BGB-3111-218: Single-Arm, Open-Label, Multicenter Study of the Bruton Tyrosine Kinase Inhibitor Zanubrutinib Monotherapy in Patients with *CD79B*-Mutated Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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CONCLUSIONS

- Zanubrutinib monotherapy demonstrated encouraging antitumor activity and a tolerable safety profile in pretreated *CD79B*-mutated R/R DLBCL, providing clinical benefit for these patients who have limited therapeutic options
- Retrospective biomarker analyses demonstrated improved zanubrutinib response in patients with the non-GCB subtype, low baseline ctDNA levels, or co-occurring *CD79B* and *MYD88* L265P mutations
- Emerging therapeutic strategies targeting the B-cell receptor signaling pathway in DLBCL warrant further investigation, including BTK protein degraders, combination treatment regimens involving zanubrutinib, and treatment options guided by genetic subtypes

INTRODUCTION

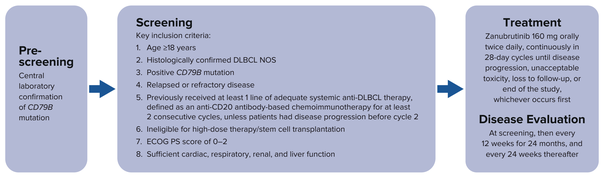
- Zanubrutinib, a potent, highly selective, next-generation Bruton tyrosine kinase (BTK) inhibitor with a favorable safety profile, is approved in over 70 countries for the treatment of at least one B cell malignancy
- Patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) face a poor prognosis, and the *CD79B* mutation is an unfavorable prognostic factor for survival. There is no established standard of care for *CD79B*-mutated R/R DLBCL, highlighting an unmet clinical need
- Zanubrutinib has demonstrated modest antitumor activity in R/R non-germinal center B-cell–like (GCB) DLBCL in clinical trials, and retrospective biomarker analyses have indicated that patients with mutations in *CD79B* show an enhanced response to zanubrutinib treatment[1,2]
- BGB-3111-218 (NCT05068440) is a phase 2, single-arm study assessing the antitumor activity and related biomarkers of zanubrutinib monotherapy for *CD79B*-mutated R/R DLBCL
- We present the final analysis of the BGB-3111-218 study

METHODS

Study Design

- The study design for BGB-3111-218 is shown in **Figure 1**

Figure 1. Study Design



Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified.

Endpoints

- The primary endpoint was investigator-assessed overall response rate (ORR) per the 2014 Lugano criteria[3]
- Secondary endpoints were complete response (CR) rate, duration of response (DoR), time to response (TTR), progression-free survival (PFS), overall survival (OS), and safety per the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0
- Exploratory endpoints included pharmacokinetic evaluations, corresponding relationships between response and clinical or genetic risk factors, as well as potential resistance biomarkers and mechanisms

Biomarker Analyses

- Comprehensive biomarker data analyses were performed to explore correlations with clinical efficacy
- Immunohistochemistry (IHC) DLBCL subtyping data were collected from local sites. For patients without local IHC data, central laboratory staining of CD10, BCL-6, and MUM1 with formalin-fixed paraffin-embedded (FFPE) tissue specimens was used to classify phenotypes using the Hans algorithm[4]
- Molecular profiling was conducted in patients with evaluable biomarkers using DNA (custom Oncolym-413 panel [Gene+]) and RNA sequencing data

RESULTS

Patients

- Between August 11, 2021, and March 31, 2025, 65 of 521 pre-screened patients were enrolled across 20 sites in China and included in the efficacy and safety analyses
- At data cutoff (March 31, 2025), the median study follow-up time was 13.9 months (range: 0.5–36.4 months)
- Baseline characteristics of the 65 enrolled patients were representative of a typical patient population with R/R DLBCL (**Table 1**)

Table 1. Baseline Patient Demographics and Disease Characteristics

Characteristic	Patients (N=65)
Median (range) age, years	66 (42–92)
Sex, n (%)	
Male	34 (52.3)
Female	31 (47.7)
ECOG performance status, n (%)	
0	12 (18.5)
1	43 (66.2)
2	10 (15.4)
Disease status at study entry, n (%)	
Relapsed	41 (63.1)
Refractory	24 (36.9)
Baseline bone marrow involvement (aspirate), n (%)	
Yes	3 (4.6)
No	57 (87.7)
N/A	1 (1.5)
Missing	4 (6.2)
Stage at study entry, n (%)	
Stage I	2 (3.1)
Stage II	6 (9.2)
Stage II bulky	3 (4.6)
Stage III	11 (16.9)
Stage IV	42 (64.6)
Missing	1 (1.5)
DLBCL IHC subtype, n (%)	
GCB	7 (10.8)
Non-GCB	56 (86.2)
COO unknown	2 (3.1)
CD79B mutant status (central laboratory), n (%)	
Positive	65 (100.0)
Negative	0
Median number (range) of prior lines	1 (1–6)

Abbreviations: COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell–like; IHC, immunohistochemistry; N/A, not applicable.

