Abstract 000323

Preliminary Safety and Efficacy Data from Patients With Relapsed/Refractory 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 is a novel BCL2 inhibitor
  - BCL2 is a key regulator of apoptosis, aberrantly expressed in many hematologic malignancies[1]
  - BCL2 inhibitors have been shown to be safe and effective, and are approved for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and acute myeloid leukemia[2]
  - 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[3,4]
- BGB-11417 was developed as a potent and highly selective inhibitor of BCL2[5]
  - Antitumor activity of BGB-11417 was superior to venetoclax in human acute lymphoblastic leukemia, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma xenograft mouse models[5]
  - BGB-11417 has a favorable pharmacokinetic profile with excellent bioavailability and selectivity for BCL2 at concentration <1nM[5]
  - Toxicology studies (data on file) have shown BGB-11417 to have a broad therapeutic index and tolerable safety profile
- The combination of a BCL2 inhibitor and a Bruton tyrosine kinase (BTK) inhibitor is tolerable with synergistic activity in patients with CLL[6-8] or MCL[9]
  - Zanubrutinib is a next-generation BTK inhibitor that has shown excellent activity and favorable toxicity in patients with CLL/SLL[10] or MCL[11] and is currently approved for the treatment of MCL, marginal zone lymphoma, and Waldenström macroglobulinemia (WM)
- Here we report preliminary results of the BGB-11417-101 trial (NCT04277637) in patients with non-Hodgkin lymphomas (NHLs) or CLL/SLL treated with BGB-11417 monotherapy or in combination with zanubrutinib

METHODS

Study Design

- BGB-11417-101 is a phase 1, open label, multicenter, dose-escalation and expansion study
- Disease-specific dose-escalation cohorts will be followed by corresponding expansion cohorts
  - BGB-11417 monotherapy cohorts (Parts 1 and 2)
  - BGB-11417 in combination with zanubrutinib cohorts (Parts 3 and 4)
- Eligible patients included those with various relapsed/refractory (R/R) B-cell malignancies (varies by cohort, see **Figure 1**)
- Dose escalation investigated up to 5 potential dose levels of BGB-11417 (40, 80, 160, 320, or 640 mg once daily) before establishing a recommended phase 2 dose
  - Patients in the combination therapy cohorts received zanubrutinib 320 mg daily (160 mg twice a day or 320 mg once a day) beginning 8-12 weeks before BGB-11417 was introduced
- Dose-limiting toxicities (DLTs; assessed from ramp-up through day 21 at intended daily dose), evaluated by Bayesian logistic regression model, were used to determine the maximum tolerated dose
- Adverse events (AEs) were reported per Common Terminology Criteria for AEs v5.0 (International Workshop on CLL [iwCLL] for select hematologic toxicities for patients with CLL)
- Response to treatment was assessed by Lugano classification[12] for patients with NHL and by iwCLL guidelines[13] for patients with CLL

Figure 1. Study Schema

Monotherapy Cohorts

Part 1: DOSE ESCALATION (BGB-11417 Monotherapy) — RP2D — Part 2: EXPANSION (BGB-11417 Monotherapy)

Cohort	Population	Disease	Planned N
1A	R/R	NHL (*FL, DLBCL, MZL, or transformed NHL*)	15-30
1B	R/R (*low TLS risk*)	CLL/SLL	15-30
1C	R/R (*high TLS risk*[a])	CLL/SLL	3-6
1D	R/R	MCL	3-6
1E	R/R	WM	3-6

RP2D per cohort will be decided based on SMC review of available safety and activity data

Cohort	Population	Disease	Planned N
2A	R/R (*Food Effect*)	Indolent NHL (*FL, MZL*)	10
2B	R/R (*Food Effect*)	Aggressive NHL (*DLBCL, transformed NHL*)	10
2C	R/R (*low TLS risk*)	CLL/SLL	20
2D	R/R (*high TLS risk*[a])	CLL/SLL	10
2E	R/R (*prior ven*)	CLL/SLL	10
2F	R/R	MCL	20
2G	R/R	WM	20

