A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Bcl-2 Inhibitor BGB-11417 in Adult Patients With Mature B-Cell Malignancies: Preliminary Data

Abstract 2989

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INTRODUCTION

- Bcl-2 is a key regulatory protein of the apoptotic pathway and is abnormally expressed in many hematologic malignancies, leading to prevention of apoptosis of tumor cells[1]
- The efficacy of Bcl-2 inhibitors in CLL/SLL was established by the approval of agents such as venetoclax across all lines of therapy. However, AEs related to venetoclax[2] and the development of *BCL2* mutations leading to resistance[3] may limit the utility of venetoclax in the clinic
- Compared to venetoclax, BGB-11417 is a more potent (>10 fold in biochemical assays) and highly selective Bcl-2 inhibitor[4] with the potential to achieve deeper target inhibition and clinical responses[5]
- Here we show preliminary data from the phase 1 BGB-11417-102 study

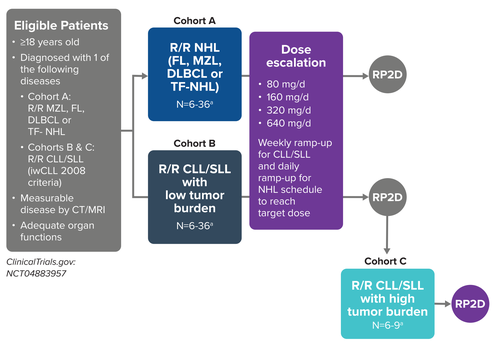
OBJECTIVE

- To determine the safety, maximum tolerated dose or maximum administered dose, and the RP2D of BGB-11417 monotherapy for the selected B-cell malignancy dose-finding cohorts

METHODS

- BGB-11417-102 (NCT04883957) is a phase 1 study evaluating the safety, tolerability, PK, and preliminary antitumor activity of Bcl-2 inhibitor BGB-11417 in adult patients with mature B-cell malignancies (**Figure 1**)
- Patients with R/R B-cell malignancies received escalating doses of BGB-11417 monotherapy (80, 160, 320, or 640 mg once daily) with a weekly ramp-up for CLL/SLL and a daily ramp-up for NHL to the intended target dose
- DLT for each dose cohort was evaluated by a Bayesian logistic regression model during dose ramp-up through day 21 at intended dose
- For patients with CLL who had hematologic toxicities, AE grades were evaluated based on the grading scale for hematologic toxicity in CLL; otherwise, AE grades were evaluated based on NCI-CTCAE v5.0
- MRD was evaluated in peripheral blood with 6-cycle intervals and in both peripheral blood and bone marrow aspirate when achieving CR
  - In patients with CLL/SLL, MRD was assessed by a flow cytometry assay with a sensitivity of 10^{-4}, and uMRD4 was defined as a proportion of CLL cells out of total nucleated cells of $<10^{-4}$

Figure 1. Study Design



ClinicalTrials.gov: NCT04883957

Primary endpoints: RP2D and/or MTD, safety, tolerability, incidence and severity of TLS-relevant events

Secondary endpoints: derived PK parameters and ORR of BGB-11417 monotherapy per disease-specific response assessment guidelines as determined by investigator

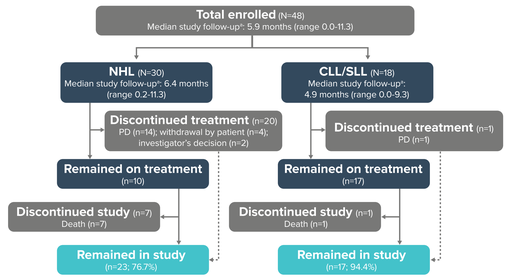
Exploratory endpoints: preliminary antitumor activity per disease type, including TTR, DOR, PFS, OS

[a]The number of patients in each cohort is an estimate and may vary with the data collected.

RESULTS

- As of Aug 11, 2022, 48 patients have been treated. Thirty patients with R/R NHL and 18 patients with R/R CLL/SLL received ≤640 mg/d dose levels (**Figure 2**)
- A total of 21 patients (20 NHL and 1 CLL/SLL) discontinued the study treatment (15 progressive disease, 4 withdrawal by patient, and 2 investigator decision)
- Baseline characteristics are depicted in **Table 1**

Figure 2. Patient Disposition



*Study follow-up time is defined as the time from the first dose date to the death date or end of study date (whichever occurs first) for patients discontinued from the study, or the database cutoff date for ongoing patients.

