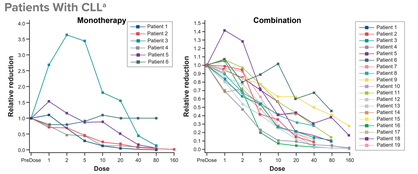
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; SPD, sum of product of perpendicular diameters.

Figure 6. Duration of Treatment and Best Response



CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; WM, Waldenström macroglobulinemia.

Figure 7. Activity of BGB-11417: Reduction in ALC Over Ramp-Up in Patients With CLL[a]



[a]Figures represent reduction in ALC above the ULN (4x10⁹/L) compared to pre–BGB-11417 baseline before next dose escalation (or after 1 week at target dose) per dose. Patients receive each BGB-11417 dose level for 1 week before escalating to the next dose. Combination patients were also receiving zanubrutinib during BGB-11417 ramp-up, beginning 8-12 weeks before the first BGB-11417 dose (Note: 1 patient with normal baseline ALC is excluded from monotherapy figure).
ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia; ULN, upper limit of normal.

CONCLUSIONS

- These early phase 1 results suggest that BGB-11417 is tolerable in patients with CLL or NHL at the dose levels tested
  - Dose escalation concluded for monotherapy patients with NHL with only 1 DLT seen and no MTD reached; only 1 DLT was seen in monotherapy patients with CLL
  - Grade ≥3 AEs have been infrequent and manageable
  - Findings so far suggest that the combination of BGB-11417 and zanubrutinib is well tolerated, similar to BGB-11417 monotherapy
  - Risk of TLS appears limited and manageable; laboratory TLS has been seen in only 1 patient with high TLS-risk CLL receiving monotherapy
- Transient neutropenia was the most frequent Grade ≥3 AE
- Substantial decreases in ALC have been seen during ramp-up for patients with CLL, with promising early response rates among patients with R/R CLL

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DISCLOSURES

JDS: consulting role with AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Genentech/Roche, Seattle Genetics, TG Therapeutics; research funding from Adaptive Biotechnologies, BeiGene, BostonGene, Genentech/Roche, GSK, Moderna, TG Therapeutics

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