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

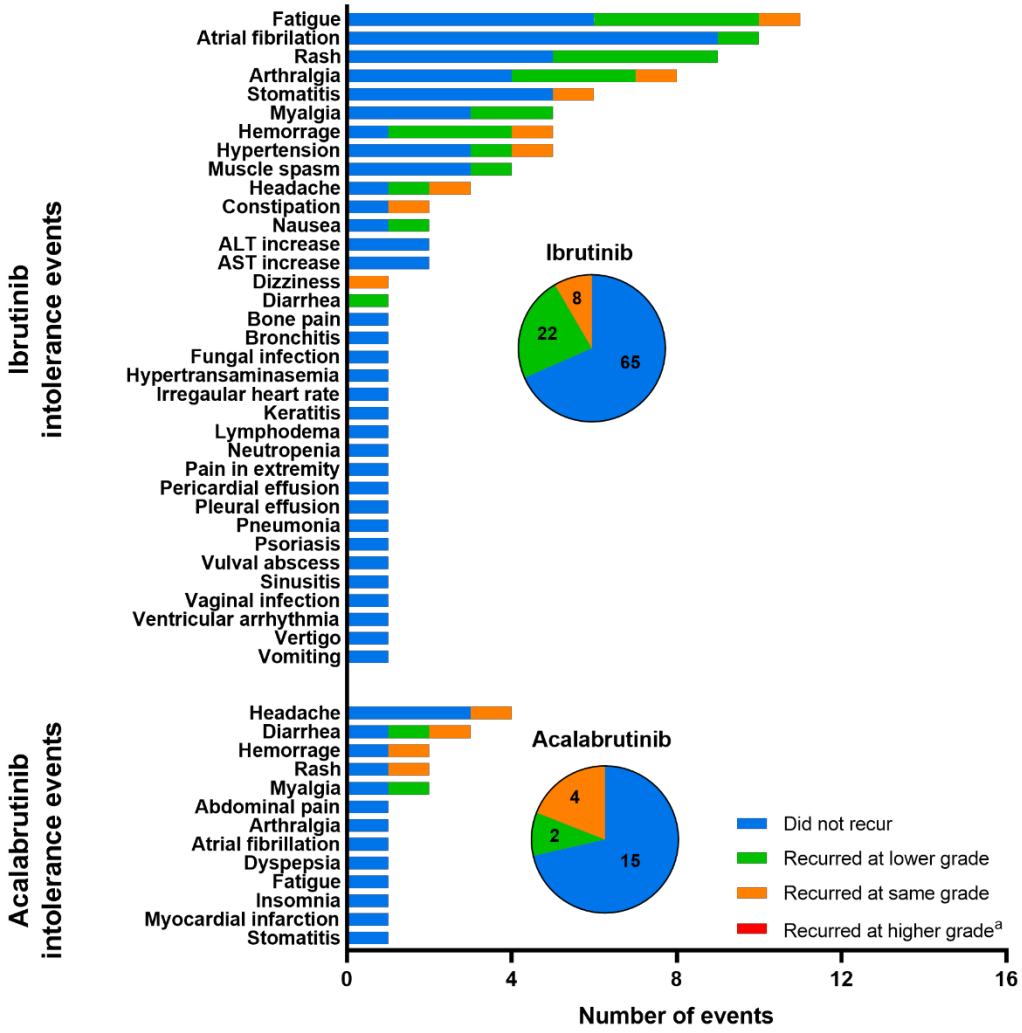
Methods: Patients with CLL/SLL who were intolerant of ibrutinib, acalabrutinib, or both (without progression on prior BTKi) were given zanubrutinib monotherapy (160 mg twice daily [BID] or 320 mg once daily [QD]). Safety, including recurrence of AEs that led to intolerance of ibrutinib and/or acalabrutinib,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

Results: As of Jan 3, 2023 (median follow-up, 25.6 mo), 61 patients with CLL/SLL (44 intolerant of only ibrutinib; 17 intolerant of acalabrutinib [9 intolerant of acalabrutinib only; 8 intolerant of acalabrutinib and ibrutinib]) were enrolled and received ≥1 zanubrutinib dose (160 mg BID, 43 [70%]; 320 mg QD, 18 [30%]). Median age was 71 y (range, 49-91 y); median duration of zanubrutinib treatment was 23.7 mo (range, 0.5-36.2 mo). The most common prior BTKi-intolerance AEs were fatigue (n=12 events), rash (n=11), and atrial fibrillation (n=10). With zanubrutinib, 61% of patients did not experience recurrence of any prior BTKi-related intolerance AE. At the event level, 68% (65/95) of ibrutinib- and 71% (15/21) of acalabrutinib-intolerance AEs did not recur with zanubrutinib (**Figure**). Of the ibrutinib-intolerance AEs that did recur, 73% (22/30) recurred at a lower grade and 27% (8/30) recurred at the same grade. Of the acalabrutinib-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 patients remained on treatment; 20 discontinued treatment (progressive disease, 6; AEs, 5; other, 9) and 12 discontinued the study (death, 6; patient withdrawal, 4; lost to follow-up, 2). The most common treatment-emergent AEs (TEAEs) were 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 patients (51%); the most common grade ≥3 TEAE was neutropenia (n=7 [11%]). Serious TEAEs were reported in 16 patients (26%), TEAEs requiring dose interruption in 30 (49%), and TEAEs leading to dose reduction in 15 (25%). One patient experienced a TEAE (COVID-19 pneumonia) that led to death. In 57 efficacy-

evaluable patients, the disease control and 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 patients to discontinue ibrutinib or acalabrutinib treatment were unlikely to recur with zanubrutinib, and their disease continued to be controlled, suggesting that patients intolerant of ibrutinib or acalabrutinib are likely to continue receiving clinical benefit by switching to zanubrutinib.

Figure. Recurrence and Change in Severity 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.