Pooled Analysis of Safety Data from Zanubrutinib (BGB- 3111) Monotherapy Studies in Hematologic Malignancies

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Background: Bruton's tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration and adhesion. Zanubrutinib is a potent, selective and irreversible BTK inhibitor. It has demonstrated profound BTK inhibition with minimal inhibition of off-target kinases such as EGFR, ITK, JAK3, HER2, and TEC, providing a good scientific rationale for a reduced toxicity profile.

Aims: To demonstrate the safety profile of zanubrutinib.

Methods: Safety data from patients (pts) in 6 ongoing zanubrutinib monotherapy studies were analyzed. All pts have been treated with ≥ 1 dose of oral (po) zanubrutinib at 40 mg once-daily to 160 mg twice-daily (bid). The analysis included frequency and severity of adverse events (AEs), AEs of special interest, and AEs leading to treatment discontinuation.

Results: A total of 424 pts were included in the pooled analysis, with a data cutoff date of September 15, 2017. The median age was 64 years (range 20-87) and 71.9% were males. The median follow-up

duration was 4.8 months (range 0.03-36.0). The most common (occurring in ≥10% of pts) AEs were upper respiratory tract infection (23.8%), contusion (17.5%), diarrhea (14.2%), cough (13.0%), rash (12.7%), anemia (11.8%), and neutrophil count decreased (11.6%). Serious AEs (SAEs) were reported in 24.3%, including 7.5% that were assessed as related to zanubrutinib. The most common SAEs included pneumonia (3.5%), lung infection (1.7%) and febrile neutropenia (1.2%). AEs of special interest are shown in the Table. The most common bleeding events included contusion (17.5%) and hematuria (8.3%). Major hemorrhage, defined as serious or Grade ≥ 3 bleeding of any site, or central nervous system bleeding of any grade included gastrointestinal hemorrhage, purpura (0.5% each), melena, hemorrhagic cystitis, hematuria, renal hematoma, cerebral hemorrhage and hemothorax (0.2% each). The median time to first major hemorrhage was 23 days (range 3-262). The fatal event of cerebral hemorrhage was reported in a 70 year old male pt with mantle cell lymphoma who developed left occipital lobe hemorrhage after treatment with zanubrutinib 160 mg bid for 6 days. Amongst pts with atrial fibrillation/flutter (8 pts) a majority had known risk factors including hypertension (2 pts), pre-existing cardiovascular disease (2 pts) and concurrent infection (1 pt). The rates of Grade ≥ 3 infections were 10.1 events/100 pts in the first 3 months, 3.1 in months 3 to 6, and 5.5 after 6 months. The most common second primary malignancies included basal cell carcinoma (3.5%) and squamous cell carcinoma of skin (2.8%) with 2.1% of pts having a prior history of skin cancer. AEs led to treatment discontinuation in 5.9% of pts with 2.4% related to zanubrutinib.

Conclusions: Zanubrutinib has shown a favorable safety and tolerability profile in pts with various B-cell malignancies. In zanubrutinib's cumulative safety experience, events of interest with BTK inhibitors, such as atrial fibrillation (1.9%), major hemorrhage (2.1%), and severe diarrhea (0.7%) have been infrequent. Additionally, treatment discontinuation due to zanubrutinib-related adverse events was uncommon (2.4% of pts). These data suggest that exposure levels of zanubrutinib resulting in complete and sustained BTK inhibition can be safely achieved, resulting in low tolerability-related treatment failure rates.

Table.

AEs of Special Interest	All Patients (N=424)	
	All Grades, %	Grade ≥ 3, %
Hemorrhage	38.0	2.1
Major hemorrhage	2.1	2.1
Atrial fibrillation/flutter	1.9	0.2
Hypertension	4.2	1.4
Diarrhea	14.4	0.7
Infections	51.9	12.0
Second primary malignancies	7.1	2.4