Combination Cohorts

Part 3: DOSE FINDING (BGB-11417 + Zanubrutinib Combination) — RP2D — Part 4: EXPANSION (BGB-11417 + Zanubrutinib Combination)

Cohort	Population	Disease	Planned N
3A	R/R	CLL/SLL	15-30
3B	R/R	MCL	3-6

RP2D per cohort will be decided based on SMC review of available safety and activity data

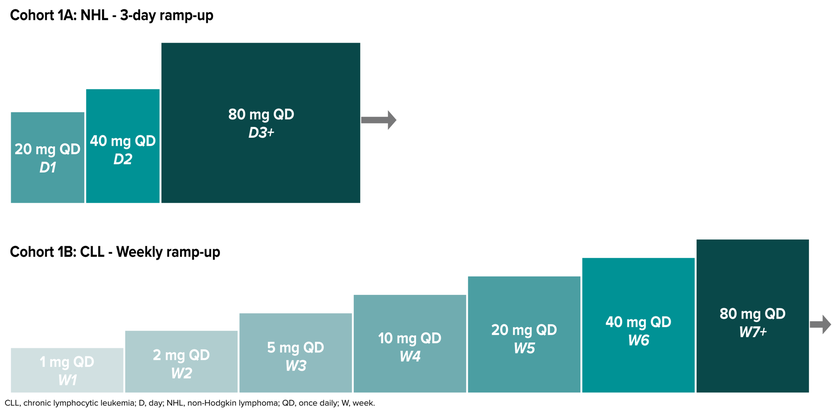
Cohort	Population	Disease	Planned N
4A	R/R	CLL/SLL	30
4B	TN	CLL/SLL	20
4C	R/R	MCL	20

Data for Cohorts 1A, 1B , 3A, and 3B are presented here.
[a]High TLS risk was 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, chronic lymphocytic leukemia; 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; SLL, small lymphocytic lymphoma; SMC, safety monitoring committee; TLS, tumor lysis syndrome; TN, treatment naive; ven, venetoclax; WM, Waldenström macroglobulinemia.

Dose Escalation

- To protect against potential tumor lysis syndrome (TLS), all patients received a dose ramp-up to the target dose level (**Figure 2**)
  - Patients with NHLs 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 or MCL received a longer ramp-up over several weeks, with weekly dose increases (beginning with 1 mg daily, and 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 following 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 for select ramp-up visits: TLS laboratory results and pharmacokinetics were monitored frequently at select time points

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



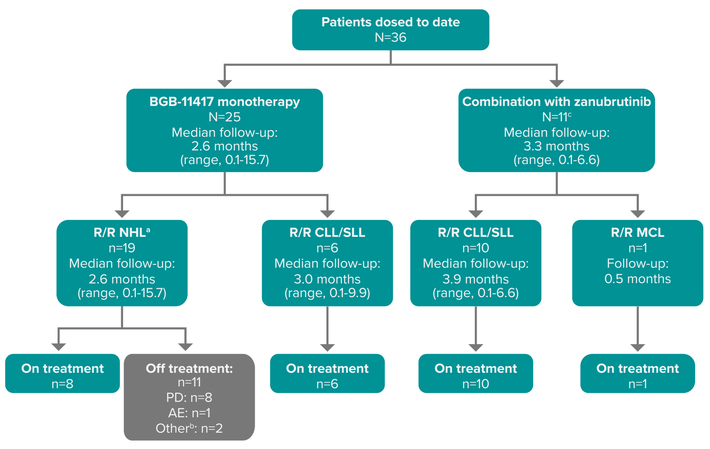
CLL, chronic lymphocytic leukemia; D, day; NHL, non-Hodgkin lymphoma; QD, once daily; W, week.

RESULTS

Disposition and Baseline

- Data cutoff was 25 September 2021
- As of data cutoff, Cohorts 1A, 1B, 3A, and 3B have opened and enrolled patients (**Figure 3**)

Figure 3. Patient Disposition (Data Cutoff 25 September 2021)



[a]FL, DLBCL, tNHL, and MZL. [b]Includes "other" or "physician decision." [c]N=4 still in zanubrutinib pretreatment phase.
AE, adverse event; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; tNHL, transformed NHL.

