A Phase 1 Study With the Novel B-Cell Lymphoma 2 Inhibitor BGB-11417 as Monotherapy or in Combination With Zanubrutinib in Patients With Non-Hodgkin Lymphoma or Waldenström

Abstract 000233

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INTRODUCTION

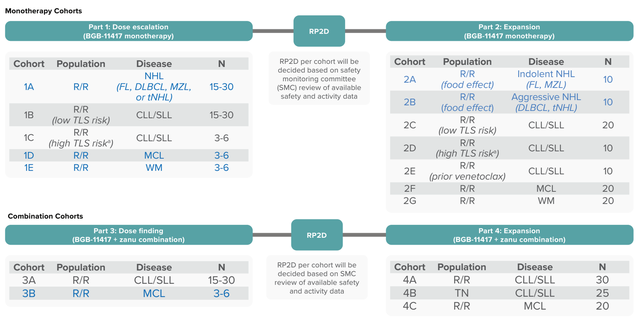
- BGB-11417 is a Bcl-2 inhibitor and key regulator of apoptosis, aberrantly expressed in many hematologic malignancies[1]
  - The currently approved Bcl-2 inhibitor, venetoclax, has been shown to be safe and effective and is approved for the treatment of patients with CLL/SLL and AML[2,3]
  - Treatment with venetoclax can be limited by common GI toxicities, neutropenia, and the emergence of specific BCL2 mutations around the BH3-binding groove[4]
- BGB-11417 was developed as a potent and highly selective inhibitor of Bcl-2[5]
  - BGB-11417 inhibits Bcl-2 in vitro with an IC_{50} of 0.01 nM compared to 0.20 nM for venetoclax
  - Antitumor activity of BGB-11417 appears to be more potent than venetoclax in human ALL and MCL cell lines and in xenograft mouse models of DLBCL[6]
  - BGB-11417 has a favorable PK profile with excellent bioavailability and selectivity for Bcl-2
  - Toxicology studies have shown BGB-11417 to have a broad therapeutic index and tolerable safety profile[7]
- Zanubrutinib (zanu) is a next-generation BTK inhibitor that elicited activity and favorable toxicity/tolerability and has been approved for the treatment of patients with CLL/SLL, MCL, MZL, and WM[8-14]
- Zanu achieved superior PFS vs ibrutinib in a final analysis of the phase 3 ALPINE trial with less atrial fibrillation and a favorable safety profile[15]
- The combination of ibrutinib with venetoclax in patients with R/R MCL or TN CLL/SLL appears to be effective, but the side-effect profile can be problematic, with high rates of diarrhea in some trials[16,17]
- Here, we report preliminary results of the BGB-11417-101 trial (NCT04277637) in patients with NHL, including separate cohorts for MCL and WM, treated with either BGB-11417 monotherapy or in combination with zanu

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 were followed by the corresponding expansion cohorts:
  - BGB-11417 monotherapy cohorts (parts 1 and 2)
  - BGB-11417 in combination with zanu cohorts (parts 3 and 4)
- Eligible patients included those with various B-cell malignancies
- Dose escalation investigated up to 5 potential dose levels of BGB-11417 (40, 80, 160, 320, or 640 mg QD) before establishing RP2D
- AEs were reported per CTCAE v5.0
- Response to treatment was assessed by Lugano classification for patients with NHL and Owen criteria for patients with WM[18,19]

Figure 1. Study Design

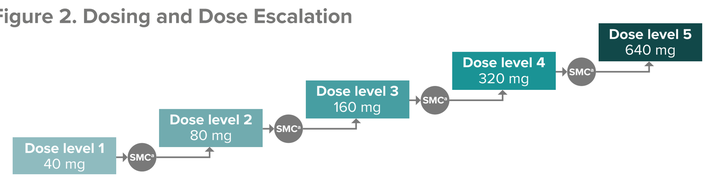


Blue text indicates cohorts presented in this poster.
[a]High TLS risk defined as the presence of any lymph node ≥10 cm or the presence of any lymph node ≥5 cm with concurrent absolute lymphocyte count ≥25×10⁹/L.

