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

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

Results: As of November 1, 2020 (cutoff), 44 pts (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 zanu, 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 pts received ibr only, 4 received ibr and acala, and 1 received acala only. The median number of ibr- or acala-intolerant AEs per pt was 2 (range, 1-5). 83% of ibr- and 78% of acala-intolerant events did not recur on zanu; **Table**. At cutoff, 43 pts remained on treatment; 1 withdrew consent due to zanu-unrelated grade 3 syncope. Overall, 34 pts (77.3%) reported any AE; most commonly reported AEs 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 AEs were reported in 6 pts (13.6%), serious AEs in 1 pt (2.3%, febrile neutropenia and salmonella infection), AEs requiring dose interruptions in 6 pts (13.6%), and AEs leading to dose reduction in 2 pts (4.5%). No AEs led to zanu discontinuation. No deaths were reported. All efficacy evaluable pts (26/26 [100%]) maintained (10 [38.5%]) or achieved deepening (16 [61.5%]) of their response.

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

Table/Figure:

Recurrence and Severity Change of AEs Leading to Ibr or Acala Intolerance

	AEs leading to ibr and acala intolerance, N	Recurrence on zanu, n (%)		Severity change of recurrence on zanu, n (%)	
		No	Yes	Recurred at lower severity	Recurred at same severity
Ibr	87	72 (82.8)	15 (17.2)	13 (86.7)	2 (13.3)
Acala	9	7 (77.8)	2 (22.2)	1 (50.0)	1 (50.0)

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