Table 1. Patient and Disease Characteristics

Characteristic	BGB-11417 Monotherapy (N=25)	BGB-11417 + Zanubrutinib Combination (N=11)	All Patients (N=36)
Age, median (range), year	72 (55-86)	60 (41-75)	68.5 (41-86)
ECOG PS, n (%)			
0	10 (40)	7 (63.6)	17 (47.2)
1	13 (52)	4 (36.4)	17 (47.2)
2	2 (8)	0	2 (5.6)
Disease types, n (%)			
CLL	6 (24)	10 (90.9)	16 (44.4)
DLBCL	12 (48)	—	12 (33.3)
FL	4 (16)	—	4 (11.1)
MZL	3 (12)	—	3 (8.3)
MCL	0	1 (9.1)	1 (2.8)
No. of prior lines of therapy, median (range)	2 (1-5)	1 (1-2)	1 (1-5)
Time from end of most recent systemic therapy to first dose median (range), months	7.7 (9-49.7)	45.5 (1.6-194.4)	11.4 (1.7-34.2)

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; —, not applicable.

Safety

- Safety data for all 36 patients (from monotherapy cohorts and combination cohorts) are shown in **Table 2** and **Figure 4**

Table 2. Overall Treatment-Emergent Adverse Events

AEs, n (%)	BGB-11417 Monotherapy (N=25)	BGB-11417 + Zanubrutinib Combination (N=11)	All Patients (N=36)
Any AE	22 (88)	9 (82)	31 (86)
Grade ≥3 AEs	11 (44)	0	11 (30)
Serious AEs	9 (36)	0	9 (25)
Leading to death	2 (8)	0	2 (6)[a]
AEs leading to hold of BGB-11417	4 (16)	0	4 (11)[b]
AEs leading to dose reduction of BGB-11417	0	0	0
AEs leading to discontinuation of BGB-11417	1 (4)	0	1 (3)[c]

[a]Neither related to study drug; 1 death secondary to disease progression and 1 GI hemorrhage subsequent to bowel surgery. [b]ALT increased and GGT increased; neutropenia, pyrexia, and febrile neutropenia; GI hemorrhage and small intestinal obstruction; neutropenia. [c]GI hemorrhage subsequent to bowel surgery.
AE, adverse event; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; GI, gastrointestinal.

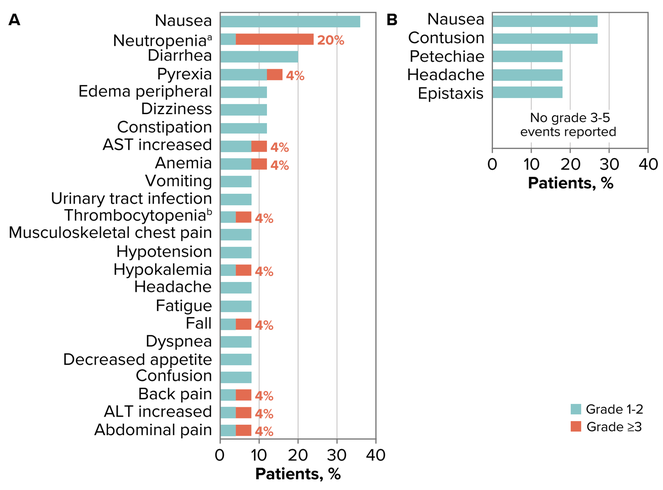
Table 3. Dose-Limiting Toxicities in Dose-Escalation Cohorts

Cohort	40 mg	80 mg	160 mg	320 mg	640 mg
Monotherapy					
NHL (1A)	0/3	0/4	1/4	0/3	TBD
CLL (1B)	—	1/4	TBD	TBD	TBD
Combination					
CLL (3A)	0/4	0/3	TBD	TBD	TBD

CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; TBD, to be decided; —, not applicable.

