EXTENDED FOLLOW-UP OF A PHASE 2 TRIAL OF THE BRUTON TYROSINE-KINASE INHIBITOR ZANUBRUTINIB (BGB-3111) IN CHINESE PATIENTS WITH RELAPSED/REFRACTORY WALDENSTRÖM MACROGLOBULINEMIA

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Background: Zanubrutinib is a highly selective, potent, and irreversible Bruton tyrosine kinase inhibitor approved globally including in the United States, China, and Europe for treatment of adult patients with relapsed/refractory (R/R) Waldenström macroglobulinemia (WM). BGB-3111-210 (NCT03332173) is a pivotal, open-label, multicenter, phase 2 study investigating zanubrutinib in Chinese patients with R/R WM, a group with limited data.

Aims: To evaluate the long-term efficacy and safety of zanubrutinib in patients with R/R WM with a median follow up of 33.0 (range, 3.2-36.5) months.

Methods: Eligible patients with R/R WM and ≥1 prior standard chemotherapy-containing regimen received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Major response rate (MRR) was assessed by an independent review committee according to an adaptation of the 6th International Workshop on WM response criteria (primary objective), and by the investigator (data shown here). Secondary endpoints included progression-free survival (PFS), overall response rate, duration of major response, and safety.

Results: As of January 11, 2021, 44 patients were enrolled and evaluated for safety and 43 evaluated for efficacy (1 was excluded owing to baseline immunoglobulin M level <5 g/L), as shown in Table 1. Patients enrolled had relatively poor prognostics: 43.2% were aged >65 years, median number of prior anticancer regimens was 2, 45.5% were high-risk, 75% had baseline

anemia, and 15.9% had *MYD88*^{WT}. Best responses to the last regimen were stable disease in 45.5% and progressive disease in 22.7% of patients enrolled.

MRR was 69.8%, with a very good partial response or better in 32.6%. All mutational subgroups examined benefited from zanubrutinib treatment; MRR was 73.0% in patients with *MYD88*^{L265P} and 50.0% in patients with *MYD88*^{WT}. Higher response rates were observed in patients with *MYD88*^{L265P}/*CXCR4*^{WT} vs other mutational subgroups. Median PFS and median duration of major response were not reached.

The most frequently reported treatment-emergent adverse events (TEAEs) included neutrophil count decreased (59.1%), white blood cell count decreased (31.8%), upper respiratory tract infection, platelet count decreased, and pneumonia (29.5% each). The most frequently reported grade ≥3 TEAEs were neutrophil count decreased (31.8%) and platelet count decreased and pneumonia (20.5% each). Most bleeding events were grade 1 or 2, originating in skin or mucous membranes. Major hemorrhage (serious or grade ≥3 bleeding, or central nervous system bleeding of any grade) was reported in 2 patients (4.5%). TEAEs leading to discontinuation of zanubrutinib (n=1 each) included pneumonia, laryngeal cancer, WM (investigator reported and suspected transformation), intracranial mass, acute hepatitis B, and multiple organ dysfunction syndrome. One patient had a dose reduction owing to arthralgia. Two patients died within 30 days of last study treatment: 1 owing to acute hepatitis B and multiple organ dysfunction syndrome, and 1 owing to an unknown reason (investigator assessed as unlikely to be related to study drug). No atrial fibrillation/flutter or tumor lysis syndrome were reported.

Conclusions: Zanubrutinib treatment led to high, durable, and deep responses in Chinese patients with R/R WM across mutational subgroups. Zanubrutinib may provide an improved treatment option with a potentially positive benefit–risk profile for WM.

Table 1. Patient Baseline Characteristics, Efficacy, and Safety

Patient baseline characteristics	**N=44**
Sex, n (%)	
Male	27 (61.4)
Female	17 (38.6)
Median age, years (range)	65 (41–83)
Aged >65 years, n (%)	19 (43.2)
ECOG PS, n (%)	
0	18 (40.9)
1	23 (52.3)
2	3 (6.8)
Median no. of prior systemic therapy regimens (range)	2 (1–6)
WM prognostic score,[a] n (%)	
Low risk	11 (25.0)
Intermediate risk	13 (29.5)
High risk	20 (45.5)

Genotype, n (%)	
MYD88^{L265P}/*CXCR4*^{WT}	32 (72.7)
MYD88^{L265P}/*CXCR4*^{WHIM}	5 (11.4)
MYD88^{WT}	7 (15.9)
Efficacy per investigator	**N=43[b]**
BOR, n (%)	
CR	0
VGPR	14 (32.6)
PR	16 (37.2)
MR	3 (7.0)
SD	2 (4.7)
PD	7 (16.3)
Discontinued study prior to first tumor assessment	1 (2.3)
CR + VGPR rate, n (%); (95% CI)[c]	14 (32.6); (19.08, 48.54)
Major response rate (PR or better), n (%); (95% CI)[c]	30 (69.8); (53.87, 82.82)
Overall response rate (MR or better), n (%); (95% CI)[c]	33 (76.7); (61.37, 88.24)
Safety, n (%)	**N=44**
Any TEAE[d]	44 (100)
Any grade ≥3 TEAE	34 (77.3)
TEAE leading to zanubrutinib discontinuation	5 (11.4)
Grade 5 TEAE	2 (4.5)
SAE	25 (56.8)

Abbreviations: BOR, best overall response; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; MR, minor response; PD, progressive disease; PR, partial response; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

[a]Determined using the International Prognostic Scoring System for Waldenström Macroglobulinemia. Low-risk group includes patients aged ≤65 years who have a score of 0 or 1; intermediate-risk group includes those aged >65 years or any patient with a score of 2; high-risk group includes patients of any age who have a score of ≥3. Score is based on the following criteria (each afforded 1 point): age >65 years, hemoglobin level ≤115 g/L, platelet count ≤100 × 10^9/L, β2-microglobulin level >3 mg/L, and serum monoclonal protein concentration >7 g/dL.
[b]One patient was excluded from the efficacy analysis owing to baseline immunoglobulin M level <5 g/L.
[c]Calculated using the Clopper-Pearson method.
[d]TEAE is defined as an adverse event that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days after the last dose of study drug or initiation of new anticancer therapy. Worsening of an event to grade 5 beyond day 30 after last dose of study drug of a TEAE is also considered a TEAE (if it is prior to new anticancer therapy start)