Title: Phase 2 Study of Zanubrutinib in Patients with Relapsed/Refractory B-Cell Malignancies Intolerant to Ibrutinib/Acalabrutinib

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Background: Bruton tyrosine kinase (BTK) inhibitors (BTKi) have been shown to improve outcomes in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); however, adverse events (AEs) were the most common reason for ibrutinib and acalabrutinib discontinuation (median time ≤6 mo; Mato et al, *Haematologica* 2018;103:874; Yazdy et al, *Blood* 2019; Supplement1: 4311). Off-target effects of ibrutinib have been implicated in BTKi-related AEs. Zanubrutinib, a BTKi approved for treatment of mantle cell lymphoma (MCL) and in development for other hematologic malignancies, was specifically engineered to optimize selectivity and maximize BTK occupancy. In the head-to-head ASPEN trial of zanubrutinib vs ibrutinib in patients with Waldenström macroglobulinemia (WM), zanubrutinib showed a lower rate of AEs leading to death, discontinuation, dose reduction, and dose holds (Dimopoulos et al, EHA 2020; Abstract S225). We conducted a prospective clinical trial of zanubrutinib in patients with relapsed/refractory B-cell malignancies who have become intolerant to prior BTKi (ibrutinib and/or acalabrutinib) therapy.

***Methods*:** In this ongoing phase 2, multicenter, US, single-arm, open-label study (NCT04116437; BGB-3111-215), the safety and efficacy of zanubrutinib monotherapy (160 mg twice daily or 320 mg once daily) is being evaluated in patients with B-cell malignancies who meet requirements for treatment and have become intolerant to prior BTKi therapy. An intolerant event was defined as an unacceptable toxicity where, in the opinion of the investigator (INV), treatment should be discontinued despite optimal supportive care as a result of 1 of the following: grade

≥2 nonhematologic toxicities for >7 days (with or without treatment), grade ≥3 nonhematologic toxicity of any duration, grade 3 neutropenia with infection or fever, or grade 4 hematologic toxicity that persists to the point that the INV chose to stop therapy due to toxicity and not disease progression (PD). All enrolled patients must not have documented PD during prior BTKi therapy. Response assessment was evaluated by INV for CLL per modified International Workshop on CLL criteria (Hallek et al, *Blood* 2008;131:2745; Cheson et al, *J Clin Oncol* 2012;30:2820), for SLL, MCL, and marginal zone lymphoma per Lugano criteria (Cheson et al, *J Clin Oncol* 2014;32:3059), and for WM per modified 6th International Workshop on WM criteria (Owen et al, *Br J Haemtol* 2013;160:171). Disease parameters (imaging and laboratory parameters) performed at study entry were used as the baseline for response assessment.

***Results*:** As of 01 June 2020 (data cutoff), 17 patients with CLL/SLL were enrolled, received ≥1 dose of zanubrutinib, and were analyzed for safety. Median age was 70 years (range, 49-91) and median duration of treatment exposure was 3.02 mo (range, 0.56-7.59). The median number of prior regimens was 1 (range, 1-3). All patients had received ibrutinib. At data cut off, no patients had received acalabrutinib. At data cutoff, 16 patients remained on zanubrutinib treatment. One patient withdrew herself from the study following an AE (grade 3 syncope) unrelated, as per INV, to study treatment. Of the 31 BTKi-related AEs associated with intolerance (Table 1), 30 (96.8%) did not recur, and 1 event (3.2%; atrial fibrillation) recurred at a lower grade (grade 3 vs 2) and for a shorter duration (14 vs 3 days) vs the initial ibrutinib-intolerant event. Ten patients (58.8%) reported ≥1 AE. AEs reported in ≥10% of patients on zanubrutinib included dizziness (n=3; 17.6%) and cough (n=2; 11.8%). Grade ≥3 AEs were reported in 2 patients (11.8%): neutropenia and syncope (n=1 each; 5.9%). AEs of interest included hemorrhage and infections (n=3 each, 17.6%) and anemia, neutropenia, and atrial fibrillation (n=1 each; 5.9%). No AEs led to dose modification or treatment discontinuation. No serious AEs or deaths were reported. As of data cutoff, 10 patients were evaluable for efficacy with ≥1 response assessment. All 10 patients achieved at least stable disease, and 60% of these patients achieved a deepening of response since initiating zanubrutinib. Enrollment is ongoing and the presentation will include additional patients.

***Conclusions*:** Zanubrutinib demonstrated efficacy and tolerability in CLL/SLL patients who were intolerant to previous BTKi. These data suggest that zanubrutinib may provide a potential option after intolerance to other BTKi.

Table 1: Reoccurrence and Severity Change of Ibrutinib/Acalabrutinib-Intolerant Events

	Intolerant to Prior Ibrutinib/Acalabrutinib*		Reoccurrence on Zanubrutinib	
AEs	**No. of AEs**	**Severity Grade, Median (Range)**	**No. of AEs**	**Severity Grade, Median (Range)**
Any AE	31	2 (2-4)	1	2 (2)
Atrial fibrillation/flutter	5	3 (2-3)	1	2 (2)
Transaminases increased	3	4 (3-4)	0	—
Hypertension	3	3 (2-3)	0	—
Fatigue	3	2 (2-3)	0	—

Nausea	2	2.5 (2-3)	0	—
Arthralgia	2	2 (2-2)	0	—
Muscle spasm	2	2 (2-2)	0	—
Neutropenia	1	4 (4)	0	—
Headache, synovial rupture, vertigo, vomiting	1 each	3 (3) each	0	—
Bone pain, contusion, edema, myalgia, rash pustular, subcutaneous abscess	1 each	2 (2) each	0	—

*All patients received prior ibrutinib.
AE, adverse event.