A phase 2 study of zanubrutinib in previously treated B-cell malignancies intolerant to ibrutinib and/or acalabrutinib: Preliminary results for patients with CLL/SLL

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ABSTRACT

Introduction: Patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) treated with Bruton tyrosine kinase inhibitors (BTKi) can have adverse events (AEs) that lead to treatment (tx) discontinuation. Interim data from BGB-3111-215 (NCT04116437) suggests that zanubrutinib (zanu), a next generation BTKi, is well-tolerated in pts with B-cell malignancies who are intolerant to ibrutinib (ibr) or acalabrutinib (acala). Preliminary safety results for pts with CLL/SLL treated with zanu after intolerance to ibr or acala are presented here.

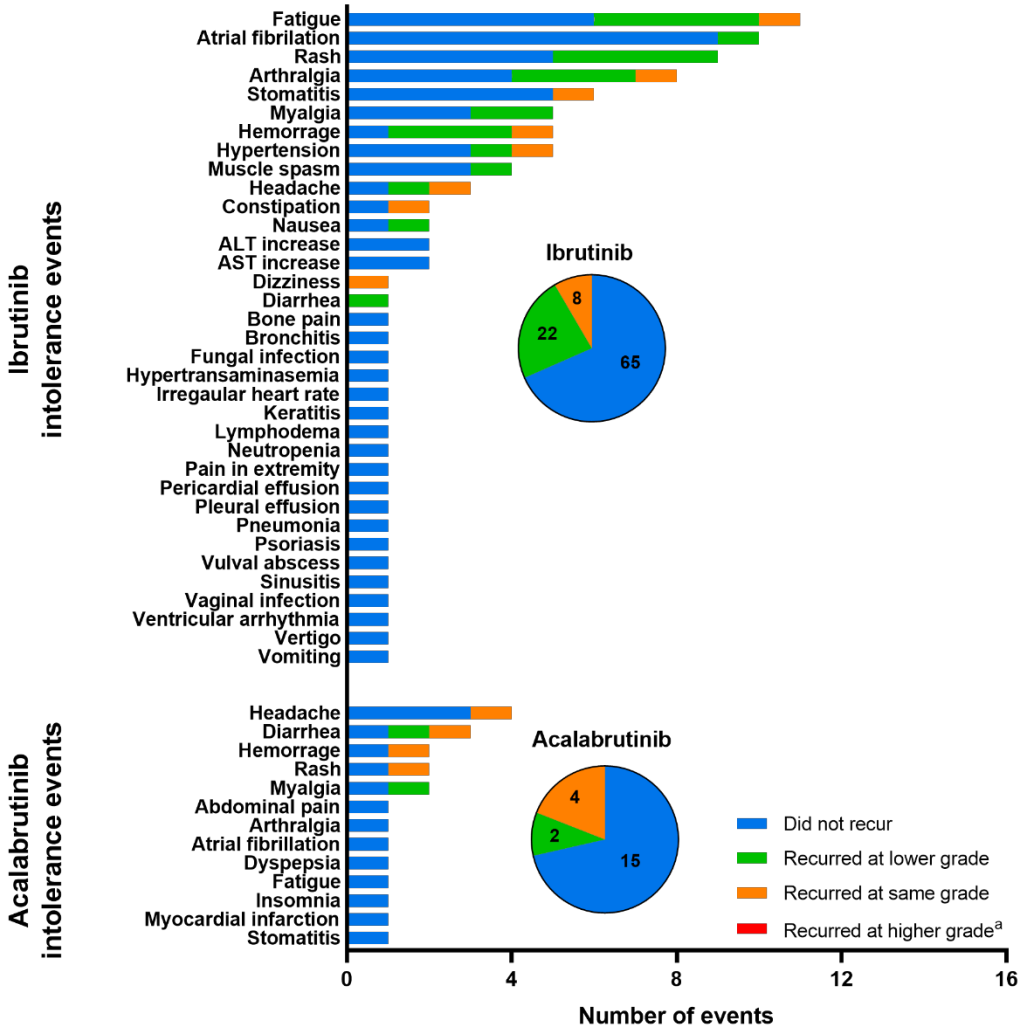
Methods: Pts with CLL/SLL intolerant to ibr, acala, or both (without progression on prior BTKi) were given zanu monotherapy (160 mg twice daily [BID] or 320 mg once daily [QD]). Safety, including recurrence of AEs that led to intolerance on ibr and/or acala, and efficacy were assessed.

Results: As of Jan 3, 2023 (median follow-up: 25.6 mo), 61 pts with CLL/SLL (44 intolerant to only ibr, 17 acala intolerant [9 intolerant to acala only; 8 intolerant to acala and ibr]) were enrolled and received ≥1 zanu dose (160 mg BID: 43 [70%], 320 mg QD: 18 [30%]). Median age

was 71 y (range, 49–91), median duration of tx was 23.7 mo (range, 0.5–36.2). The most common prior BTKi intolerance AEs were fatigue (n=12 events), rash (n=11) and atrial fibrillation (n=10). On zanu, 61% of pts did not experience recurrence of any prior BTKi-related intolerance AE. At the event level, 68% (65/95) of ibr- and 71% (15/21) of acala-intolerance AEs did not recur with zanu (**Figure**). Of the ibr-intolerance AEs that did recur, 73% (22/30) recurred at a lower grade and 27% (8/30) recurred at the same grade. Of the acala-intolerance AEs that did recur, 33% (2/6) recurred at a lower grade and 67% (4/6) recurred at the same grade. No intolerance AEs recurred at a higher grade. At data cutoff, 41 pts remained on tx; 20 discontinued tx (progressive disease, 6; AEs, 5; other, 9) and 12 discontinued the study (death, 6; pt withdrawal, 4; lost to follow-up, 2). Most common tx-emergent AEs (TEAEs): fatigue (n=18, 30%), COVID-19 (n=14, 23%), contusion (n=13, 21%), diarrhea (n=12, 20%), arthralgia, myalgia, and cough (n=10 each, 16%). Grade ≥3 TEAEs were reported in 31 pts (51%); most common Grade ≥3 TEAE: neutropenia (n=7, 11%). Serious TEAEs were reported in 16 pts (26%), TEAEs requiring dose interruption in 30 pts (49%), and TEAEs leading to dose reduction in 15 pts (25%). One pt experienced a TEAE (COVID-19 pneumonia) that led to death. Among 57 efficacy evaluable pts, the disease control and the overall response rates were 95% (n=54) and 72% (n=41), respectively. Progression-free survival rates at 6- and 12-mo were 95% and 88%, respectively.

Conclusions: AEs that previously caused pts to discontinue ibr or acala tx were unlikely to recur with zanu and their disease continued to be controlled, suggesting pts intolerant to ibr or acala are likely to continue receiving clinical benefit by switching to zanu.

Figure. Recurrence and severity change of intolerance adverse events from prior ibrutinib or acalabrutinib exposure during zanubrutinib treatment in patients with CLL/SLL



[a]No intolerance adverse events recurred at a higher grade.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.