Preliminary Results From a Phase 1/1b First-In-Human Study of BGB-21447, a Next-Generation BCL2 Inhibitor, in Patients With B-Cell Non-Hodgkin Lymphoma

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CONCLUSIONS

- Initial first-in-human data demonstrate that BGB-21447 is well tolerated in heavily pretreated patients with B-NHL
- The safety profile of BGB-21447 has been consistent with that of other BCL2 inhibitors; hematologic toxicities are the most common all-grade and grade ≥3 TEAEs observed
- Encouraging antitumor activity has been observed with BGB-21447, with ORRs of 48% and 33% in patients with FL/MZL and DLBCL, respectively

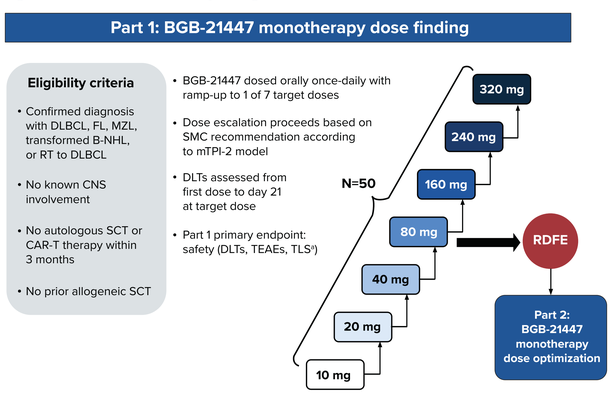
INTRODUCTION

- B-cell lymphoma 2 (BCL2)–mediated resistance to the intrinsic apoptosis pathway is a key factor in the pathogenesis and chemoresistance of hematologic malignancies[1]
- BGB-21447 is a novel, orally bioavailable BH3 mimetic that was designed to be a highly potent inhibitor of both wild-type and mutant BCL2
- BGB-21447-101 (NCT05828589) is a first-in-human phase 1/1b study of BGB-21447 in patients with B-cell malignancies
- Presented here are preliminary safety data and antitumor activity in all dose-limiting toxicity (DLT)–evaluable patients with B-cell non-Hodgkin lymphoma (B-NHL) treated with different dosing of BGB-21447 monotherapy in part 1 (dose finding)

METHODS

- BGB-21447-101 is an ongoing, global, open-label, dose-escalation and dose-optimization study to evaluate BGB-21447 in adults with mature B-cell malignancies (**Figure 1**)

Figure 1. BGB-21447-101 Study Design



[a]TLS is assessed according to Howard 2011 criteria.

Abbreviations: B-NHL, B-cell non-Hodgkin lymphoma; CAR-T, chimeric antigen receptor T-cell; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; FL, follicular lymphoma; mTPI-2, Modified Toxicity Probability Method for Dose Escalation; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; RDFE, recommended dose for expansion; RT, Richter transformation; SCT, stem cell transplant; SMC, safety monitoring committee; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome.

RESULTS

- As of September 10, 2025, 50 patients with B-NHL had received BGB-21447 in dose-escalation cohorts with target doses ranging from 10 mg to 320 mg
- The median age for all study patients was 59 years (range, 32-84 years), 54% of patients were male, and 84% were Asian (**Table 1**)
  - Most patients had either follicular lymphoma (FL; 34%) or diffuse large B-cell lymphoma (DLBCL; 28%) and 34% had bulky disease
  - The median number of prior lines of treatment was 3 (range, 0-7) and included chimeric antigen receptor T-cell (CAR-T) therapy for 10% of patients and bispecific or trispecific antibody treatment for 6%
  - Patients had a median duration of treatment at target dose of 2.6 months (range, 0.2-26.4 months) and a median study follow-up time of 9.3 months (range, 0.6-26.7 months)

