PRELIMINARY SAFETY DATA FROM PATIENTS WITH RELAPSED/REFRACTORY (R/R) B-CELL MALIGNANCIES TREATED WITH THE NOVEL B-CELL LYMPHOMA 2 (BCL2) INHIBITOR BGB-11417

Abstract EP525

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INTRODUCTION

- This is the initial clinical report of the first-in-human trial of BCL2 inhibitor BGB-11417
- BCL2, a key regulator of the apoptotic pathway, is aberrantly expressed in many hematologic malignancies[1]
  - Treatment with BCL2 inhibitors has shown benefit in a variety of malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma) CLL/SLL and non-Hodgkin lymphomas (NHLs)[2,3]
- As previously reported, BGB-11417 is a potent and highly selective inhibitor of BCL2[4]
  - In vitro binding assays showed BGB-11417 was >10 fold more potent than venetoclax at inhibiting BCL2: IC_{50} 0.014 nM with BGB-11417 vs 0.20 nM with venetoclax[4]
- Continued treatment of patients with CLL/SLL with the BCL2 inhibitor venetoclax results in emergence of clones, with mutations affecting amino acids surrounding the BH3 binding groove of BCL2, such as G101V, that confer venetoclax resistance[5]
  - The potency of BGB-11417 for inhibiting BCL2-G101V mutant protein was >50 fold than that of venetoclax: IC_{50} 0.59 with BGB-11417 vs 34 nM with venetoclax[4]
- In vitro testing has shown BGB-11417 is very selective, exhibiting ≥2000-fold selectivity for BCL2 vs BCL-xL, BCL-W, MCL-1, and BCL2A1[4]
- BGB-11417 has shown superior antitumor activity to venetoclax in a number of xenograft models, including acute lymphoblastic leukemia, mantle cell lymphoma, and diffuse large B-cell lymphoma (DLBCL)[4]
- Venetoclax use can also be limited by neutropenia and is commonly associated with mild gastrointestinal (GI) toxicities[6]
- Toxicology study results (data on file) have shown BGB-11417 to have an encouraging safety profile with a Human equivalent NOAEL between 1440 – 3240 mg daily in 28-day repeat dose toxicology studies of mice and dogs, much higher than the expected treatment dose
  - BGB-11417 has a favorable pharmacokinetic (PK) profile with low plasma clearance

METHODS

Study Design/Objectives

- BGB-11417-101 is a first-in-human phase 1/1b study (dose escalation and expansion) to determine safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose of BGB-11417 in patients with R/R B-cell malignancies (NCT04277637; **Figure 1** – data for cohorts in blue presented here)
- Dose-escalation (Part 1) occurs in independent cohorts categorized by patient disease type; these cohorts will continue until a recommended phase 2 dose (RP2D) is identified, which is then used in corresponding expansion cohorts (Part 2)
  - Cohort 1A opened first: once ≥1 tolerable dose level was determined, Cohort 1B could be opened
  - All dose cohorts would be reviewed by a safety monitoring committee before opening subsequent dose levels or declaring an MTD/RP2D
- The study also includes dose escalation and expansion cohorts for the combination of BGB-11417 and Bruton tyrosine kinase (BTK) inhibitor zanubrutinib in patients with CLL/SLL and mantle cell lymphoma (MCL), but as of data cutoff, no patients have received this combination

Figure 1. Study Schema (Monotherapy Cohorts)

Part 1: DOSE ESCALATION (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*)*	CLL/SLL	3-6
1D	R/R	MCL	3-6
1E	R/R	WM	3-6

RP2D

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

Part 2: EXPANSION (BGB-11417 Monotherapy)

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*)*	CLL/SLL	10
2E	R/R *(prior ven)*	CLL/SLL	10
2F	R/R	MCL	20
2G	R/R	WM	20

Data for Cohorts 1A and 1B presented here.

Note: study will include cohorts to explore dose escalation and expansion of BGB-11417 in combination with zanubrutinib that are not shown in this diagram.

*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 (ALC) ≥25 × 10^9/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; ven, venetoclax; WM, Waldenstrom macroglobulinemia.

Dose Escalation

- For dose escalation, patients were enrolled in 1 of 5 planned daily oral BGB-11417 dose levels in cohorts of at least 3 patients: 40 mg, 80 mg, 160 mg, 320 mg, 640 mg
- A Bayesian logistic regression model is used for target dose escalation to model the relationship between the dose levels and the DLT rates seen at each dose level

METHODS *(CONTINUED)*

Dose Ramp-Up

- To protect against potential tumor lysis syndrome (TLS) in this first-in-human BCL2 inhibitor trial, all patients received a dose ramp-up to the target dose level (**Figure 2**)
  - Patients with NHLs as part of Cohort 1A received 3-day ramp-up (day 1, 25% of target dose; day 2, 50%) before reaching the target daily dose (day 3+, 100%)
  - Patients with CLL/SLL as part of Cohort 1B received a weekly ramp-up (beginning with 1 mg daily, 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: TLS labs and PK monitored frequently
    - NHL: required during ramp-up for at least the first 3 ramp-up doses
    - CLL: required for day 1 of each week for at least the first 3 ramp-up doses