Table 1. Baseline Characteristics

Characteristics	NHL (N=30)	CLL/SLL (N=18)	All (N=48)
Median age (min, max), years	60.0 (31, 74)	63.0 (50, 84)	61.5 (31, 84)
Male, n (%)	14 (46.7)	13 (72.2)	27 (56.3)
ECOG PS, n (%)			
0-1	26 (86.6)	16 (88.9)	42 (87.5)
2	4 (13.3)	2 (11.1)	6 (12.5)
Median no. of prior therapy regimens (range)	2.0 (1-7)	2.5 (1-6)	2.0 (1-7)
Median time from initial diagnosis to first dose of study drug (min, max), years	2.43 (0.1, 6.9)	5.33 (0.3, 18.8)	2.56 (0.1, 18.8)
Cancer type, n (%)			
DLBCL	16 (53.3)	-	16 (33.3)
FL	7 (23.3)	-	7 (14.6)
MZL	4 (13.3)	-	4 (8.3)
Transformed B-cell NHL	3 (10.0)	-	3 (6.3)
CLL	-	14 (77.8)	14 (29.2)
SLL	-	4 (22.2)	4 (8.3)

Safety

- Serious TEAEs were reported in 10.4% of patients, and TEAEs leading to dose modification were reported in 14.6%. No patients reported TEAEs leading to death or treatment discontinuation (**Table 2**)

Table 2. Summary of TEAEs[a]

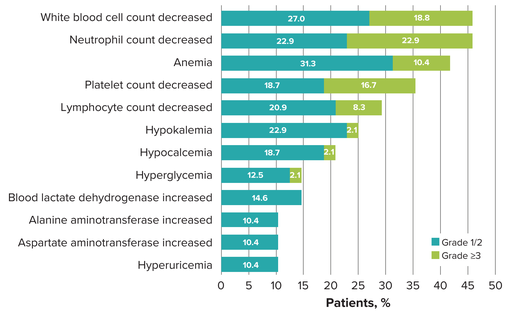
n (%)	NHL (N=30)	CLL/SLL (N=18)	All (N=48)
Patients with ≥1 TEAE	**28 (93.3)**	**16 (88.9)**	**44 (91.7)**
Grade ≥3 AEs	15 (50.0)	9 (50.0)	24 (50.0)
Serious AEs	2 (6.7)	3 (16.7)	5 (10.4)
Leading to death	0	0	0
Leading to treatment discontinuation	0	0	0
Leading to dose modification	3 (10.0)	4 (22.2)	7 (14.6)
Patients with any treatment-related AEs	**25 (83.3)**	**15 (83.3)**	**40 (83.3)**
Grade ≥3 AEs	12 (40.0)	8 (44.4)	20 (41.7)
Serious AEs	1 (3.3)	1 (5.6)	2 (4.2)
Leading to death	0	0	0
Leading to treatment discontinuation	0	0	0
Leading to dose modification	3 (10.0)	3 (16.7)	6 (12.5)

[a]Patients with >1 event for a given preferred term and system organ class were counted only once at the worst severity for the preferred term and system organ class, respectively.

Safety (cont.)

- Most of the TEAEs observed in this study were grade 1/2 events, and the most common grade ≥3 TEAE was neutrophil count decreased (22.9%), which was transient and controllable (**Figure 3**)

Figure 3. TEAEs With Incidence ≥10%



- DLT events were reported in 3 (7.4%) patients (grade 3 febrile neutropenia and grade 3 platelet count decreased at 80 mg/d dose level each; grade 3 bone pain at 160 mg/d dose level; **Table 3**)
- No clinical TLS events occurred. Laboratory TLS events were reported in 2 (4.2%) patients, and all were controlled without dose modification

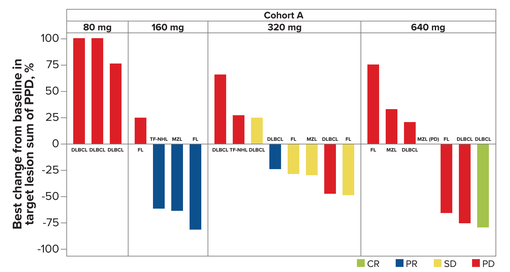
Table 3. DLT Events per Dose in Patients With NHL and CLL/SLL

n (%)	80 mg (n=3)	160 mg (n=5)	320 mg (n=10)	640 mg (n=9)	All (n=27)
DLT-evaluable patients with NHL					
Patients with ≥1 DLT event	1 (33)	1 (20)	0	0	2 (7)
Grade 3 platelet count decreased	1 (33)	0	0	0	1 (4)
Grade 3 bone pain	0	1 (20)	0	0	1 (4)
	80 mg (n=5)	**160 mg (n=4)**	**320 mg (n=3)**	**640 mg (n=0)**	**All (n=12)**
DLT-evaluable patients with CLL/SLL					
Patients with ≥1 DLT event	1 (20)	0	0	0	1 (8)
Grade 3 febrile neutropenia	1 (20)	0	0	0	1 (8)

