POOLED ANALYSIS OF SAFETY DATA FROM MONOTHERAPY STUDIES OF THE BRUTON TYROSINE KINASE (BTK) INHIBITOR, ZANUBRUTINIB (BGB-3111), IN B-CELL MALIGNANCIES

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Aims

We conducted an analysis of pooled safety data from patients (pts) with non-Hodgkin lymphoma (NHL), Waldenström's Macroglobulinemia (WM) and CLL/SLL in 6 ongoing zanubrutinib monotherapy studies.

Methods

Patients received oral zanubrutinib at doses of 320 mg once daily or 160 mg twice daily. The analysis included frequency and severity of adverse events (AEs), AEs of interest (AESIs), and AEs leading to death, dose reduction or treatment discontinuation (d/c).

Results

In total, 671 pts were included in this pooled analysis (data cutoff date 16 SEPT, 2018). The median age was 64 years (range, 20-90), 68.4% were male, and 45.6% were from study sites in China. The median duration of zanubrutinib exposure was 11 months (range, 0.1-46.9). AEs reported in ≥10% of pts were upper respiratory tract infection, absolute neutrophil count (ANC) decreased, diarrhea, rash, cough, contusion, anemia, platelet count decreased, urinary tract infection, hematuria, fatigue, and white blood cell count decreased. Grade (Gr) ≥3 AEs reported in at least 3% of pts were ANC decreased, anemia, neutropenia, pneumonia, platelet count decreased, lung infection, and hypertension. The most common serious AEs were pneumonia (5%) and lung infection (3.0%). AEs of special interest are shown in the Table. Infection rates were 12.5 events/100 person-mo (Gr ≥3, 1.9 events/100 person-mo); 39.9% of pts reported infection in the first 3 mo, 16.6% in mo 3-6, and 13.5% in mo 6-12. The most common bleeding events were contusion (17.0%) and hematuria (11.0%). Major hemorrhage (defined under Table) incidence was 0.21 events/100 person-mo, most commonly upper gastrointestinal (GI) hemorrhage (4 pts), retinal hemorrhage and hematuria (2 pts each). The median time to 1st major hemorrhage was 62.5 days (range, 3-601). Among the 12 pts with atrial fibrillation/flutter, mosthad risk factors including hypertension (4 pts), cardiovascular disease (7 pts), hyperlipidemia (4 pts) and/or concurrent infection (4 pts). Second primary malignancies were reported in 53 pts, most commonly basal cell (24 pts, 83% from Australia [AUS]/New Zealand [NZL]) and cutaneous squamous cell (13 pts, all from AUS/NZL) carcinomas. AEs leading to death in >1 pt were pneumonia (6 pts), septic shock (2 pts), unspecified (5 pts), and multiple organ dysfunction (2 pts). AEs led to zanubrutinib d/c in 10.0% of pts (10.5%, 9.9%, and 5.4% in pts with WM, NHL and CLL, respectively); 4.5% discontinued for treatment-related AEs. Treatment-related AEs leading to d/c in >1 patient were pneumonia (4 pts), lung infection (4 pts) and thrombocytopenia (2 pts). The median time to d/c for AEs was 3.5 mo (range, 0.1-40.6). A total of 28 pts (4.2%) required ≥1 dose reduction for AEs.

Adverse Events of Special Interest	All Patients (N=671)	
	All Grades, %	Grade ≥3, %
Infections	66.6	21.3
All Hemorrhage	46.3	2.2
Major hemorrhage*	2.7	2.2
Diarrhea	18.2	1.0
Hypertension	8.3	3.1
Atrial fibrillation/flutter	1.8	0.6

*Major hemorrhage is defined as serious or Grade ≥3 bleeding at any site, or central nervous system bleeding of any grade (including subdural hemorrhage or hematoma).

Conclusion

Zanubrutinib was generally well-tolerated in pts with various B-cell malignancies with <5% d/c for treatment-related AEs; dose reductions were uncommon. As previously reported (Tam, EHA 2018), AESIs such as atrial fibrillation and major hemorrhage were infrequent. These data demonstrated low, safety-related treatment failure rates at doses of zanubrutinib associated with complete and sustained BTK inhibition in clinical trials.