Table 1. Baseline Patient Characteristics

Characteristic	10 mg (n=6)	20 mg (n=6)	40 mg (n=3)	80 mg (n=7)	160 mg (n=14)	240 mg (n=7)	320 mg (n=7)	Total (N=50)
Age, median (range), years	49.5 (32-62)	54.0 (50-77)	54.0 (43-57)	56.0 (48-78)	65.5 (37-84)	61.0 (51-75)	71.0 (51-81)	59.0 (32-84)
Male, n (%)	3 (50.0)	2 (33.3)	2 (66.7)	4 (57.1)	9 (64.3)	4 (57.1)	3 (42.9)	27 (54.0)
Race, n (%)								
Asian	6 (100)	6 (100)	3 (100)	6 (85.7)	10 (71.4)	5 (71.4)	6 (85.7)	42 (84.0)
White	0	0	0	1 (14.3)	4 (28.6)	2 (28.6)	1 (14.3)	8 (16.0)
ECOG PS, n (%)								
0	4 (66.7)	0	1 (33.3)	1 (14.3)	4 (28.6)	3 (42.9)	3 (42.9)	16 (32.0)
1	1 (16.7)	5 (83.3)	2 (66.7)	6 (85.7)	9 (64.3)	4 (57.1)	4 (57.1)	31 (62.0)
2	1 (16.7)	1 (16.7)	0	0	1 (7.1)	0	0	3 (6.0)
Cancer type, n (%)								
DLBCL	1 (16.7)	5 (83.3)	0	2 (28.6)	3 (21.4)	2 (28.6)	1 (14.3)	14 (28.0)
FL	4 (66.7)	0	2 (66.7)	3 (42.9)	4 (28.6)	2 (28.6)	2 (28.6)	17 (34.0)
MZL	0	1 (16.7)	0	0	2 (14.3)	3 (42.9)	2 (28.6)	8 (16.0)
Transformed B-cell NHL	1 (16.7)	0	1 (33.3)	1 (14.3)	3 (21.4)	0	0	6 (12.0)
RT to DLBCL	0	0	0	1 (14.3)	2 (14.3)	0	2 (28.6)	5 (10.0)
Bulky disease (LDi ≥5 cm), n (%)	3 (50.0)	0	3 (100)	1 (14.3)	6 (42.9)	1 (14.3)	3 (42.9)	17 (34.0)
Prior lines of systemic therapy, n (%)								
0	1 (16.7)	0	0	0	1 (7.1)	0	1 (14.3)	3 (6.0)
1	0	2 (33.3)	0	0	0	1 (14.3)	0	3 (6.0)
2	1 (16.7)	1 (16.7)	0	4 (57.1)	7 (50.0)	1 (14.3)	0	14 (28.0)
≥3	4 (66.7)	3 (50.0)	3 (100)	3 (42.9)	6 (42.9)	5 (71.4)	6 (85.7)	30 (60.0)
Prior CAR-T therapy, n (%)	1 (16.7)	1 (16.7)	0	1 (14.3)	1 (7.1)	1 (14.3)	0	5 (10.0)
Prior bispecific or trispecific antibodies, n (%)	0	0	0	1 (14.3)	1 (7.1)	1 (14.3)	0	3 (6.0)

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; LDi, longest diameter; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; RT, Richter transformation.

- DLTs occurred in 1 patient in the 20-mg cohort (grade 3 thrombocytopenia) and 1 patient in the 160-mg cohort (grade 3 thrombocytopenia and grade 4 blood creatine phosphokinase increased) (**Table 2**)
- Any grade treatment-emergent adverse events (TEAEs) occurred in 98% of patients; grade 3 or higher TEAEs occurred in 66%
- The most common TEAEs of any grade and of grade 3 or higher were hematologic toxicities (**Table 3**)
- Three patients (6%) had TEAEs that led to treatment discontinuation: cardiac failure and respiratory failure (80 mg, n=1; neither event was treatment-related), blood creatine phosphokinase increased (160 mg, n=1; treatment-related), and sepsis (320 mg, n=1; not treatment-related)
- Three patients (6%) experienced TEAEs that led to death and none of the fatal events were considered treatment-related: septic shock (20 mg, n=1); cardiac failure and respiratory failure (80 mg, n=1); sepsis and pneumonia (320 mg, n=1)
- One patient had laboratory tumor lysis syndrome (TLS) that resolved within 3 days with no sequelae; no clinical TLS was observed
- With doses up to the maximum assessed dose, 320 mg, the maximum tolerated dose of BGB-21447 was not reached

