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

Abstract 7558

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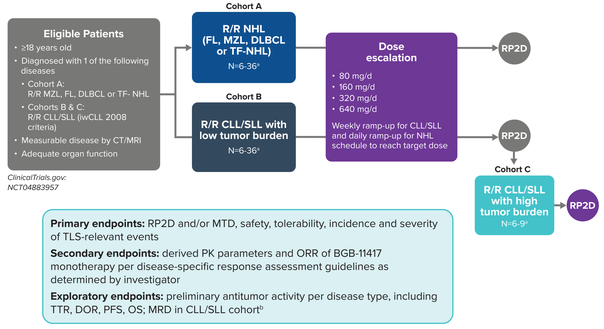
INTRODUCTION

- B-cell lymphoma 2 (Bcl-2), a key regulatory protein of the intrinsic apoptotic pathway, is abnormally expressed in many hematologic malignancies and promotes tumor cell resistance to apoptosis[1]
- The Bcl-2 inhibitor venetoclax is approved for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) across all therapy lines; however, adverse events (AEs)[2] and the development of venetoclax resistance[3] may limit its clinical utility
- Compared with 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]

METHODS

- BGB-11417-102 (NCT04883957) is an ongoing phase 1 study to evaluate the safety, tolerability, and antitumor activity of BGB-11417 in adults with B-cell malignancies (**Figure 1**)
- Daily (non-Hodgkin lymphoma [NHL]) or weekly (CLL/SLL) BGB-11417 dose ramp-up schedules were used to lessen the risk of tumor lysis syndrome (TLS)
- Dose-limiting toxicity (DLT) for each dose cohort was evaluated by a Bayesian logistic regression model during dose ramp-up through day 21

Figure 1. Study Design



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

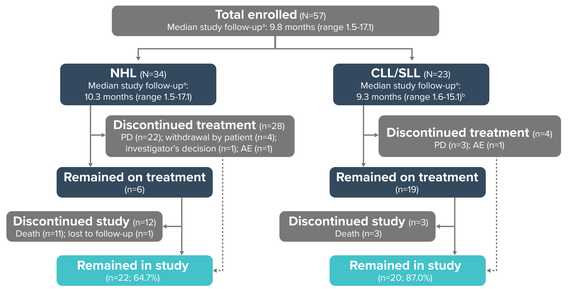
Exploratory endpoints: preliminary antitumor activity per disease type, including TTR, DOR, PFS, OS; MRD in CLL/SLL cohort[b]

[a]The number of patients per cohort is estimated and may vary; [b]MRD was assessed by flow cytometry in 6-cycle intervals (peripheral blood) and upon CR (peripheral blood and bone marrow aspirate); uMRD4 was defined as <1 CLL cell in 10^4 leukocytes.
CR, complete response; iwCLL, International Workshop on CLL; MRD, minimal residual disease; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; TF-NHL, transformed NHL; TLS, tumor lysis syndrome; TTR, time to response; uMRD, undetectable minimal residual disease.

RESULTS

- As of February 4, 2023, 57 patients (R/R NHL, n=34; R/R CLL/SLL, n=23) had received BGB-11417 doses of ≤640 mg (**Figure 2**)
- Of those 57 patients, 32 (NHL, n=28; CLL/SLL, n=4) discontinued study treatment
- Baseline characteristics are shown in **Table 1**

Figure 2. Patient Disposition



[a]Study follow-up time is defined as the time from the date of first dose to the date of death, the study end date (for patients who discontinued the study), or the database cutoff date (for patients who remain on treatment), whichever occurs first; [b]Median study follow-up data is not included for 1 patient in cohort C.
PD, progressive disease.

