

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

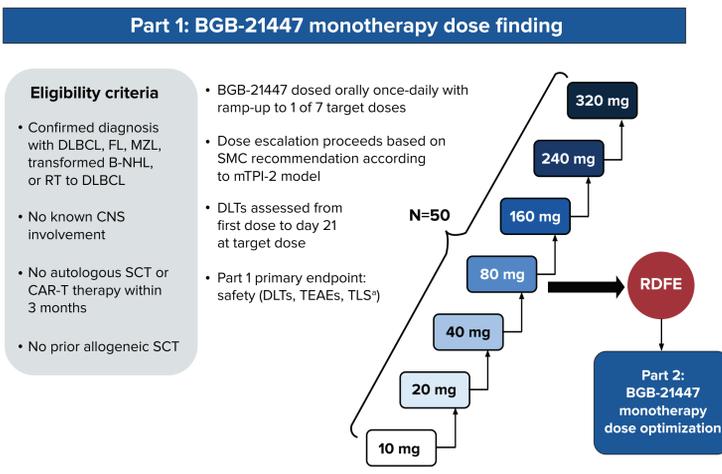
INTRODUCTION

- B-cell lymphoma 2 (BCL2)-mediated resistance to the intrinsic apoptosis pathway is a key factor in the pathogenesis and chemoresistance of hematologic malignancies¹
- 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



¹TLS 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; mTP-2, Modified Toxicity Probability Method for Dose Escalation; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; RDPE, 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)

- 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*	0	1 (16.7)	0	0	1 (7.1)	0	0	2 (4.0)

*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								
Grade ≥3	0	1 (16.7)	0	0	0	0	0	1 (2.0)

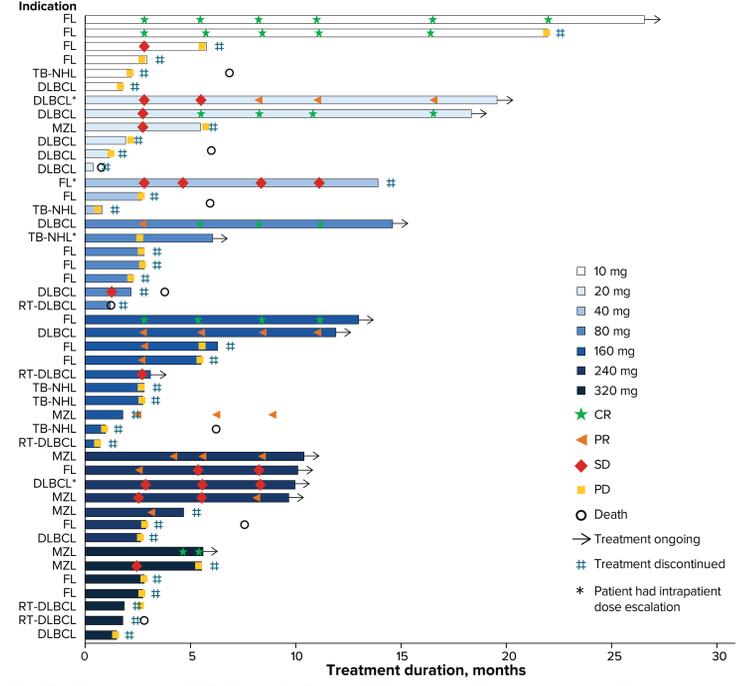
- In 23 evaluable patients with FL/marginal zone lymphoma (MZL), the overall response rate (ORR) was 48% (Table 4 and Figure 2), including complete responses (CRs) in 17% of patients
- In 12 evaluable patients with DLBCL, the ORR was 33%, with CRs seen in 17% of patients
- Median time to first response 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.

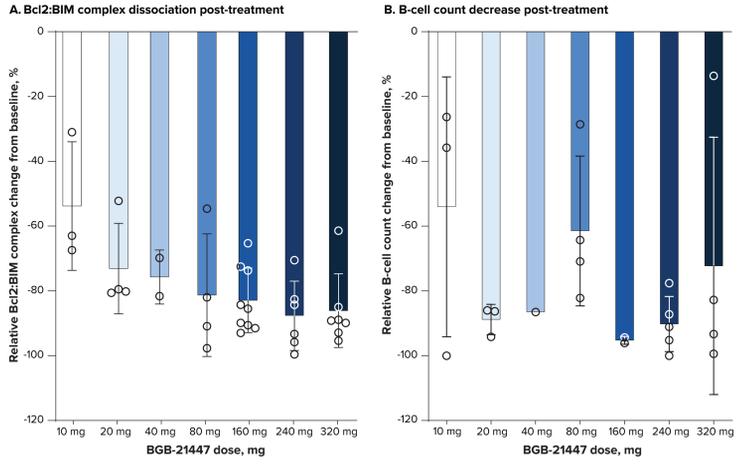
Figure 2. Treatment Duration and Investigator-Assessed Responses



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



^aBoth 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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ACKNOWLEDGMENTS

The authors thank the investigators, site support staff, and especially the patients for participating in this study. This study was sponsored by BeOne Medicines, Ltd. Medical writing support was provided by Amanda Martin, PhD, of Nucleus Global, an Inizio company, and supported by BeOne Medicines.