Dosing and Dose Escalation

- BGB-11417 dosed QD ≤30 minutes after a low-fat meal
- For combination therapy, zanu (160 mg BID or 320 mg QD) started 8-12 weeks (depending on tumor burden) before starting BGB-11417
- Starting target dose level for a cohort may be >40 mg if established as safe in other cohorts per SMC

Figure 2. Dosing and Dose Escalation

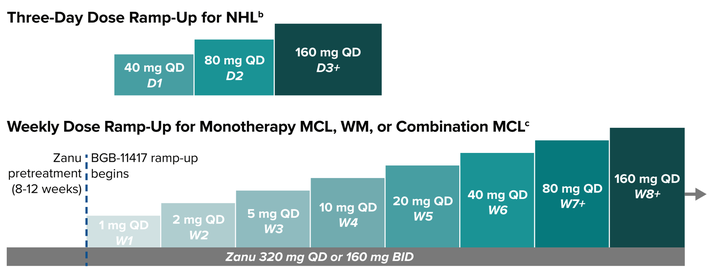


[a]SMC review of dose-level cohort data before dose escalation.

TLS Prophylaxis

- To mitigate potential TLS, all patients received a dose ramp-up to the target dose (**Figure 3**)
  - Patients with NHL (excluding MCL and WM) received a 3-day ramp-up, with daily dose increases (25%, 50%, and 100% of the target dose during days 1-3)
  - Patients with MCL or WM received weekly dose increases, beginning with 1 mg QD then doubling until the target dose was reached
  - Required hospitalization at first 3 visits for ramp-up dose (no longer required)
- Other TLS prophylaxis
  - Hydration: oral or intravenous 1.5-2 L/day from ≥1 day before until ≥1 day after each new dose level
  - Antihyperuricemics (allopurinol or rasburicase): from ≥2 days before first dose until 1 week after reaching final target dose level
  - TLS laboratory results and PK monitored frequently at select time points

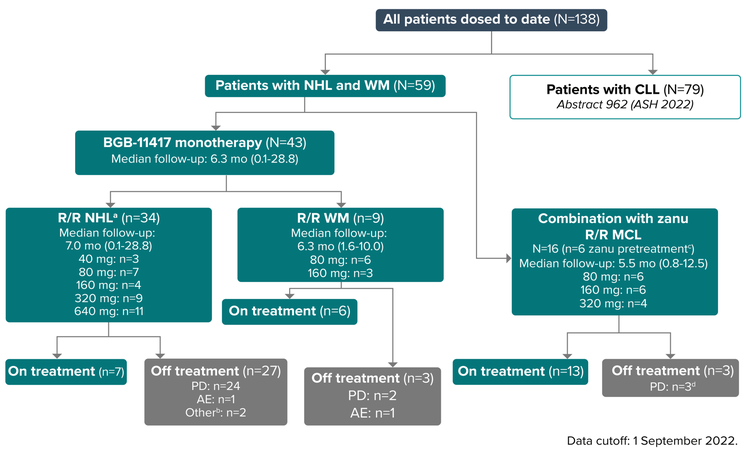
Figure 3. Examples of Ramp-Up Schedules[a]



[a]Ramp-up will depend on target dose: examples show 160 mg target dose. [b]Three-day ramp-up doses vary depending on target dose: D1 25%, D2 50%, D3+ 100%. [c]Weekly ramp-up target doses follow the same weekly ramp-up schedule, stopping once they reach the target dose (lower target dose = shorter ramp-up). Ramp-up is identical for monotherapy.

RESULTS

Figure 4. Patient Disposition



Data cutoff: 1 September 2022.

[a]Includes DLBCL (n= 18), FL (n=6), MZL (n=7), MCL (n=3). [b]Includes other or physician decision. [c]Patients who are still in the zanu pretreatment phase and have not yet received BGB-11417. [d]One patient progressed on zanu pretreatment before receiving BGB-11417.