Efficacy

- Of the 25 patients with R/R NHL available for tumor assessment, 5 patients achieved responses: 3 in the 160 mg/d dose level, 1 in the 320 mg/d dose level, and 1 in the 640 mg/d dose level. Remission continued in 4 responders (**Figures 4 and 5**)

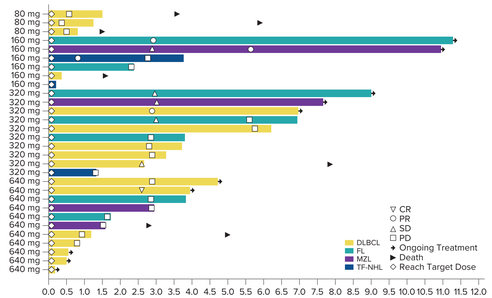
Figure 4. Response in Patients With NHL[a]



[a]No SPD data for 3 patients owing to PD assessed by PET only or missing CT scans owing to COVID-19.

Efficacy (cont.)

Figure 5. Duration of Treatment and Best Response in Patients With NHL



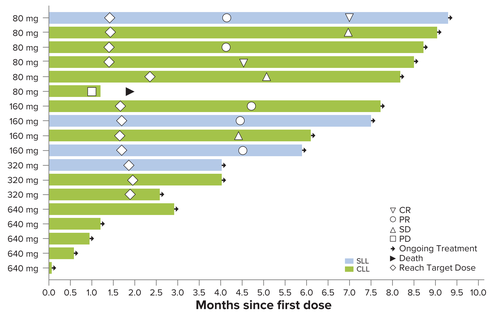
- Of the 10 patients with R/R CLL/SLL available for tumor assessment, 6 patients achieved responses (2 CR and 1 PR in the 80 mg/d dose level and 3 PR in the 160 mg/d dose level). Remission continued in all the responders (**Table 4** and **Figure 6**)
  - Response data are not available for patients in the 320 mg/d and 640 mg/d cohorts owing to the short follow-up
- Seven patients with R/R CLL/SLL (5 dosed with 80 mg/d, 2 dosed with 160 mg/d) were available for MRD assessment, and 2 achieved uMRD4
  - One patient with CLL achieved both blood and bone marrow aspirate uMRD4 after 4.5 months of BGB-11417 monotherapy with 80 mg/d dose
  - Another patient with CLL achieved blood uMRD4 after 7.1 months of BGB-11417 monotherapy with 160 mg/d dose

Table 4. Best Overall Response in Patients With CLL/SLL

Best overall response, n (%)	80 mg (n=6)	160 mg (n=4)	320 mg (n=3)	640 mg (n=5)	All (n=18)
Overall response rate (95% CI)[a]	3 (50) (12, 88)	3 (75) (19, 99)	0 (0, 71)	0 (0, 52)	6 (33) (13, 59)
CR/CRi	2 (33)	0	0	0	2 (11)
nPR	0	0	0	0	0
PR	1 (17)	3 (75)	0	0	4 (22)
SD	2 (33)	1 (25)	0	0	3 (17)
PD	1 (17)	0	0	0	1 (6)
NE	0	0	0	0	0
Unknown	0	0	3 (100)	5 (100)	8 (44)

[a]The 95% CI was estimated using the Clopper-Pearson method.

Figure 6. Duration of Treatment and Best Response in Patients With CLL/SLL



CONCLUSIONS

- This phase 1 study indicated that BGB-11417 monotherapy was well tolerated at all tested doses up to 640 mg/d, with no dose-dependent toxicity increase
- TLS risk is low and manageable with no clinical TLS observed
- BGB-11417 monotherapy also showed promising initial efficacy results, reporting patients with R/R CLL/SLL achieving responses at lower dose levels
- Preliminary activity was observed in patients with NHL with BGB-11417 monotherapy; further expansion data are being generated
- Dose escalation is still ongoing, and MTD/MAD has not been determined

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ABBREVIATIONS

AE, adverse event; BCL2, B-cell lymphoma 2; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete blood count recovery; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IwCLL, International Workshop on Chronic Lymphocytic Leukemia; MAD, maximum administered dose; MRD, measurable residual disease; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NE, not evaluable; NHL, non-Hodgkin lymphoma; nPR, nodular partial response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PK, pharmacokinetics; PPD, product of perpendicular diameters; PR, partial response; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma; SPD, sum of the product of diameters; TEAE, treatment-emergent AE; TF-NHL, transformed NHL; TLS, tumor lysis syndrome; TTR, time to response; uMRD4, undetectable MRD (<1 CLL cell/10[4] leukocytes).

DISCLOSURES

LZ, ZS, ZL, BW: employment and stock with BeiGene
CL, JW, KZ, PL, HH, FL, YD, QC, SY, XZ, HZ, DW: nothing to disclose

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