- Median time from initial diagnosis to first study drug dose for patients with NHL and CLL/SLL was 2.4 years and 5.4 years, respectively
- Among patients with NHL, 20 (58.8%) had diffuse large B-cell lymphoma (DLBCL), 7 (20.6%) had follicular lymphoma (FL), 4 (11.8%) had marginal zone lymphoma (MZL), and 3 (8.8%) had transformed B-cell NHL
- Among patients with CLL/SLL, 17 (77.3%) of those with low tumor burden had CLL; the single patient with high tumor burden had CLL

Table 1. Baseline Characteristics

Characteristics	NHL (n=34)	CLL/SLL, low tumor burden (n=22)	CLL/SLL, high tumor burden (n=1)	All (N=57)
Age, median (range), y	58.5 (31-74)	62.0 (50-84)	54.0	60.0 (31-84)
Men, n (%)	15 (44.1)	14 (63.6)	1 (100.0)	30 (52.6)
ECOG PS, n (%)				
0	12 (35.3)	10 (45.5)	1 (100.0)	23 (40.4)
1	18 (52.9)	9 (40.9)	0	27 (47.4)
2	4 (11.8)	3 (13.6)	0	7 (12.3)
Prior therapy regimens, median (range)	2 (1-7)	3 (1-7)	4	3 (1-7)
Time from initial diagnosis to first dose of study drug, median (range), y	2.4 (0.1-6.9)	5.4 (0.3-18.8)		—
Cancer type, n (%)				
DLBCL	20 (58.8)	—	—	—
FL	7 (20.6)	—	—	—
MZL	4 (11.8)	—	—	—
Transformed B-cell NHL	3 (8.8)	—	—	—
CLL	—	17 (77.3)	1 (100.0)	—
SLL	—	5 (22.7)	—	—

ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety

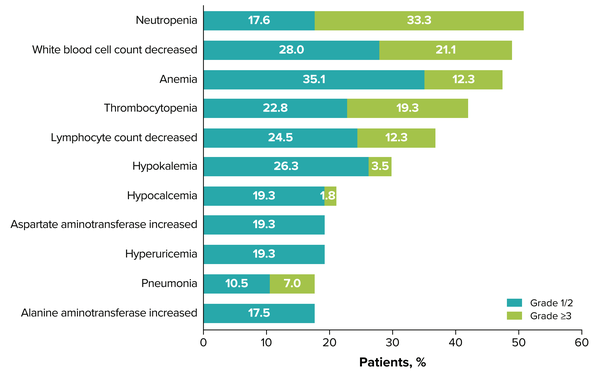
- Of all patients, 24.6% had serious treatment-emergent AEs (TEAEs) and 28.1% had TEAEs leading to treatment dose modification (**Table 2**)
- TEAEs leading to treatment discontinuation or death were reported in 1.8% and 5.3% of all patients, respectively
- Most TEAEs observed in this study were Grade 1 or 2; the most common Grade ≥3 was neutropenia (33.3%) (**Figure 3**)

Table 2. Summary of TEAEs[a]

Patients, n (%)	NHL (n=34)	CLL/SLL, low tumor burden (n=22)	CLL/SLL, high tumor burden (n=1)	All (N=57)
≥1 TEAE	**33 (97.1)**	**22 (100.0)**	**1 (100.0)**	**56 (98.2)**
Grade ≥3 TEAEs	19 (55.9)	14 (63.6)	1 (100.0)	34 (59.6)
Serious TEAEs	6 (17.6)	7 (31.8)	1 (100.0)	14 (24.6)
Leading to death	1 (2.9)	2 (9.1)	0	3 (5.3)
Leading to treatment discontinuation	0	1 (4.5)	0	1 (1.8)
Leading to dose modification	5 (14.7)	10 (45.5)	1 (100.0)	16 (28.1)
≥1 treatment-related TEAEs	**29 (85.3)**	**21 (95.5)**	**1 (100.0)**	**51 (89.5)**
Grade ≥3 TEAEs	14 (41.2)	13 (59.1)	1 (100.0)	28 (49.1)
Serious TEAEs	3 (8.8)	4 (18.2)	0	7 (12.3)
Leading to death	0	2 (9.1)	0	2 (3.5)
Leading to treatment discontinuation	0	1 (4.5)	0	1 (1.8)
Leading to dose modification	4 (11.8)	6 (27.3)	0	10 (17.5)