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

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

Reporting, etc

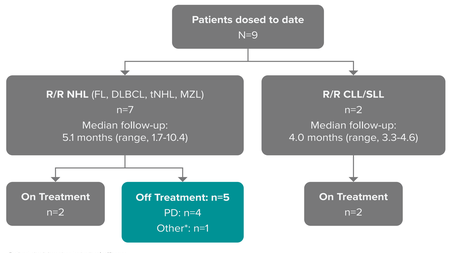
- Adverse events (AEs) were reported per CTCAE v5.0 (iwCLL for select hematologic toxicities for CLL patients[7])
- Dose-limiting toxicities (DLTs) during dose escalation were evaluated up until 21 days at the target dose per patient

RESULTS

Disposition and Baseline

- Data cutoff was 24 March 2021
- As of data cutoff, Cohorts 1A, 1B, and 3A had been opened (**Figure 3**)
  - 7 patients with R/R NHL were treated in Cohort 1A and 2 patients with R/R CLL were treated in Cohort 1B
  - No patients in Cohort 3A (R/R CLL/SLL treated with BGB-11417 in combination with zanubrutinib) had received BGB-11417 at time of data cutoff; this cohort will not be discussed in this update

Figure 3. Patient Disposition (data cutoff 24 March 2021)



*Patient decision due to lack of efficacy.

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; R/R, relapsed/refractory; tNHL, transformed NHL.

RESULTS *(CONTINUED)*

Table 1. Patient and Disease Characteristics

Characteristic	All Patients (N=9)
Age, median (range), y	76 (62-86)
ECOG performance status, n (%)	
0	3 (33.3)
1	5 (55.6)
2	1 (11.1)
Disease types, n (%)	
R/R CLL	2 (22.2)
R/R DLBCL	5 (55.6)
R/R FL	1 (11.1)
R/R MZL	1 (11.1)
No. of prior lines of therapy, median (range)	2 (1-4)
Time from end of most recent systemic therapy to first dose median (range), mo	6.1 (0.1-40.4)

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory.

Safety

- Safety data for all 9 patients (combining NHL and CLL from Cohorts 1A and 1B) are shown in **Table 2** and **Figure 4**

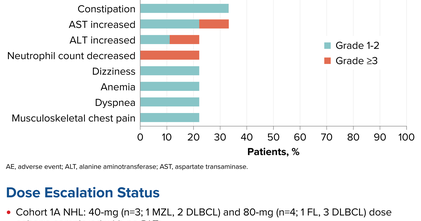
Table 2. Overall Treatment-Emergent Adverse Events

AEs, n (%)	N=9
Total	8 (88.9)
Grade ≥3 AEs	5 (55.6)
Serious AEs	4 (44.4)
AEs leading to hold of BGB-11417	4 (44.4)
AEs leading to dose reduction of BGB-11417	0
AEs leading to discontinuation of BGB-11417	0

AE, adverse event.

- The most common treatment-emergent AEs (**Figure 4**) were nausea (55.6%), constipation (33.3%), and asparatate transaminase (AST) increased (33.3%)
- Grade ≥3 AEs reported in 1 patient each: abdominal pain, enteritis, small intestinal obstruction, blood alkaline phosphatase increased, gamma-glutamyl transferase (GGT) increased, platelet count increased, cachexia, pyrexia, back pain, and laboratory TLS
- Two deaths secondary to disease progression were noted

Figure 4. Treatment-Emergent AEs Regardless of Causality Occurring in at Least 2 Patients (N=9)



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase.

Dose Escalation Status

- Cohort 1A NHL: 40-mg (n=3; 1 MZL, 2 DLBCL) and 80-mg (n=4; 1 FL, 3 DLBCL) dose cohorts completed with no DLTs
  - The 160-mg dose cohort is ongoing
- Cohort 1B CLL: started dose escalation at the 80-mg target dose level (n=2, ongoing) after declared tolerable in Cohort 1A
  - Although Cohort 1B only allowed patients with low TLS risk, a patient with high TLS risk was incorrectly enrolled
  - Retrospective review of baseline CT by site radiologist upgraded the largest node to 6.5 × 2.4 cm, with absolute lymphocyte count (ALC) 37.4 × 10^9/L