Efficacy

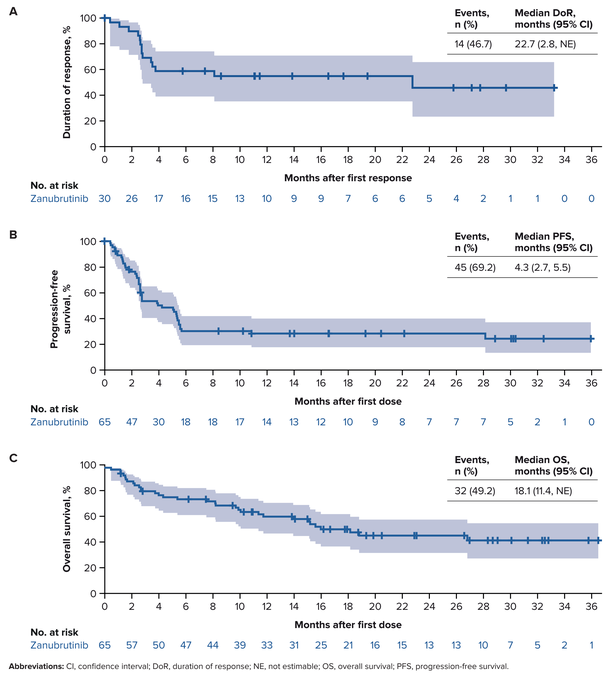
- Zanubrutinib demonstrated antitumor activity in patients with *CD79B*-mutated R/R DLBCL. The investigator-assessed ORR was 46.2% (30/65 patients; 95% confidence interval [CI]: 33.7, 59.0), including 19 (29.2%) CRs and 11 (16.9%) partial responses (**Table 2**)
- Patients with non-GCB DLBCL demonstrated a favorable clinical response to zanubrutinib monotherapy (ORR, 51.8% [29/56 patients]; 95% CI: 38.0, 65.3). No responses were observed in the seven patients with GCB DLBCL
- The median DoR was 22.7 months (95% CI: 2.8, not estimable) for the patients who had responses (**Figure 2A**); the median TTR was 2.8 months; and the median PFS and OS were 4.3 months (95% CI: 2.7, 5.5) and 18.1 months (95% CI: 11.4, not estimable), respectively (**Figure 2B** and **Figure 2C**)

Table 2. Overall Response

Response category	Patients (N=65)
Overall response rate (CR or PR), n (%)	30 (46.2)
95% CI (%)[a]	33.7, 59.0
One-sided *P* value[b]	.0044
Best overall response, n (%)	
CR	19 (29.2)
PR	11 (16.9)
SD	8 (12.3)
PD	22 (33.8)
Discontinued before first response assessment	5 (7.7)

[a]95% CI was estimated using the Clopper-Pearson method.
[b]P value was calculated from the binomial exact test of zanubrutinib versus historical rate of 0.3.
Abbreviations: CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 2. Kaplan–Meier Plots for (A) DoR, (B) PFS, and (C) OS by Investigator Assessment in Zanubrutinib-Treated Patients



Abbreviations: CI, confidence interval; DoR, duration of response; NE, not estimable; OS, overall survival; PFS, progression-free survival.