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

Figure 3. TEAEs With Incidence ≥10%

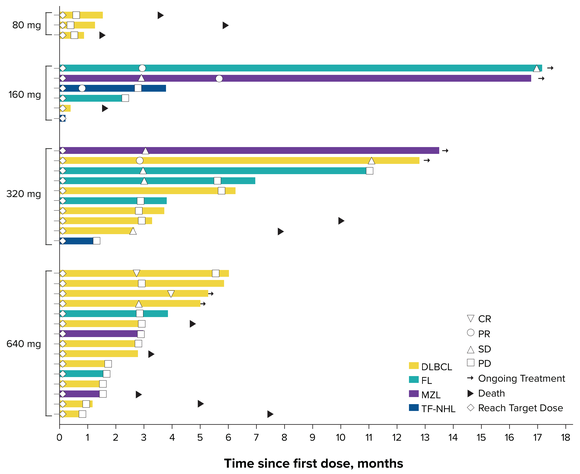


- DLTs were reported in 3 patients (NHL, n=2; CLL/SLL, n=1)
  - NHL: 1 patient (80 mg cohort) with Grade 3 platelet count decreased; 1 patient (160 mg cohort) with Grade 3 bone pain
  - CLL/SLL: 1 patient (80 mg cohort) with Grade 3 febrile neutropenia
- No clinical TLS occurred in any patients

Antitumor activity

- Of the 34 evaluable patients with NHL, 6 (17.6%) achieved a complete response (CR) or partial response (PR); both CRs occurred in patients with DLBCL in the 640 mg cohort (**Figure 4**)
- Of 23 evaluable patients with CLL/SLL, 13 (56.5%) had a PR or better (**Figure 5**)
- Of 9 minimal residual disease (MRD)-evaluable patients with CLL/SLL (80 mg, n=5; 160 mg, n=4), 3 had undetectable MRD with <1 CLL cell in 10^4 leukocytes (uMRD4)
  - One had blood and bone marrow uMRD4 after 4.5 months (80 mg cohort)
  - Two had blood uMRD4 after 7.1 months (160 mg cohort)

Figure 4. Duration of Treatment and Best Response in Patients With NHL

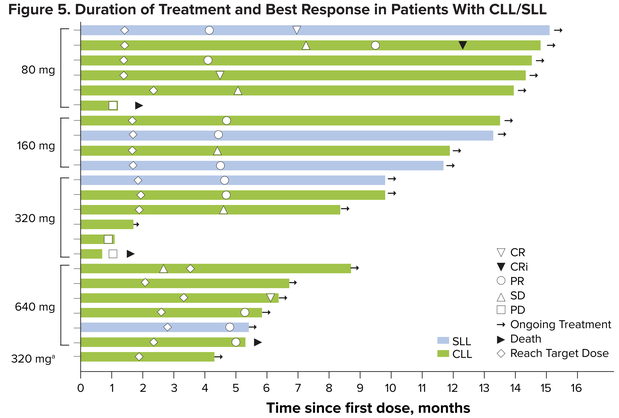


BOR, best overall response; CR, complete response; PD, progressive disease; PR, partial response, SD, stable disease; TF-NHL, transformed NHL.

CONCLUSIONS

- These initial results from BGB-11417-102 indicated that BGB-11417 monotherapy, at all tested doses up to 640 mg, was well tolerated without dose-dependent increases in toxicity
- The risk of TLS was low and manageable in this study, with no clinical TLS observed
- Initial antitumor activity of BGB-11417 monotherapy was promising; responses were observed in patients with R/R CLL/SLL at lower dose levels
- Preliminary antitumor activity was observed in patients with NHL with BGB-11417 monotherapy; further expansion data are being generated

Figure 5. Duration of Treatment and Best Response in Patients With CLL/SLL



[a]This patient had CLL with high tumor burden; all other patients had low tumor burden.
BOR, best overall response; CR, complete response; CRi, complete response with incomplete blood count recovery; PD, progressive disease; PR, partial response; SD, stable disease.

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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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