Zanubrutinib in Acalabrutinib-Intolerant Patients (Pts) with B-Cell Malignancies

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Background/Introduction: Bruton tyrosine kinase inhibitors (BTKi) are a mainstay of treatment for B-cell malignancies; however, their use can be limited by adverse events (AEs), many of which are potentially caused by off-target inhibition of other tyrosine kinases. The next-generation BTKi zanubrutinib was designed to maximize tolerability by minimizing off-target binding. Previous results from this ongoing phase 2 study (BGB-3111-215; NCT04116437) showed that zanubrutinib is well tolerated in pts intolerant to ibrutinib and/or acalabrutinib (*Blood* 2021;138[suppl 1]:1410). Here, we report updated results of the tolerability and efficacy of zanubrutinib in pts intolerant to acalabrutinib (cohort 2).

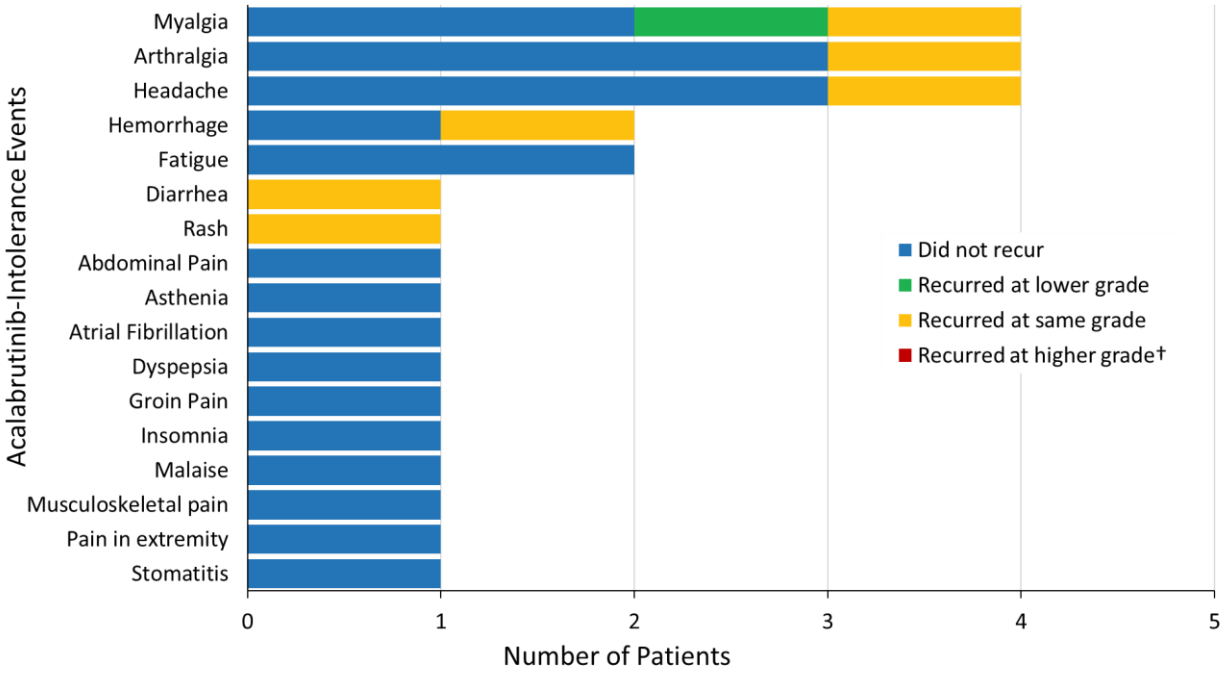
Methods: Eligible pts with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), mantle cell lymphoma (MCL), or marginal zone lymphoma (MZL) who met protocol-defined criteria for intolerance to acalabrutinib received zanubrutinib 160 mg twice daily or 320 mg once daily. Pts who progressed on prior BTKi therapy were excluded. Safety and efficacy, including recurrence of acalabrutinib intolerance events, were evaluated. Investigators assessed responses every 3 cycles based on standard response criteria for each indication using parameters at study entry as baseline.

Results: As of June 6, 2022, 17 pts received zanubrutinib in cohort 2 (12 CLL/SLL; 3 WM; 1 MCL; 1 MZL). Median age was 74 y (range, 51-87); median treatment duration was 9.2 mo (range, 0.5-20.9), with median follow-up of 10.4 mo (range, 1.1-20.9). Median number of prior therapies was 2 (range, 1-6); 9 (53%) pts received prior ibrutinib and acalabrutinib. Median cumulative exposure to acalabrutinib was 3.8 mo (range 0.5-26.9). Twelve pts remain on treatment and 5 discontinued treatment (adverse event [AE] n=2, withdrawal n=2, PD n=1). A total of 28 acalabrutinib-intolerance events were reported in the 17 pts, most commonly arthralgia, myalgia, and headache (4 each) as well as hemorrhage and fatigue (2 each). Twenty-one (75%) acalabrutinib-intolerance events did not recur on zanubrutinib, corresponding to 11 (65%) pts not experiencing any recurrence of intolerance. Seven events (25%) recurred (1 at a lower grade, 6 at the same grade, 0 at a higher grade; **Figure 1**) and 2 pts discontinued due to recurrence (myalgia and diarrhea; both recurred at same grade). Two pts who experienced the same intolerance event (pain in extremity and atrial fibrillation) on ibrutinib and acalabrutinib did not have a recurrence of those on zanubrutinib. Although many patients entered the study with well controlled disease, among the 14 efficacy-evaluable pts on zanubrutinib, 13 (93%) achieved at least stable disease and 9 (64%) achieved a deepening of response.

Conclusion: With a median zanubrutinib exposure that was longer than the reported cumulative acalabrutinib exposure before discontinuation (9.2 mo vs 3.8 mo, respectively), disease was controlled in 13 (93%) of 14 efficacy-evaluable pts treated with zanubrutinib, and 11 (65%) did not experience any recurrence of their prior acalabrutinib intolerance events. This suggests that pts intolerant to

acalabrutinib can attain clinical benefit by switching to zanubrutinib. Enrollment and follow-up are ongoing.

Figure 1. Recurrence and Severity Change of Intolerance Adverse Events from Prior Acalabrutinib Exposure to Zanubrutinib Exposure – Safety Analysis Set



†No intolerance adverse events recurred at a higher grade.