Abstract P687

A Phase 1 Study With the Novel BCL2 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 BCL2 inhibitor
  - BCL2 is a key regulator of apoptosis, aberrantly expressed in many hematologic malignancies[1]
  - The currently approved BCL2 inhibitor, venetoclax, has been shown to be safe and effective and is approved for the treatment of patients with CLL/SLL and AML[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 BCL2[5]
  - Antitumor activity of BGB-11417 appeared to be more potent than venetoclax in human ALL, MCL, and DLBCL in xenograft mouse models[5]
  - BGB-11417 has a favorable PK profile with excellent bioavailability and selectivity for BCL2 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 a venetoclax and the 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, MZL, and WM[12]
  - Early safety data show that combining zanubrutinib with venetoclax in patients with 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 NHL, WM, or CLL/SLL treated with either BGB-11417 monotherapy or 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 investigators up to 5 potential dose levels of BGB-11417 (40, 80, 160, 320, or 640 mg QD) before establishing RP2D
  - Patients in the combination therapy cohorts received zanubrutinib 320 mg QD beginning 8-12 weeks before BGB-11417 was introduced
- AEs are reported per CTCAEs v5.0 (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]

Dose Escalation

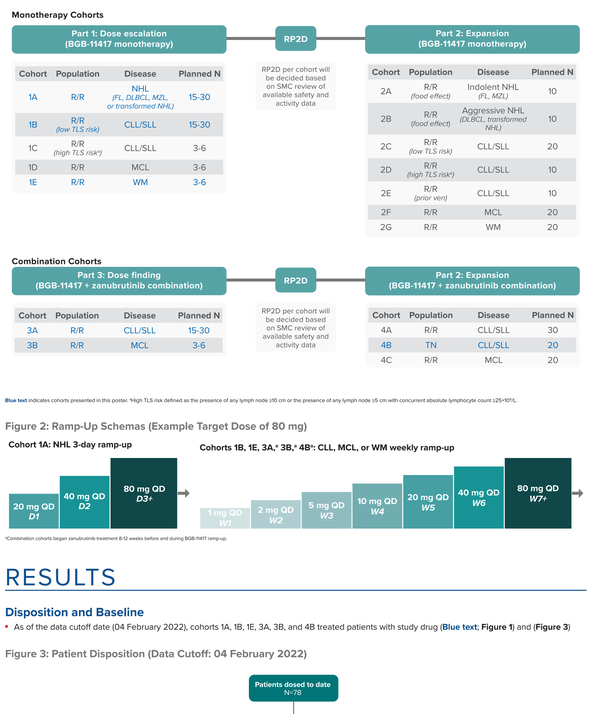
- For dose-escalation cohorts, patients were enrolled in 1 of 5 planned oral BGB-11417 dose levels in cohorts of at least 3 patients (**Figure 2**)
  - Planned daily dose levels: 40 mg, 80 mg, 160 mg, 320 mg, 640 mg
- DLTs assessed from ramp-up through day 21 at the intended daily dose, and evaluated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

Dose Ramp-Up

- To protect against potential 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 target dose level
  - Hospitalization for observation for select ramp-up visits: TLS laboratory results and PK monitored frequently at select time points

METHODS (cont.)

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.

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

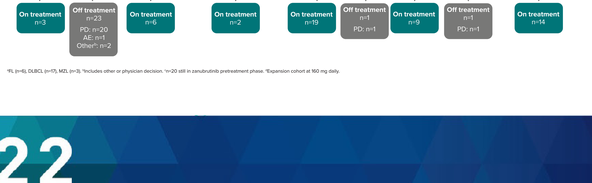
*Combination cohorts began zanubrutinib treatment 8-12 weeks before and during BGB-11417 ramp-up.

RESULTS

Disposition and Baseline

- As of the data cutoff date (04 February 2022), cohorts 1A, 1B, 1E, 3A, 3B, and 4B treated patients with study drug (**Blue text**; **Figure 1**) and (**Figure 3**)

Figure 3: Patient Disposition (Data Cutoff: 04 February 2022)



*FL (n=6), DLBCL (n=17), MZL (n=3). †Includes other or physician decision. ‡n=20 still in zanubrutinib pretreatment phase. §Expansion cohort at 160 mg daily.

RESULTS (cont.)

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), year	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 type, 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)
No. of 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)

Table 2. Overall Adverse Events

AEs, n (%)	BGB-11417 monotherapy (n=34*)	BGB-11417 + zanubrutinib combination (n=44**)	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[a] (5.9)	1 (2.3)[a]	3 (3.8)
Leading to hold of BGB-11417	5[b] (14.7)	1[b] (2.3)	6 (7.7)
Leading to dose reduction of BGB-11417	0	0	0
Leading to discontinuation of BGB-11417	1[c] (2.9)	0	1 (1.3)

*All patients are relapsed/refractory. **Includes n=20 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. [a]Includes n=14 patients who are treatment naive. [b]Neither related to study drug; 1 death secondary to disease progression and 1 gastrointestinal hemorrhage subsequent to bowel surgery. [c]Cardiac arrest, not related to study drug. Thrombocytopenia, hemoptysis and pyrexia; ALT, AST, and GGT increased; neutropenia, pyrexia, and febrile neutropenia; small intestinal obstruction; neutropenia. [d]Dose withheld due to COVID-19 infection. [e]Gastrointestinal hemorrhage subsequent to bowel surgery.