Table 2. TEAE Summary

Patients, n (%)	10 mg (n=6)	20 mg (n=6)	40 mg (n=3)	80 mg (n=7)	160 mg (n=14)	240 mg (n=7)	320 mg (n=7)	Total (N=50)
Any grade TEAE	6 (100)	6 (100)	3 (100)	6 (85.7)	14 (100)	7 (100)	7 (100)	49 (98.0)
Treatment-related any grade	5 (83.3)	6 (100)	3 (100)	4 (57.1)	11 (78.6)	6 (85.7)	7 (100)	42 (84.0)
Grade ≥3	4 (66.7)	4 (66.7)	2 (66.7)	3 (42.9)	12 (85.7)	2 (28.6)	6 (85.7)	33 (66.0)
Treatment-related grade ≥3	3 (50.0)	3 (50.0)	2 (66.7)	0	9 (64.3)	2 (28.6)	4 (57.1)	23 (46.0)
Serious TEAEs	2 (33.3)	3 (50.0)	0	2 (28.6)	8 (57.1)	1 (14.3)	2 (28.6)	18 (36.0)
Treatment-related serious	0	2 (33.3)	0	0	3 (21.4)	0	2 (28.6)	7 (14.0)
Led to dose interruption	0	2 (33.3)	0	0	5 (35.7)	0	3 (42.9)	10 (20.0)
Treatment-related led to dose interruption	0	2 (33.3)	0	0	3 (21.4)	0	3 (42.9)	8 (16.0)
Led to dose reduction	0	0	0	0	1 (7.1)	0	0	1 (2.0)
Treatment-related led to dose reduction	0	0	0	0	1 (7.1)	0	0	1 (2.0)
Led to treatment discontinuation	0	0	0	1 (14.3)	1 (7.1)	0	1 (14.3)	3 (6.0)
Treatment-related led to treatment discontinuation	0	0	0	0	1 (7.1)	0	0	1 (2.0)
Led to death	0	1 (16.7)	0	1 (14.3)	0	0	1 (14.3)	3 (6.0)
Treatment-related led to death	0	0	0	0	0	0	0	0
DLT[a]	0	1 (16.7)	0	0	1 (7.1)	0	0	2 (4.0)

[a]Percentages were based on the number of DLT-evaluable patients.

Abbreviations: DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

Table 3. TEAEs Occurring in >20% of All Patients

Patients, n (%)		10 mg (n=6)	20 mg (n=6)	40 mg (n=3)	80 mg (n=7)	160 mg (n=14)	240 mg (n=7)	320 mg (n=7)	Total (N=50)
White blood cell count decreased	Any grade	3 (50.0)	3 (50.0)	3 (100)	2 (28.6)	7 (50.0)	4 (57.1)	6 (85.7)	28 (56.0)
	Grade ≥3	3 (50.0)	1 (16.7)	0	0	4 (28.6)	1 (14.3)	2 (28.6)	11 (22.0)
Neutrophil count decreased	Any grade	3 (50.0)	4 (66.7)	1 (33.3)	3 (42.9)	7 (50.0)	4 (57.1)	3 (42.9)	25 (50.0)
	Grade ≥3	3 (50.0)	1 (16.7)	0	1 (14.3)	6 (42.9)	2 (28.6)	2 (28.6)	15 (30.0)
Lymphocyte count decreased	Any grade	5 (83.3)	2 (33.3)	2 (66.7)	1 (14.3)	4 (28.6)	2 (28.6)	3 (42.9)	19 (38.0)
	Grade ≥3	3 (50.0)	0	2 (66.7)	1 (14.3)	1 (7.1)	0	2 (28.6)	9 (18.0)
Platelet count decreased	Any grade	2 (33.3)	3 (50.0)	1 (33.3)	1 (14.3)	5 (35.7)	3 (42.9)	1 (14.3)	16 (32.0)
	Grade ≥3	0	2 (33.3)	0	0	1 (7.1)	0	0	3 (6.0)
Anemia	Any grade	4 (66.7)	2 (33.3)	1 (33.3)	1 (14.3)	2 (14.3)	2 (28.6)	3 (42.9)	15 (30.0)
	Grade ≥3	2 (33.3)	0	0	0	0	0	0	2 (4.0)
Hypokalemia	Any grade	0	3 (50.0)	1 (33.3)	0	3 (21.4)	2 (28.6)	2 (28.6)	11 (22.0)
	Grade ≥3	0	1 (16.7)	0	0	0	0	0	1 (2.0)

Abbreviation: TEAE, treatment-emergent adverse event.