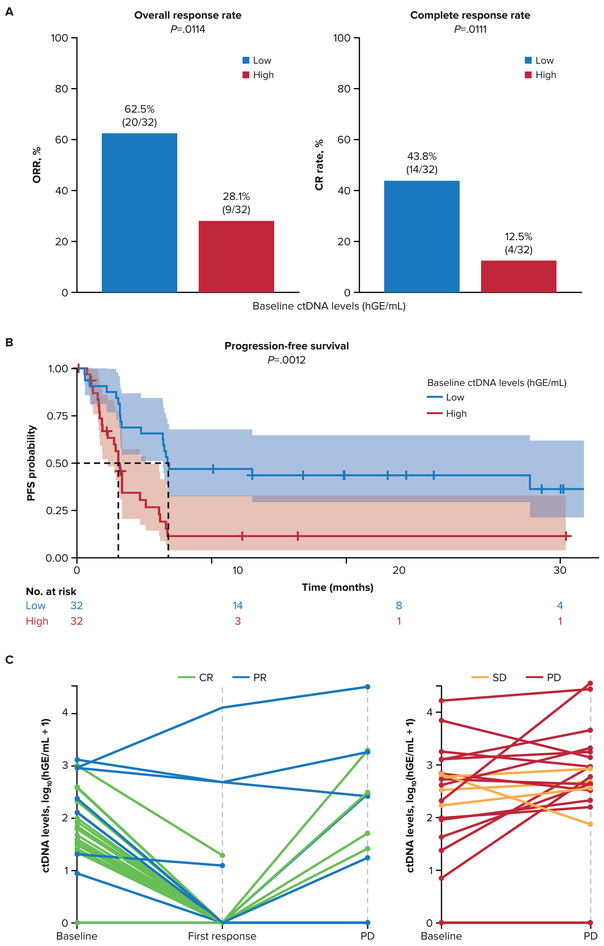
Safety

- The incidence of any treatment-emergent adverse event (TEAE) reported during the study was 90.8% (59/65 patients). TEAEs of grade ≥3 were reported in 28 (43.1%) patients, and any-grade serious TEAEs were reported in 16 (24.6%) patients
- The most frequently reported TEAEs of grade ≥3 included pneumonia (9.2%), neutrophil count decreased (7.7%), platelet count decreased (6.2%), and lymphocyte count decreased (6.2%)
- The incidence of treatment-related TEAEs (TRAEs) was 73.8% (48/65 patients), with grade ≥3 TRAEs reported in 16 (24.6%) patients and any-grade serious TRAEs reported in 6 (9.2%) patients

Circulating Tumor DNA and Mutations

- Using the median baseline circulating tumor DNA (ctDNA) level as a cutoff, patients with low ctDNA levels exhibited a better ORR (62.5% vs 28.1%; *P*=.0114) and a higher CR rate (43.8% vs 12.5%; *P*=.0111) versus patients with high ctDNA levels (**Figure 3A**)
- The 32 patients with low ctDNA levels had better PFS versus those with high ctDNA levels (32 patients; *P*=.0012; **Figure 3B**)
- When ctDNA levels were measured at first response, patients with a CR had a higher rate of undetectable ctDNA (94.4% [17/18 patients]); the rate of undetectable ctDNA in those with a PR was 37.5% (3/8) (**Figure 3C**)
- Consistent with previous studies, the most frequently mutated genes included: *PIM1* (51.6% of patients), *MYD88* (42.2%), *ETV6* (31.3%), *PCLO* (26.6%), *BTG1* (25.0%), and *TP53* (25.0%) (**Supplemental Figure 1A**)
- Patients with co-existing mutations in *CD79B* and *MYD88*^{L265P} demonstrated an improved ORR (60.9% [14/23 patients] vs 36.6% [15/41]; *P*=.0726) and a higher CR rate (43.5% [10/23 patients] vs 19.5% [8/41]; *P*=.049) versus those without *MYD88*^{L265P} (**Supplemental Figure 1B**)
- High expression of genes related to G1–S-phase cell-cycle transition, and DNA synthesis and repair, correlated with improved PFS (**Supplemental Figures 1C** and **1D**)

Figure 3. Low ctDNA Levels at Baseline and at First Response Correlated with Antitumor Activity with Zanubrutinib Monotherapy.
(A) ORR and CR rate according to baseline ctDNA levels (hGE/mL). **(B)** Correlation between baseline ctDNA levels and PFS. **(C)** The dynamic change in ctDNA levels at baseline, first response, and disease progression in responders (left) and non-responders (right).



For Figure 3A and Figure 3B, median level of baseline ctDNA abundance (hGE/mL) was used as the cutoff value.
Abbreviations: CR, complete response; ctDNA, circulating tumor DNA; hGE, haploid genome equivalents; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Supplemental Figure 1

FUNDING

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REFERENCES

1. Yang H, et al. *Blood Adv* 2022;6:1629-36.
2. Liu Y, et al. *Leuk Lymphoma* 2024;65:1079-89.
3. Cheson BD, et al. *J Clin Oncol* 2014;32:3059-68.
4. Hans CP, et al. *Blood* 2004;103:275-82.

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