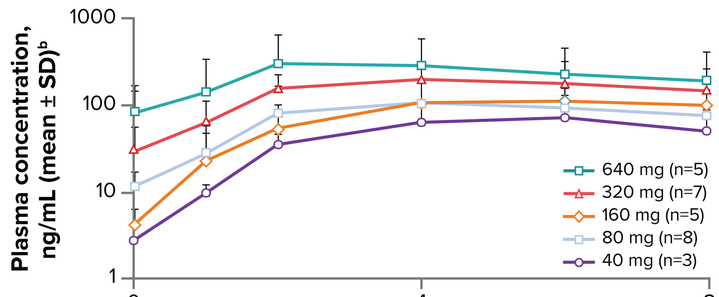
Table 1. Patient Characteristics

Characteristic	BGB-11417 monotherapy (n=43)	BGB-11417 + zanu (n=16)	All patients (N=59)
Median age (range), years	71 (48-86)	62 (45-85)	70 (45-86)
Sex, n (%)			
Male	30 (70)	12 (75)	42 (71)
Female	13 (30)	4 (25)	17 (29)
ECOG PS, n (%)			
0	18 (42)	7 (44)	25 (42)
1	22 (51)	8 (50)	30 (51)
2	3 (7)	0	3 (5)
Unknown	0	1 (6)	1 (2)
Disease type, n (%)			
DLBCL	18 (42)	0	18 (31)
FL	6 (14)	0	6 (10)
MZL	7 (16)	0	7 (12)
MCL	5 (12)	16 (100)	21 (36)
WM	9 (21)	0	9 (15)
Median no. of prior lines of therapy	2 (1-8)	1 (1-3)	2 (1-8)
Median time from end of most recent systemic therapy to first dose (range), months	3.1 (0-158)	15.9 (3-64)	8.5 (0-158)

All enrolled patients were R/R.

- Preliminary steady-state PK data from patients with NHL or CLL who received BGB-11417 monotherapy at 40 to 640 mg target doses QD for 3 weeks
  - Dose-dependent PK from 40 to 640 mg
  - Fast absorption (median T_{max}~4 hours)
  - Short half-life (median $T_{1/2}$~5 hours)
  - No significant accumulation at steady state
  - Similar PK with and without zanu

Figure 5. Steady-State PK[a]



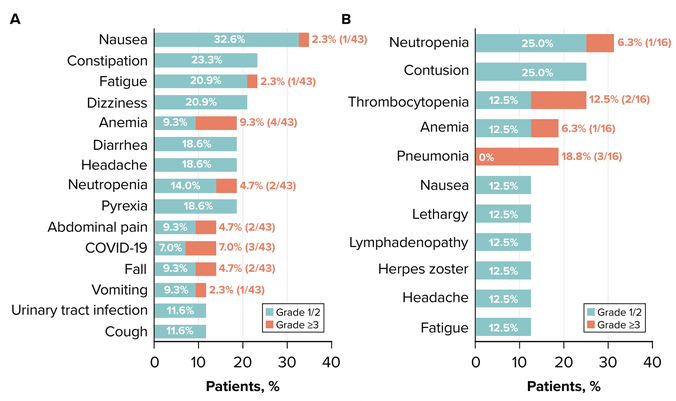
[a]PK data were pooled from all study cohorts, not just CLL. [b]Mean ±SD steady-state BGB-11417 plasma concentration profile for 40-640 mg QD in patients with NHL and CLL who received BGB-11417 monotherapy (combination PK not shown here)
SD, standard deviation.

Table 2. Overall Adverse Events and Dose Modifications Regardless of Attribution

Adverse events, n (%)	BGB-11417 monotherapy (n=43)	BGB-11417 + zanu (n=16[a])
Any AEs	40 (93)	13 (81)
Grade ≥3 AE	20 (47)	6 (38)
Serious AE	17 (40)	5 (31)
Leading to death	3 (7)[b]	2 (13)[c]
Treated with BGB-11417	43	10
Leading to hold of BGB-11417	9 (21)[d]	4 (40)[e]
Leading to dose reduction of BGB-11417	1 (2)[f]	0
Leading to discontinuation of BGB-11417	2 (5)[g]	0

[a]All patients on combination therapy have MCL; Includes 6 patients who have only received zanu. [b]Gastrointestinal hemorrhage, COVID-19 pneumonia death secondary to progression. [c]Cardiac arrest (not drug related), pleural effusion. [d]Pneumonia, sepsis, vomiting, CMV reactivation, worsening nausea, febrile neutropenia, COVID-19 pneumonia, ALT increased, AST increased, GGT increased, small intestinal obstruction, GI hemorrhage, platelet count decreased, diverticulitis, COVID-19, neutropenia. [e]Diarrhea, pneumonia, pleural effusion, lymph node pain, lymphadenopathy. [f]Gingival pain, fatigue, weight loss. [g]COVID-19 pneumonia; GI hemorrhage.

Figure 6. Adverse Events in ≥10% of Patients in (A) Monotherapy and (B) Combination Cohorts[a]



[a]Includes n=6 patients who are still in zanu pretreatment phase and have not yet received BGB-11417; All patients who received combination therapy have MCL.