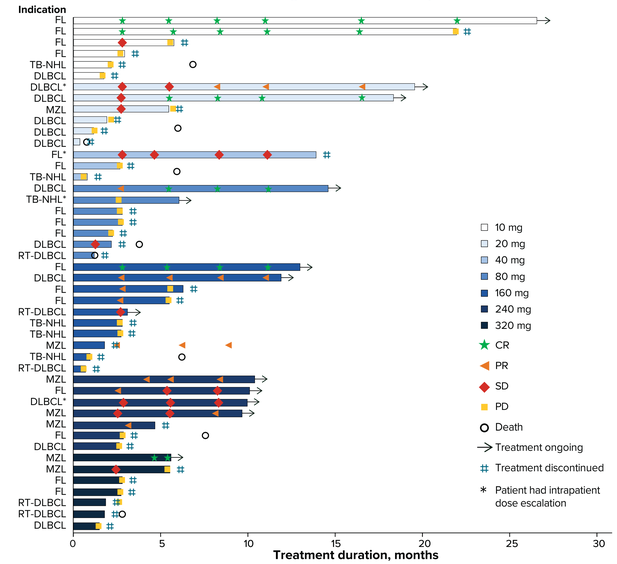
- In 23 evaluable patients with FL/marginal zone lymphoma (MZL), the overall response rate (ORR) was 48% (**Table 4** and **Figure 2**), including complete responses (CRs) in 17% of patients
- In 12 evaluable patients with DLBCL, the ORR was 33%, with CRs seen in 17% of patients
- Median time to first response was 2.8 months in patients with FL/MZL and 4.1 months in patients with DLBCL; median duration of response was 4.2 months (range, 0-19.2 months) in the FL/MZL cohort and 8.3 months in DLBCL (range, 8.3-11.1 months)

Table 4. Response Rates

BOR, n (%)	FL/MZL (n=23)	DLBCL (n=12)	RT to DLBCL (n=5)	TB-NHL (n=6)	Total (n=46)
CR	4 (17.4)	2 (16.7)	0	0	6 (13.0)
PR	7 (30.4)	2 (16.7)	0	0	9 (19.6)
SD	4 (17.4)	2 (16.7)	1 (20.0)	0	7 (15.2)
PD	8 (34.8)	5 (41.7)	2 (40.0)	6 (100)	21 (45.7)
D/c prior to first assessment	0	1 (8.3)	2 (40.0)	0	3 (6.5)

Abbreviations: BOR, best overall response; CR, complete response; d/c, discontinuation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; PR, partial response; RT, Richter transformation; SD, stable disease; TB-NHL, transformed B-cell non-Hodgkin lymphoma.

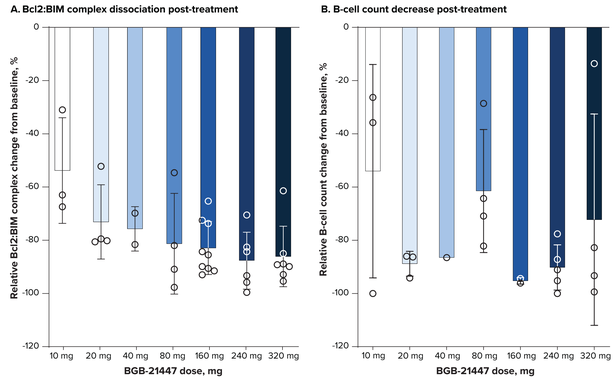
Figure 2. Treatment Duration and Investigator-Assessed Responses



Abbreviations: CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; PR, partial response; PD, progressive disease; RT-DLBCL, Richter's Transformation to DLBCL; SD, stable disease; TB-NHL, transformed B-cell non-Hodgkin lymphoma.

- BGB-21447 monotherapy led to substantial dissociation of Bcl2:BIM complex and reduction in B-cell count in peripheral blood at week 3, day 1 as compared with baseline (before first dose; **Figure 3**)
- Bcl2:BIM complex tended to dissociate more as BGB-21447 dose was increased

Figure 3. BGB-21447 Pharmacodynamics Analyses[a]



[a]Both the Bcl-2:BIM complex and B-cell count are surrogate pharmacodynamics biomarkers measured in peripheral blood. Bcl-2:BIM complex change reflects the proximal pharmacodynamics biomarker effect of target engagement, and B-cell count reflects the distal pharmacodynamics biomarker effect of cell apoptosis.

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