A Phase 1 Study With the Novel B-Cell Lymphoma 2 (Bcl-2) Inhibitor BGB-11417 as Monotherapy or in Combination With Zanubrutinib in Patients With CLL/SLL: Preliminary Data

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INTRODUCTION

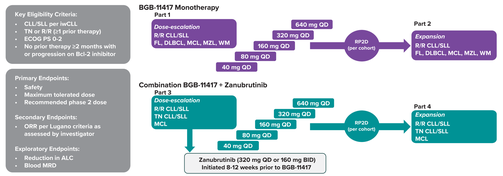
- Bcl-2 inhibition is an established mechanism for treating B-cell malignancies such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1,2]
- The combination of inhibitors of Bcl-2 (Bcl-2i) and Bruton tyrosine kinase (BTKi) has potent activity in CLL and mantle cell lymphoma (MCL)[3-6]
- Ibrutinib with venetoclax in patients with CLL/SLL appears to be effective; however, adverse events (AEs) may limit their use, leaving an unmet need for a safe and efficacious BTKi + Bcl-2i combination regimen[7]
- BGB-11417 has shown more potent and selective Bcl-2 inhibition and better activity against tumors with BCL2 mutations than venetoclax in vitro[7]
  - BGB-11417 has a 14x higher affinity for Bcl-2 than venetoclax; additionally, BGB-11417 has a relative selectivity for Bcl-xL and for BCL-w that is 6x and 9x lower, respectively, than venetoclax
- Zanubrutinib, a next-generation BTK inhibitor, has demonstrated superior efficacy and safety, especially cardiovascular, in head-to-head studies with ibrutinib[8,9]
- Here, preliminary data are presented from a phase 1 study of BGB-11417 as monotherapy or in combination with zanubrutinib in patients with CLL/SLL

METHODS

STUDY DESIGN

- BGB-11417-101 (NCT04277637) is a first-in-human, phase 1, multicenter study in patients with B-cell malignancies; the study design for the CLL/SLL cohorts is shown in **Figure 1**

Figure 1. NCT04277637 Study Design

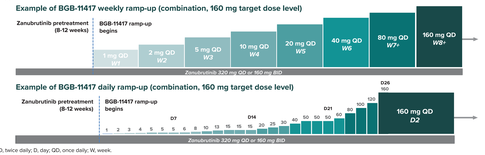


*For reduction in ALC, only data from patients with an ALC >5x10^9/L at baseline were included; minimum ALC among 1 week of each dose level was used for calculation and ALC data were pooled from both monotherapy and combination therapy cohorts; †MRD was measured by ERIC flow cytometry with 10^-4 sensitivity.
ALC, absolute lymphocyte count; Bcl-2, B-cell lymphoma 2; BID, twice daily; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ERIC, European Research Initiative on CLL; IwCLL, International Workshop on CLL; MRD, minimal residual disease; ORR, overall response rate; QD, every day; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive; ULN, upper limit of normal.

DOSE RAMP-UP

- To mitigate potential tumor lysis syndrome (TLS), all patients received either a weekly or daily dose ramp-up to the BGB-11417 target dose (**Figure 2**)
- TLS prophylaxis also included hydration starting 24-48 hours prior to first dose, allopurinol starting 2-3 days prior to first dose, and rasburicase as indicated

Figure 2. Example BGB-11417 Dose Ramp-up Schedules

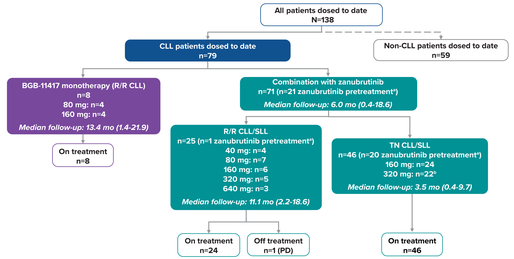


BID, twice daily; D, day; QD, once daily; W, week.

RESULTS

- As of September 1, 2022, 79 patients with CLL/SLL received either BGB-11417 as monotherapy (n=8) or in combination with zanubrutinib (n=71; **Figure 3**)

Figure 3. Patient Disposition



Data cutoff date: September 1, 2022. ‡Patients in the zanubrutinib pretreatment phase who have not yet received BGB-11417; bAll patients were assigned to a weekly ramp-up schedule except for n=4 TN patients (320 mg dose level).
CLL, chronic lymphocytic leukemia; mo, month; PD, progressive disease; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive.