Selected Adverse Events

- A single case of laboratory **TLS** was observed in a patient with MZL (640 mg target dose level: food-effect cohort)
  - Elevated phosphate, urate, and potassium
  - Occurred after first dose of 160 mg, which was given 7 days before day 1 as part of food effect evaluation
  - Circulating tumor cells and spleen normalized within 24 hours after first dose
  - Patient was hydrated and the laboratory changes resolved within 24 hours; received full dosing as planned from day 1 with no recurrence of TLS
- **GI toxicity** was the most common monotherapy toxicity, but all cases were mild with grade ≥3 nausea or vomiting seen in only 1 patient each (**Figure 5**)
  - Diarrhea mostly grade 1, with grade 2 observed in 2 patients
- **Neutropenia** was the most common toxicity (combination therapy) or hematologic toxicity (monotherapy), but was typically mild with grade ≥3 seen in 2 patients who received monotherapy and 1 patient who received combination therapy (**Figure 5**)
  - Febrile neutropenia occurred in 2 patients on monotherapy; no events were observed in patients who received combination therapy
  - Among 12 patients who received G-CSF (median course 3-days), 3 received >1 course of the therapy during treatment

Dose-Limiting Toxicities

- Only 1 DLT of febrile neutropenia noted among patients with NHL (**Table 3**)
- DLT occurrence was not dose dependent, and zanu combination did not appear to increase its risk
- Findings are consistent with previous BGB-11417 CLL data, which has reviewed up to 320 mg so far with no MTD reached

Table 3. Dose-Limiting Toxicities

DLTs, n/N	40 mg	80 mg	160 mg	320 mg	640 mg
BGB-11417 (NHL)	0/3	0/4	1/4	0/9	0/6
BGB-11417 (WM)	-	0/5	TBD	TBD	TBD
BGB-11417 + zanu (MCL)	-	0/5	0/3	TBD	TBD

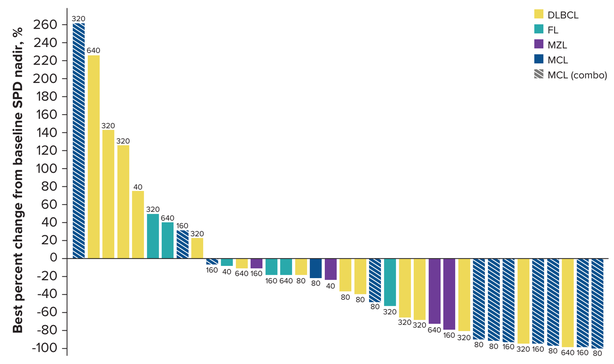
- Patient response to therapy is presented in **Table 4** along with the change in SPD in patients with NHL and treatment duration in **Figures 5** and **6**
- NHL (R/R monotherapy)
  - Significant reductions in SPD from baseline were noted in most patients
  - Disease control (CR+PR+SD) in 10 of 28 (36%) patients: 2 PRs at 160 and 640 mg and 1 CR at 320 mg
- WM (R/R monotherapy)
  - Follow-up was limited; however, 3 of 7 (43%) patients with at least 1 assessment reached PR at 80 mg
- MCL (R/R combination)
  - Response in 7 of 10 (70%) patients with at least 1 assessment
  - At 80 mg, 4 of 6 (67%) patients achieved CR
  - At 160 mg, 2 of 4 (50%) patients achieved CR and 1 reached PR

Table 4. Efficacy of BGB-11417 as Monotherapy and in Combination With Zanu

Response, n (%)	BGB-11417 monotherapy (n=43)		BGB-11417 + zanu combination (n=16)
	R/R NHL, DLBCL, MZL, FL, tFL, MCL (n=34)[a]	R/R WM (n=9)[b]	R/R MCL (n=16)[c]
Treated with BGB-11417	34	9	10
Efficacy evaluable	29[d]	7	9
Best overall response,[e]	3 (10)	3 (43)	7 (78)
CR	1 (3)	0	6 (67)
PR	2 (7)	3 (43)	1 (14)
SD	7 (24)	2 (29)	0
PD	18 (62)	1 (14)	2 (22)
Discontinued before assessment	1 (3)	1 (14)	0
Follow-up, months (range)	7 (0.1-29)	6 (2-10)	5 (1-13)