BCL2 Inhibitor Adverse Events of Interest

- TLS
  - The incorrectly enrolled patient with high baseline TLS risk developed laboratory TLS and had a major tumor flare on BTK inhibitor withdrawal during early ramp-up
    - Lactate dehydrogenase 1500, largest node to 5-10 cm, ALC 135.9 × 10^9/L
  - This patient also had baseline and history of hyperuricemia
  - During dose escalation, patient met criteria for laboratory TLS per Howard criteria[8] in late ramp-up at both the 40 mg and 80 mg dose levels
  - Urate baseline: 430 mmol/L; urate peak: 570 mmol/L; phosphate baseline: 0.35 mmol/L; phosphate peak: 2.16 mmol/L
  - The patient experienced no sequalae from laboratory TLS and resolved by the next day
    - BGB-11417 did not need to be held
- Neutropenia observed in 2 patients; both grade 3 and both recovered

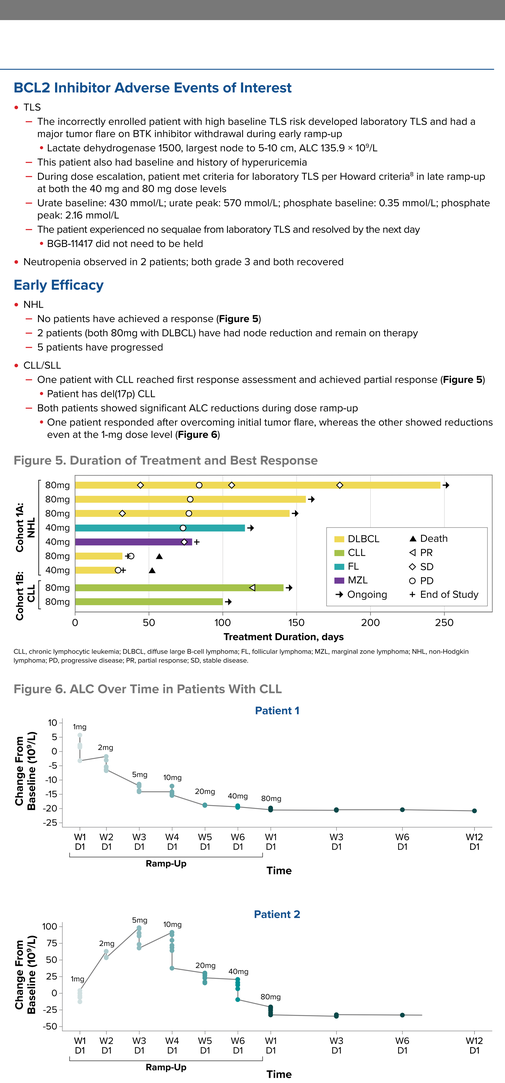
Early Efficacy

- NHL
  - No patients have achieved a response (**Figure 5**)
  - 2 patients (both 80mg with DLBCL) have had node reduction and remain on therapy
  - 5 patients have progressed
- CLL/SLL
  - One patient with CLL reached first response assessment and achieved partial response (**Figure 5**)
    - Patient has del(17p) CLL
  - Both patients showed significant ALC reductions during dose ramp-up
    - One patient responded after overcoming initial tumor flare, whereas the other showed reductions even at the 1-mg dose level (**Figure 6**)

Figure 5. Duration of Treatment and Best Response

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 6. ALC Over Time in Patients With CLL



Note: multiple dots indicate multiple ALC assessments during D1 of each week.

ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia; D, day; W, week.

CONCLUSIONS

- These early phase 1 results suggest that BGB-11417 is tolerable in patients at the dose levels tested
  - No DLTs seen across 2 dose levels
  - Grade ≥3 AEs have been infrequent and manageable
    - Only 2 patients experienced neutropenia
  - Risk of TLS appears limited and manageable: only 1 instance of laboratory TLS was seen in a patient with high TLS-risk
  - Preliminary activity in this patient population will be assessed with increased enrollment and follow-up
    - Enrollment of patients with R/R CLL has only recently started, but decreases in ALC have been seen at the initial ramp-up dose of 1 mg
- Evaluation of patients with MCL and Waldenström macroglobulinemia, and the combination of BGB-11417 and BTK inhibitor zanubrutinib, is planned for future cohorts

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DISCLOSURES

CYC received honoraria from Roche, Janssen, MSD, Gilead, Ascentage Pharma, Acerta, Loxo Oncology, and TG Therapeutics, served as a consultant for Roche, Janssen, MSD, Gilead, Ascentage Pharma, Acerta, Loxo Oncology, and TG Therapeutics, received research funding from Celgene, Roche, and AbbVie and received travel expenses from Roche

EV received research funding from Janssen-Cilag

CST received honoraria and research funding from AbbVie, Janssen, and BeiGene, and served as a consultant for BeiGene

JDH is an employee of and has equity ownership in BeiGene

YG is an employee of, has equity ownership, and has received travel expenses from BeiGene

JH is an employee of, has a leadership role, equity ownership, patents, and has received travel expenses from BeiGene

DS is an employee of and has equity ownership in BeiGene, served as a consultant for AbbVie, Roche, and Janssen and received research funding from Roche, MSD, Acerta, Pharmacyclics, Sanofi, GCK, Janssen, AbbVie, Celgene, and Amgen

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