- The overall study population had a median age of 62 years and 79% of patients were male (**Table 1**)
- Del(17p) and *TP53* mutation were found in 17% and 23% of patients, respectively

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	BGB-11417 monotherapy (n=8)	BGB-11417 + zanubrutinib (n=71)	All patients (N=79)
Median age, (range), years	68.5 (55-84)	61.0 (35-84)	62.0 (35-84)
Sex, n (%)			
Male	6 (75.0)	56 (78.9)	62 (78.5)
Female	2 (25.0)	15 (21.1)	17 (21.5)
ECOG PS, n (%)			
0	3 (37.5)	49 (69.0)	52 (65.8)
1	5 (62.5)	21 (29.6)	26 (32.9)
2	0	1 (1.4)	1 (1.3)
Disease type, n (%)			
CLL	8 (100)	70 (99)	78 (99)
SLL	0	1 (1)	1 (1)
R/R, n (%)	8 (100)	25 (35.2)	33 (41.8)
Number of prior lines of therapy, median (range)	2 (1-3)	1 (1-2)	1 (1-3)
Time from end of most recent systemic therapy to first dose, median (range), months	0.4 (0.0-10.2)	57.0 (1.6-194.4)	45.4 (0.0-194.4)
TN, n (%)	0	46 (64.8)	46 (58.2)
Risk status, n (%)			
del(17p)	2 (25)	11 (15.5)	13 (16.5)
TP53[a,c]	3 (37.5)	15 (21.1)	18 (22.8)

CLL, chronic lymphocytic leukemia; del(17p), deletion in chromosome 17p; ECOG, Eastern Cooperative Oncology Group Performance Status; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive; *TP53*[a,c], mutation of p53.

SAFETY

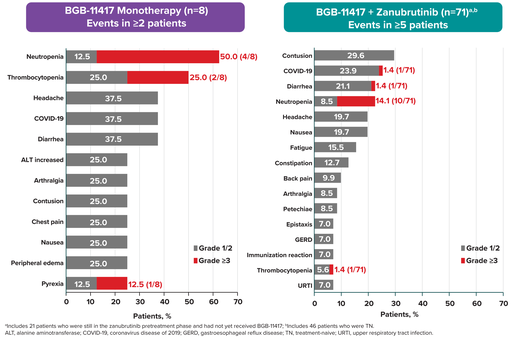
- Toxicity did not seem dose dependent; only 1 DLT (febrile neutropenia) occurred among patients receiving monotherapy (80 mg) and no DLTs have been observed to date with combination therapy at any dose level (**Table 2**)
- No AEs leading to death or BGB-11417 discontinuation occurred in any patients
- The most common AEs are shown in **Figure 4**; TEAEs of interest included TLS, GI toxicity, and neutropenia
  - No clinical TLS occurred; one event of laboratory TLS occurred in a patient with high tumor burden who was receiving monotherapy
    - No TLS was observed with daily ramp-up (TN combination, 320 mg; n=3)
  - Diarrhea was mostly grade 1; 12.5% in the monotherapy cohort and 5.6% in the combination cohort had grade ≥2 diarrhea and 1 patient in the combination cohort had grade 3 diarrhea
- Granulocyte-colony stimulating factor (G-CSF) was administered to 50% of patients in the monotherapy cohort and 14.1% in the combination cohort to treat neutropenia
  - 3.8% of patients received >1 course of G-CSF to treat neutropenia

Table 2. Safety Summary

TEAE, n (%)	BGB-11417 monotherapy (n=8)	BGB-11417 + zanubrutinib (n=71)	All patients (N=79)
Any AEs	8 (100)	61 (86)	69 (87)
Grade ≥3	5 (63)	20 (28)	25 (32)
Serious AEs	2 (25)	7 (10)	9 (11)
Treated with BGB-11417	8	50	58
Leading to hold of BGB-11417	5 (62.5)	14 (28)	19 (33)
Leading to dose reduction of BGB-11417	0	1 (2)	1 (2)

AE, adverse event; TEAE, treatment-emergent adverse event.