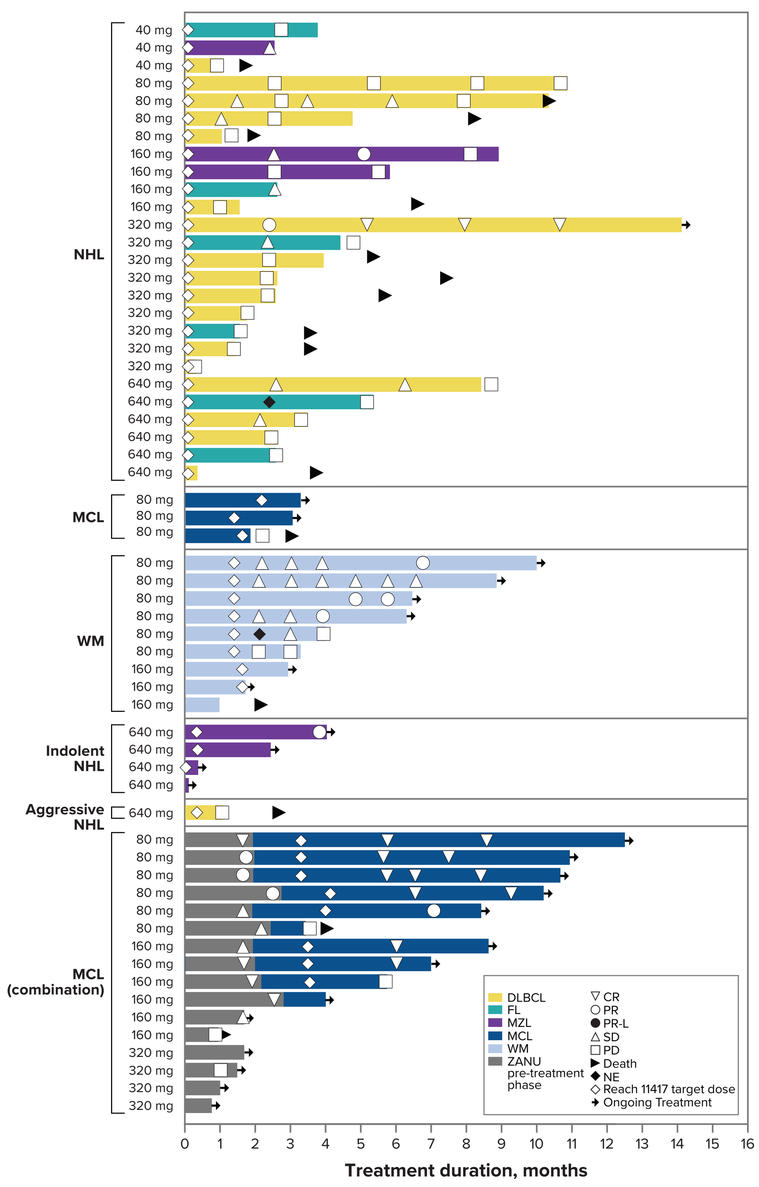
[a]At 40 mg: n=3; 80 mg: n=7; 160 mg: n=4; 320 mg: n=9; 640 mg: n=11. [b]At 80 mg: n=6; 160 mg: n=3. [c]At 80 mg: n=12; 160 mg: n=4. [d]One patient with MCL on monotherapy was efficacy evaluable. [e]PR or better.

Figure 7. Change in SPD Among Patients With NHL and MCL[a]



[a]All patients had at least 1 postbaseline scan result.

Figure 8. Duration of Treatment and Response[a]



[a]Safety analysis set.
All received treatments were monotherapy except patients in part 3B, which were combo MCL.

CONCLUSIONS

- BGB-11417 is tolerable in patients with NHL or WM at doses up to 640 mg
  - For patients with NHL on monotherapy, there was only 1 DLT and MTD was not reached
  - BGB-11417 in combination with zanu was also well tolerated at doses of BGB-11417 ≤320 mg, with dose escalation ongoing in patients with MCL
  - No clinical TLS was observed; there was 1 case of laboratory TLS that was resolved within 24 hours
- These data demonstrate the efficacy of BGB-11417 monotherapy (NHL, WM) and with zanu (MCL), with more responses observed at higher dose levels
- The study continues to determine RP2D in monotherapy and combination therapy

ABBREVIATIONS

AE, adverse event; ALL, acute lymphoblastic leukemia; ALT, alanine transaminase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; BCL2, B-cell lymphoma 2; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; D, day; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GGT, gamma-glutamyltransferase; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; IC, inhibitory concentration; MCL, mantle cell lymphoma; MTD, minimum tolerated dose; MZL, marginal zone lymphoma; NE, not evaluable; NHL, non-Hodgkin lymphoma; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; QD, daily; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma; SMC, safety monitoring committee; SPD, sum of the product of the diameters; $T_{1/2}$, half-life; tFL, transformed FL; TBD, to be determined; TLS, tumor lysis syndrome; T_{max}, maximum time; TN, treatment naïve; tNHL, transformed NHL; W, week; WM, Waldenström macroglobulinemia; zanu, zanubrutinib.

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