Updated Safety and Activity of the Investigational Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) in Patients with Mantle Cell Lymphoma

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Background: Investigational Bruton tyrosine kinase (BTK) inhibitor zanubrutinib has demonstrated greater selectivity vs other TEC• and EGFR• family kinases in biochemical assays and favorable pharmacokinetic/pharmacodynamic properties in preclinical studies. In phase 1 testing, high plasma concentrations were achieved, resulting in complete and sustained 24-hour BTK inhibition in blood and lymph nodes in patients treated at 160 mg twice daily (bid; Tam et al. *Blood* 2016;128:642). A recent update of clinical data suggested that complete and sustained 24-hour BTK occupancy is associated with durable responses in patients with non-Hodgkin lymphomas (Tam et al. *Blood* 2017;130:152). Here, we present updated safety and efficacy data from patients with mantle cell lymphoma (MCL).

Methods: Study AU-003 is a global, open•label, multicenter, phase 1b trial investigating zanubrutinib in patients with B•cell malignancies. After dose escalation, the expansion phase enrolled disease•specific cohorts at the recommended phase 2 dose of zanubrutinib (320 mg/day once daily or 160 mg bid). Treatment emergent adverse events (TEAEs) were summarized according to NCI CTCAE v4.03 and response was assessed per International Conference on Malignant Lymphoma criteria (Cheson et al. *J Clin Oncol* 2014;32:3059). Positron-emission tomographic (PET) scan was not required for response assessment.

Results: As of 28 Feb 2018, 43 patients were enrolled: 38 relapsed/refractory and 5 treatment-naïve (**Table**). Median follow-up was 10.3 months (range, 0.1–39.2). Twenty patients have discontinued treatment (12 due to progressive disease; 8 due to TEAEs). Most common TEAEs of any cause (≥15% of patients) included diarrhea (30.2%), petechiae/purpura/contusion (30.2%), upper respiratory tract infection (27.9%), constipation (18.6%), fatigue (18.6%), and rash (16.3%). Two cases of atrial fibrillation/flutter (4.7%) and 3 cases of major hemorrhage (7.0%; renal hematoma, gastrointestinal hemorrhage, and tumor hemorrhage, all grade 3) were reported. Most common grade ≥3 TEAEs of any cause (≥2 patients) included anemia (7.0%), cellulitis (7.0%), pneumonia (7.0%), myalgia (7.0%), neutropenia (4.7%), back pain (4.7%), peripheral edema (4.7%), hypertension (4.7%), and acute kidney injury (4.7%). Fourteen patients experienced ≥1 serious TEAE (SAE) of any cause; SAEs occurring in >1 patient included pneumonia (7.0%) and cellulitis (4.7%). Nine TEAEs led to discontinuation of zanubrutinib in 8 patients: pneumonia, cognitive disorder, antineutrophil cytoplasmic antibody-positive vasculitis and acute kidney injury (same patient), joint effusion, and myelodysplastic syndrome; 3 of the 9 were fatal TEAEs designated by the investigator as unrelated to zanubrutinib including pneumonia, congestive cardiac failure, and cerebral infarction. Three patients who had not yet reached their first response assessment were not evaluable for response. As shown in the **Table**, overall response rate was 90.0% (n=36/40) including 20.0% (n=8) with complete response. Response was based on computed tomography (CT) scan alone for the majority of patients as PET was not required. The 4 non-responders included 1 with progressive disease, 1 with stable disease, and 2 patients who discontinued because of TEAEs (pneumonia, congestive cardiac failure) before the first response assessment. Median progression-free survival was 18.0 months (**Table, Figure**).

Conclusions: Zanubrutinib monotherapy was demonstrated to be highly active in patients with relapsed/refractory MCL, with a safety profile consistent with that of previous reports of zanubrutinib.

Table. Patient Characteristics, Safety, and Efficacy

Patient characteristics	**N = 43**
Median (range) age, y	71 (42–87)
ECOG PS, n (%)	
0	21 (48.8)
1	19 (44.2)
2	3 (7.0)
Median (range) no. of prior therapies	1 (0–4)
Median (range) follow-up, mo	10.3 (0.1–39.2)
Disease status, n (%)	
Treatment-naïve	5 (11.6)
Relapsed/refractory	38 (88.4)
Bulky disease >10 cm, n (%)	3 (7.0)
Safety, n (%)	**N = 43**
Any AE	40 (93.0)
Grade ≥3 AE	23 (53.5)
Serious AE	14 (32.6)
AE leading to zanubrutinib discontinuation	8 (18.6)
Fatal AE	3 (7.0)
Efficacy	
Best response per investigator	**n = 40[a]**
Overall response rate, n (%); 95% CI	36[b] (90.0); 76.3, 97.2
Complete response, n (%)	8 (20.0)
Partial response, n (%)	28 (70.0)
Stable disease, n (%)	1 (2.5)
Progressive disease, n (%)	1 (2.5)
Discontinued before first assessment due to AE, n (%)	2 (5.0)
Duration of response (months)	**n = 36**
Number of events, n (%)	12 (33.3)
Median (95% CI)	15.4 (11.5, 28.2)
Progression-free survival (months)	**n = 40**
Number of events, n (%)	16 (40.0)
Median (95% CI)	18.0 (12.7, 30.7)

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]Four treatment-naïve patients in the efficacy evaluable population. The majority of responses were based on CT scan as PET-CT was not required.

[b]All 4 treatment-naïve patients achieved partial response (100.0% ORR). Among 36 relapsed/refractory patients, 32 responded (88.9% ORR).

Figure. Progression-Fre