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)	-	1/4	TBD	TBD	TBD
WM (1E)	-	TBD	TBD	TBD	TBD
			Combination		
CLL (3A)	0/4	0/3	0/3	TBD	TBD
MCL (3B)	-	0/3	TBD	TBD	TBD

*Not tested in cohorts 1B, 1E and 3B because this dose has been cleared in other cohorts by the time these cohorts were open.

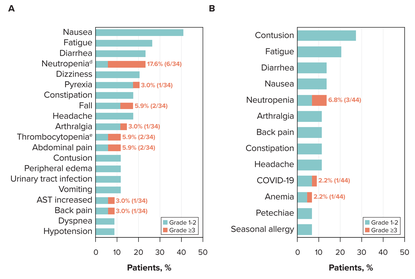
Monotherapy

- 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 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 daily; 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*) or (B) Combination Therapy (N=44[b,c])



*All patients are relapsed/refractory. †Includes n=20 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. ‡Includes n=14 patients who were treatment naive. §Neutropenia: Includes neutrophil count decreased and neutropenia. ¶Thrombocytopenia: Includes platelet count decreased and thrombocytopenia.

BCL2 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 were 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 (**Figure 5** and **6**)
- NHL (R/R monotherapy)
  - Significant reductions in SPD from baseline were seen in most patients (**Figure 5**)
  - Two of 20 (10%) patients have responded: 1 PR at 160 mg and 1 CR at 320 mg
- WM (R/R monotherapy)
  - Follow-up is limited; 1 of 2 (50%) patients have achieved a minor response at 80 mg
- MCL (R/R combination)
  - Five of 10 (50%) patients 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 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 (67%) patients have achieved PR-L or better so far at either 80 or 160 mg
  - Combination therapy
    - R/R: 16 of 20 (80%) patients 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

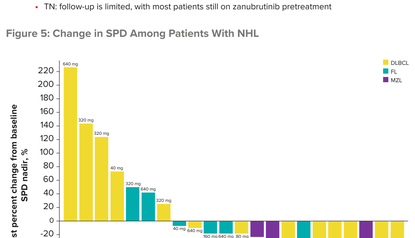


Figure 6. Duration of Treatment and Best Response

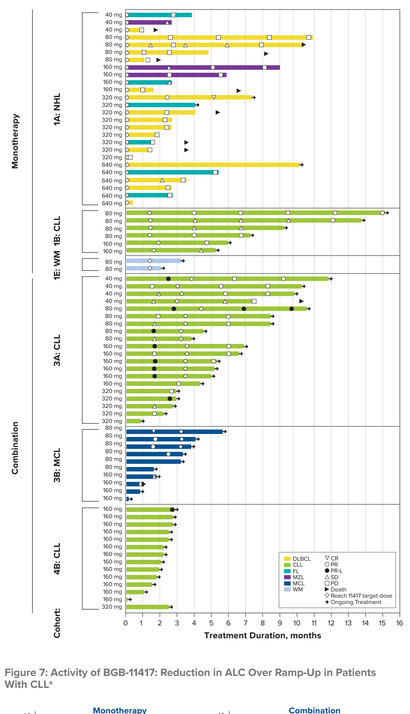
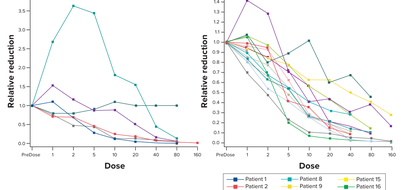


Figure 7: Activity of BGB-11417: Reduction in ALC Over Ramp-Up in Patients With CLL[a]



[a]Figures represent reduction in ALC above the ULN (4×10⁹/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).

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 amongst 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

SO: honoraria from Roche, Janssen, AbbVie, Celgene, Takeda, Merck, Gilead, AstraZeneca; consulting role with Roche, Janssen, AbbVie, Celgene, Takeda, Merck, Gilead, Mundipharma, AstraZeneca, CSL; research funding from BeiGene, Roche, Janssen, AbbVie, Takeda, Merck, Gilead, Epizyme, AstraZeneca; travel from Roche
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ML: travel expenses from Celgene
EV: research funding from Janssen Cilag Pty Ltd
PJB: consulting role with MSD, EUSA Pharma; research funding from BeiGene, Roche, Shire
HC: consulting role with Janssen, AbbVie, GSK, EUSA Pharma
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, Morphosys, TG Therapeutics
EGB: consulting role with Janssen, AbbVie, BeiGene, Kowa, EUSA Pharma; speakers bureau for Janssen, AbbVie, Takeda, Roche, EUSA Pharma; travel expenses from Janssen, AbbVie, Roche
JHL, YF, DS: employment and stock ownership with BeiGene
JHu: employment with BeiGene; leadership role with BeiGene, Protara; stock ownership with BeiGene, Roche; research funding and patents from BeiGene
CST: honoraria from Janssen, AbbVie, BeiGene, Loxo, Novartis; research funding from Janssen, AbbVie, BeiGene

ABBREVIATIONS

AEs, adverse events; ALC, absolute lymphocyte count; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate transaminase; BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; CTCAEs, 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-glutamyl transferase; iwCLL, International Workshop on CLL; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; N/A, not applicable; NHL, non-Hodgkin lymphoma; PD, progressive disease; PK, pharmacokinetic; PR, partial response; PR-L, partial response with lymphocytosis; QD, once daily; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma; SMC, safety monitoring committee; SPD, sum of product of perpendicular diameters; TBD, to be decided; TEAEs, treatment-emergent adverse events; TLS, tumor lysis syndrome; TN, treatment naive; tNHL, transformed NHL; ULN, upper limit of normal; ven, venetoclax; W, week; WM, Waldenström macroglobulinemia.

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