PRELIMINARY RESULTS OF THE PHASE 2 STUDY OF ZANUBRUTINIB IN PATIENTS WITH PREVIOUSLY TREATED B-CELL MALIGNANCIES INTOLERANT TO IBRUTINIB AND/OR ACALABRUTINIB

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Background: Many patients with B-cell malignancies require continuous treatment with Bruton tyrosine kinase inhibitors (BTKi). Adverse events are a common reason for ibrutinib or acalabrutinib discontinuation. Early data from BGB-3111-215 showed zanubrutinib was well tolerated in patients with B-cell malignancies who were intolerant to either ibrutinib or acalabrutinib. Here we report preliminary results of the BGB-3111-215 trial, with a median follow-up of 4.2 months.

Aims: To assess the safety of zanubrutinib and recurrence of adverse events that led to prior BTKi intolerance.

Methods: Patients meeting protocol criteria for intolerance to ibrutinib, acalabrutinib, or both (without documented progressive disease) were given zanubrutinib monotherapy (160 mg twice daily or 320 mg once daily). Recurrence of adverse events that led to intolerance of prior BTKi and additional safety measures were assessed based on the Common Terminology Criteria for Adverse Events v5.0. Investigators determined responses using disease status at study entry as baseline and established disease criteria.

Results: As of November 1, 2020 (data cutoff), 44 patients (n=34 chronic lymphocytic leukemia/small lymphocytic lymphoma, n=6 Waldenström macroglobulinemia, n=2 mantle cell lymphoma, n=2 marginal zone lymphoma) were enrolled, received ≥1 dose of zanubrutinib, and analyzed for safety. The median age was 70.5 y (range, 49-91); median duration of

treatment was 4.2 months (range, 0.1-12.6). The median number of prior regimens was 2 (range, 1-12). Regarding prior BTKi, 39 patients received ibrutinib only, 4 received ibrutinib and acalabrutinib, and 1 received acalabrutinib only. The median number of ibrutinib- or acalabrutinib-intolerant adverse events per patient was 2 (range, 1-5). 83% of ibrutinib and 78% of acalabrutinib intolerant events did not recur on zanubrutinib; **Table**. At data cutoff, 43 patients remained on treatment; 1 withdrew consent due to zanubrutinib-unrelated grade 3 syncope. Overall, 34 patients (77.3%) reported any adverse event; most commonly reported adverse events were myalgia (n=9; 20.5%), contusion (n=8; 18.2%), dizziness (n=7; 15.9%), fatigue (n=7; 15.9%), and cough (n=5; 11.4%). Grade ≥3 adverse events were reported in 6 patients (13.6%), serious adverse events in 1 patient (2.3%, febrile neutropenia and salmonella infection), adverse events requiring dose interruptions in 6 patients (13.6%), and adverse events leading to dose reduction in 2 patients (4.5%). No adverse events led to zanubrutinib discontinuation. No deaths were reported. All efficacy evaluable patients (26/26 [100%]) maintained (10 [38.5%]) or achieved deepening (16 [61.5%]) of their response.

Conclusion/summary: Zanubrutinib provided an additional treatment option after intolerance to other BTKi, demonstrating tolerability and sustained or improved efficacy. Updated results will be presented.

Recurrence and Severity Change of Adverse Events Leading to Ibrutinib or Acalabrutinib Intolerance

	Adverse events leading to ibrutinib and acalabrutinib intolerance, N	Recurrence on zanubrutinib, n (%)		Severity change of recurrence on zanubrutinib, n (%)	
		No	Yes	Recurred at lower severity	Recurred at same severity
Ibrutinib	87	72 (82.8)	15 (17.2)	13 (86.7)	2 (13.3)
Acalabrutinib	9	7 (77.8)	2 (22.2)	1 (50.0)	1 (50.0)

Note: Multiple events of the same preferred term for a patient are counted once for the event per the worst grade experienced before and after enrollment.