Safety and Activity of the Investigational Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) in Patients With Mantle Cell Lymphoma 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 blood and lymph node biopsies from patients treated at 160 mg twice daily (bid; Tam et al. *Blood* 2016;128:642), and was associated with durable responses in patients with non-Hodgkin lymphoma (Tam et al. *Blood*

2017; 130:152). Here, we present initial safety and efficacy data from a phase 2 trial of zanubrutinib in patients with relapsed or refractory mantle cell lymphoma (R/R MCL).

Methods: Conducted in China, BGB-3111-206 (clinicaltrials.gov NCT03206970) is a pivotal, single-arm, open-label, multicenter phase 2 study. Patients with R/R MCL aged 18-75 years and with 1-4 prior treatment regimens received zanubrutinib 160 mg bid until disease progression (PD) or unacceptable toxicity. The primary objective is to evaluate the efficacy of zanubrutinib as measured by overall response rate (ORR) assessed by an Independent Review Committee (IRC). Response was assessed with PET-CT scans (in subjects with FDG-avid disease) and CT or MRI scans (in subjects with FDG non-avid disease) at each response assessment and for confirmation of complete response (CR) per the International Conference on Malignant Lymphoma (Lugano) criteria (Cheson, 2014). Key secondary endpoints included progression free survival (PFS), time to response (TTR), duration of response (DOR) and safety. Treatment-emergent adverse events (TEAEs) were assessed according to NCI CTCAE v4.03.

Results: As of 27 March 2018, 86 patients with R/R MCL were enrolled and treated. Patient characteristics are summarized in the Table. Over one-half (52.3%) of patients were refractory to their last prior therapy. Median follow-up was 36 weeks (range, 1-56) at the data cut. Twenty-one patients discontinued zanubrutinib (13 for PD; 6 for TEAEs; 1 withdrew consent; and 1 per investigator's discretion). One patient was not evaluable for response due to a lack of central pathologic confirmation of MCL. Of the 85 evaluable patients, ORR per the IRC was 84% (n=71; Table), with CR reported in 59% of patients (n=50). The estimated event-free rate for responders was 90% at 24 weeks after response. In total, 12 patients have progressed; the estimated PFS rate was 82% at 24 weeks. The most frequent (≥15%) TEAEs due to any cause included decreased neutrophil count (31.4%), upper respiratory tract infection (29.1%), rash (29.1%), decreased platelet count (22.1%), and decreased white blood cell (WBC) count (17.4%). Grade ≥3 TEAEs due to any cause reported in >2 patients included decreased neutrophil count (11.6%), lung infection (5.8%), anemia (4.7%), and decreased WBC count 3.5%). Petechia/purpura/contusion and hematuria were each reported in 4 patients (4.7%, all grade 1/2); major hemorrhage (serious or grade ≥3 bleeding or central nervous system bleeding of any grade) was reported in 1 patient (1.2%); no cases of atrial fibrillation/flutter or tumor lysis syndrome were reported. Six patients died within 30 days of last study treatment, 1 from PD, 4 due to Grade 5 TEAEs and 1 due to a Grade 5 event that was not treatment emergent. TEAEs leading to discontinuation of zanubrutinib included (n=1 each): infection, pneumonia, lung infection, interstitial lung disease, and two Grade 5 TEAEs (cerebral hemorrhage and road traffic accident).

Conclusions: Zanubrutinib was shown to be highly active in patients with R/R MCL, as demonstrated by a high rate of CR documented by PET-based imaging. Zanubrutinib was generally well-tolerated, consistent with previous reports of zanubrutinib treatment in patients with various B-cell malignancies.

Table. Patient Characteristics, Efficacy and Safety

Patient Characteristics	**N = 86**
Median age, y (range)	60.5 (34–75)
ECOG PS, n (%)	
0	60 (69.8)
1	22 (25.6)
2	4 (4.7)
Median no. of prior lines of therapy (range)	2 (1–4)
Bulky disease, n (%)	
>10 cm	7 (8.1)
> 5 cm	37 (43.0)
Stage IV disease, n (%)	64 (74.4)
Intermediate/high-risk per MIPI-b, n (%)	72 (83.7)
Efficacy (Best Response per IRC)	**n = 85**
Overall response rate, n (%); 95% CI	71 (83.5); 73.9, 90.7
Complete response, n (%)	50 (58.8)
Partial response, n (%)	21 (24.7)
Stable disease, n (%)	2 (2.4)
Progressive disease, n (%)	6 (7.1)
Discontinued prior to first response assessment, n (%)	5 (5.9)
No evidence of disease at baseline (per IRC), n (%)	1 (1.2)
Safety, n (%)	**N=86**
Any TEAE	81 (94.2)
Any Grade ≥3 TEAE	28 (32.6)
TEAE leading to zanubrutinib discontinuation	6 (7.0)
Grade 5 TEAE	4 (4.7)

ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; MIPI-b, Mantle Cell International Prognostic Index-biologic; PET-CT, positron-emission/computed tomography; TEAE, treatment-emergent adverse event