- One DLT of grade 3 febrile neutropenia was seen in a patient with R/R NHL receiving BGB-11417 monotherapy at a dose of 160 mg
  - No DLTs were seen at the 320-mg dose level
- One DLT of grade 4 neutropenia was seen in a patient with R/R CLL receiving BGB-11417 monotherapy at a dose of 80 mg
- No DLTs have been seen among patients with R/R CLL receiving combination therapy at doses of 80 mg or less

Figure 4. Treatment-Emergent AEs Regardless of Causality Occurring in ≥2 Patients Receiving (A) Monotherapy (N=25) or (B) Combination Therapy (N=11)



[a]Neutropenia: combines "neutrophil count decreased" and "neutropenia." [b]Thrombocytopenia: combines "platelet count decreased" and "thrombocytopenia."
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase.

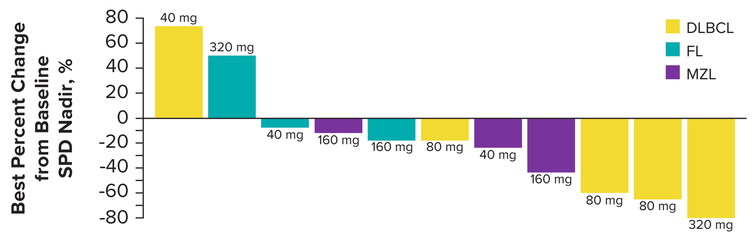
BCL2 Inhibitor Events of Interest

- One patient receiving monotherapy with high baseline TLS risk had a marked tumor flare on BTK inhibitor withdrawal and developed laboratory TLS in late ramp-up
  - The patient experienced no sequalae from laboratory TLS and resolved by the next day; BGB-11417 did not need to be held
- Neutropenia was observed in 6 patients receiving monotherapy; of them, 5 experienced grade ≥3 neutropenia

Early Efficacy

- Efficacy data are limited as dose escalation is not complete for any cohort and not all patients have reached their first response assessment, but responses have been observed at preliminary dose levels
- NHL
  - To date, no patients with NHL have achieved a response to BGB-11417 monotherapy
  - Decreases in sum of the products of perpendicular diameters have been seen at all dose levels tested (**Figure 5**)

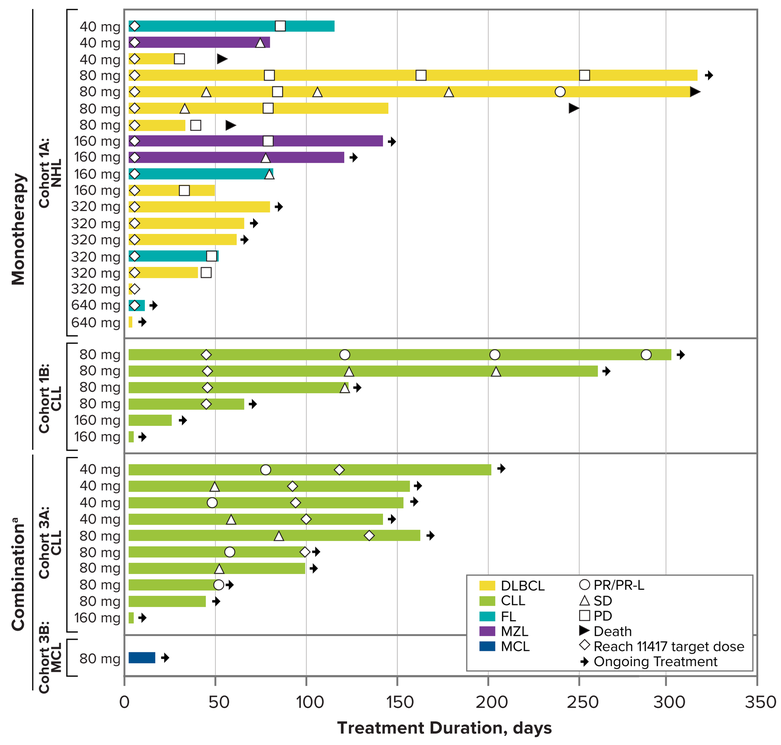
Figure 5. Change in SPD among Patients with NHL[a]



[a]Includes all patients from Cohort 1A that had a post-baseline CT scan as of data cutoff (n=11).
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; SPD, sum of the products of perpendicular diameters.