Figure 4. Most Frequent AEs



[a]Includes 21 patients who were still in the zanubrutinib pretreatment phase and had not yet received BGB-11417; [b]Includes 46 patients who were TN.
ALT, alanine aminotransferase; COVID-19, coronavirus disease of 2019; GERD, gastroesophageal reflux disease; TN, treatment-naive; URTI, upper respiratory tract infection.

EFFICACY

- With a median follow-up of 13.4 months in the BGB-11417 monotherapy cohort and 11.1 months in the BGB-11417 combination cohort, patients with R/R CLL/SLL had an ORR of 67% and 95%, respectively (**Table 3**)

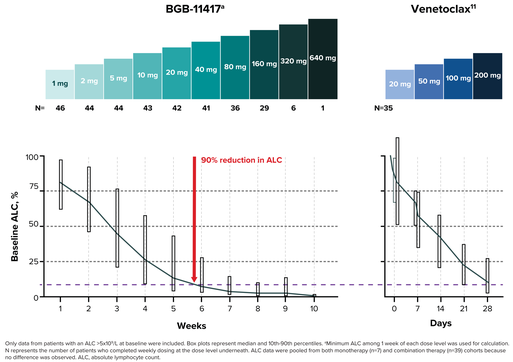
Table 3. ORR

Parameter	BGB-11417 monotherapy R/R (n=8)	BGB-11417 + zanubrutinib R/R (n=25)	BGB-11417 + zanubrutinib TN (n=46)
Treated with BGB-11417	8	24	26
Efficacy-evaluable	6	20[a]	11[a]
ORR	4 (67)	19 (95)	11 (100)
CR	2 (33)	6 (30)	2 (18)
PR	2 (33)	13 (65)	9 (82)
SD	2 (33)	1 (5)	0
PD	0	0	0
Median follow-up, months (range)	13.4 (1.4-21.9)	11.1 (2.2-18.6)	3.5 (0.4-9.7)

[a]n=2 (R/R) and n=11 (TN) responded after zanubrutinib pretreatment but have not yet had response assessment on combination treatment; they are not included here.
CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive.

- After weekly ramp-up to 40 mg BGB-11417, a reduction of ~90% in absolute lymphocyte count (ALC) was observed (**Figure 5**; BGB-1147 at 40 mg + venetoclax at 200 [1:5])
- Blood minimal residual disease (MRD) negativity was observed at ≥80 mg after 6 months (monotherapy and combination cohorts, R/R CLL/SLL; data not shown)
- The undetectable MRD (uMRD) rate increased with longer follow-up and higher dose (160 mg and 320 mg were immature at the time of data cutoff; data not shown)

Figure 5. Reduction in Absolute Lymphocyte Counts



Only data from patients with an ALC >5x10^9/L at baseline were included. Box plots represent median and 10th-90th percentiles. [a]Minimum ALC among 1 week of each dose level was used for calculation. N represents the number of patients who completed weekly dosing at the dose level underneath. ALC data were pooled from both monotherapy (n=7) and combination therapy (n=39) cohorts because no difference was observed. ALC, absolute lymphocyte count.

CONCLUSIONS

- BGB-11417, alone or in combination with zanubrutinib, was well tolerated in patients with TN or R/R CLL/SLL
  - Dose escalation continues to 640 mg with only 1 DLT; MTD was not achieved
  - Grade ≥3 neutropenia and grade ≥2 diarrhea were uncommon and manageable
  - Only 1 event of laboratory TLS was seen; TLS was mitigated by the prophylactic measures and ramp-up schedule
  - The AEs observed in this trial were consistent with those observed in a BGB-11417 study in patients with NHL[9], in which doses up to 640 mg were tested and no MTD was reached
- Promising efficacy was seen with BGB-11417 as monotherapy and in combination with zanubrutinib in both TN and R/R CLL/SLL
- Based on ALC reduction, BGB-11417 may be ~5X as potent as venetoclax by dose
- MRD data are preliminary but appear promising
- A cohort of venetoclax-treated patients with CLL/SLL is currently recruiting

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DISCLOSURES

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