Safety and Efficacy of the Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) in Patients with Waldenström Macroglobulinemia from a Phase 2 Trial

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Background: The Bruton tyrosine kinase (BTK) inhibitor zanubrutinib has demonstrated greater selectivity for BTK versus other TEC- and EGFR-family kinases in biochemical assays, and favorable pharmacokinetic/pharmacodynamic properties in preclinical studies. In a phase 1 clinical trial, zanubrutinib showed complete and sustained 24-hour BTK occupancy in both peripheral blood mononuclear cells and lymph node biopsies from patients treated with 160 mg twice daily (Tam et al. *Blood* 2016;128:642). Zanubrutinib was also associated with high and durable responses in

patients with Waldenström macroglobulinemia (WM) (Tam, ASCO 2020, abstract 8007; Dimopoulos, EHA 2019, abstract PF487;Trotman, EHA 2019, abstract PF481). Here we present initial safety and efficacy data from a phase 2 trial of zanubrutinib in patients with relapsed or refractory (R/R) WM.

Methods: BGB-3111-210 (ClinicalTrials.gov: NCT03332173) is a pivotal, single-arm, open-label, multicenter, phase 2 study conducted in China. Patients with R/R WM aged ≥18 years and with ≥1 prior line of standard chemotherapy-containing regimen (with completion of ≥2 continuous treatment cycles) receive zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. The primary objective is to evaluate the efficacy of zanubrutinib as measured by major response rate (MRR), defined as the proportion of patients achieving complete response (CR), very good partial response (VGPR), or partial response (PR), as assessed by an independent review committee (IRC) according to an adaptation of the 6th International Workshop on WM response criteria. Secondary endpoints include progression-free survival (PFS), overall response rate (ORR), duration of major response, and safety. The safety analysis set includes all patients who received ≥1 dose of zanubrutinib. All efficacy endpoints are analyzed in patients with pathologically confirmed WM and with baseline immunoglobulin M (or M-protein) ≥5 g/L. Adverse event (AE) severity is graded according to NCI CTCAE v4.03.

Results: As of August 31, 2019, a total of 44 patients with R/R WM were enrolled and treated, with a median follow-up of 18.58 months. Baseline characteristics are summarized in Table 1. For the 43 patients evaluable for efficacy (1 patient was excluded from the efficacy analysis due to baseline immunoglobulin M <5g/L), MRR per IRC was 69.8% (n=30, Table 1), with ≥ VGPR achieved in 32.6% of patients (n=14). As of data cutoff date, median PFS and median duration of major response were not reached. The most frequently reported (≥20%) treatment-emergent AEs (TEAEs) included neutrophil count decreased (56.8%), platelet count decreased (29.5%), white blood cell count decreased and upper respiratory tract infection (27.3% each), diarrhea (25.0%), weight increased and arthralgia (20.5% each). Grade 3 or higher AEs reported in ≥5% of patients included neutrophil count decreased (31.8%), platelet count decreased (20.5%), lung infection (13.6%), white blood cell count decreased (11.4%), pneumonia (9.1%), anemia and upper respiratory tract infection (6.8% 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%). No cases of atrial fibrillation/flutter or tumor lysis syndrome were reported. Two patients died within 30 days of last study treatment: one due to acute hepatitis B and multiple organ dysfunction syndrome, both of which were related to study

drug per investigator's judgment, the other due to unknown reason, which was unlikely to be related to study drug as assessed by the investigator. TEAEs leading to discontinuation of zanubrutinib (n=1 each) included lung infection, laryngeal cancer, WM (investigator reported WM as AE due to unexpected rapid progression and suspected it to be a transformation), intracranial mass, acute hepatitis B (grade 5), and multiple organ dysfunction syndrome (grade 5).

Conclusions: Zanubrutinib was shown to be highly active in patients with R/R WM, as demonstrated by a high MRR, ⩾VGPR rate. Zanubrutinib was generally well tolerated, consistent with previous reports of zanubrutinib treatment in patients with various B-cell malignancies.

Table 1. Patient Baseline Characteristics, Efficacy, and Safety

Patient Baseline Characteristics	**N=44**
Median age, years (range)	65 (41–83)
ECOG PS, n (%)	
0	18 (40.9)
1	23 (52.3)
2	3 (6.8)
Median number 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)
Efficacy per IRC	**N=43[b]**
BOR, n (%)	
CR	0
VGPR	14 (32.6)
PR	16 (37.2)
MR	4 (9.3)
SD	4 (9.3)
PD	2 (4.7)
Unknown	3 (7.0)
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]	34 (79.1); (63.96, 89.96)
Safety, n (%)	**N=44**
Any TEAE[d]	44 (100)
Any grade 3 or higher TEAE	32 (72.7)
TEAE leading to zanubrutinib discontinuation	5 (11.4)
Grade 5 TEAE leading to death	2 (4.5)
SAE	22 (50.0)

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; 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] 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 or more. Score is based on the following criteria (each afforded 1 point): age >65 years, hemoglobin ≤115 g/L, platelet count ≤100 × 10^9/L, β2-microglobulin >3 mg/L, serum monoclonal protein concentration >7 g/dL.

[b] One patient was excluded from the efficacy analysis due to baseline immunoglobulin M <5g/L.

[c] Calculated using the Clopper-Pearson method.

[d] TEAE is defined as an AE 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, whichever occurred first.