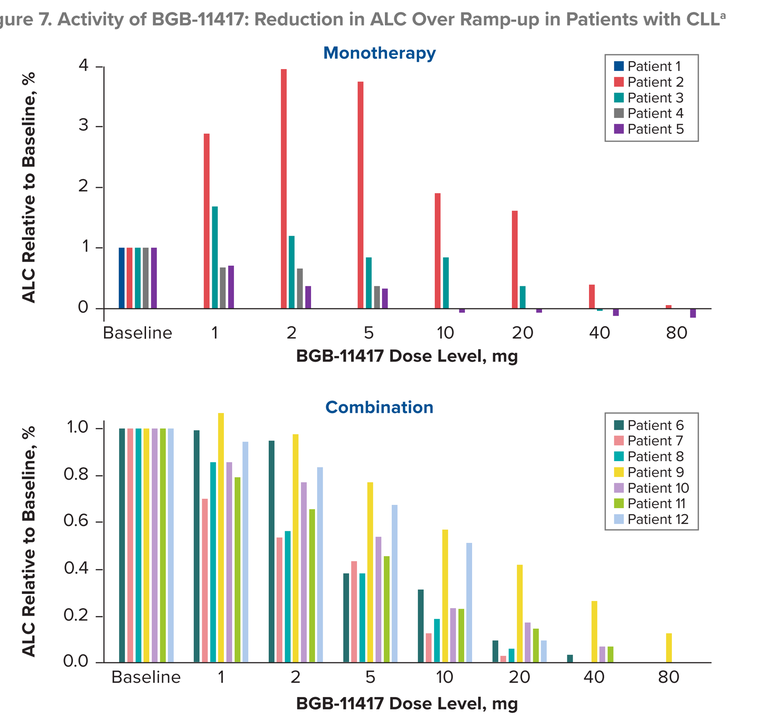
- CLL/SLL
  - Monotherapy treatment resulted in 1 of 4 patients responding at the 80-mg dose level, whereas with combination treatment 4 of 10 patients responded with partial response with lymphocytosis or better (n=2 at both 40 mg and 80 mg)
  - Significant reduction in absolute lymphocyte count (ALC) was noted among all patients with CLL during ramp-up, with reduction in lymphocytes noted at dose levels as low as 1 mg

Figure 6. Duration of Treatment and Best Response



[a]Duration of treatment includes 8-12 weeks of zanubrutinib monotherapy prior to initiation of BGB-11417 + zanubrutinib combination
CLL, chronic lymphocytic leukemia; 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, PR with lymphocytosis; SD, stable disease.

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. Patients on combination therapy 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 was excluded from the monotherapy figure).
ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia.

CONCLUSIONS

- These early phase 1 results suggest that BGB-11417 is tolerable in patients with CLL or NHL at the dose levels tested
  - Only 1 DLT was seen across the 4 dose levels tested in NHL, and 1 DLT was seen in a CLL cohort
  - Grade ≥3 AEs have been infrequent and manageable, with none seen so far in combination cohorts
- Risk of TLS appears limited and manageable: laboratory findings suggesting TLS were seen in 1 patient with CLL who had high TLS risk
- Transient neutropenia has been the most frequent grade ≥3 AE
- Substantial decreases in ALC have been seen during ramp-up for CLL patients
- Evaluation of patients with MCL, treatment-naive CLL, or WM is planned for future cohorts

DISCLOSURES

KL: research funding from Novartis, Takeda, Jansen, Abbvie, Amgen; consultant for Abbvie, Beigene, Takeda, Iqone; advisory board for AbbVie, AstraZeneca, Iqone, GSK, Astellas, Beigene, Novartis

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AA: travel expenses from Amgen

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JH: employed by and stock ownership with BeiGene

YF: employed by and equity ownership with BeiGene

JH: employed by BeiGene; equity, stock, and divested equity ownership with BeiGene and Protara Therapeutics; advisory board for Protara Therapeutics; travel expenses from BeiGene and Protara Therapeutics

DS: employed by and stock ownership with BeiGene; research funding from AbbVie, Amgen, Celgene, Roche, MSD, Acerta, Pharmacyclics, GSK, and Janssen; honoraria and travel expenses from AbbVie

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FPO

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