Zanubrutinib (Zanu) in Patients (Pts) With B-Cell Malignancies Intolerant to Acalabrutinib (Acala)

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Background: Treatment-related adverse events (AE) limit the use of Bruton tyrosine kinase inhibitors (BTKi), potentially due to off-target activity. A phase 2 study (BGB-3111-215; NCT04116437) demonstrated that zanu, a next-generation BTKi designed to maximize tolerability by minimizing off-target binding, is well tolerated in pts intolerant to ibrutinib (ibr) and/or acala. Updated results of the tolerability and efficacy of zanu in pts intolerant to acala (cohort 2) are reported.

Methods: 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 acala intolerance, and had not progressed on prior BTKi therapy, received zanu 160 mg twice daily or 320 mg once daily. Safety and efficacy were evaluated. Investigators used parameters at study entry as baseline and assessed response every 3 cycles based on standard response criteria.

Results: As of June 6, 2022, 17 pts received zanu (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), median follow-up was 10.4 mo (range, 1.1-20.9), median number of prior therapies was 2 (range, 1-6), and 9 (53%) pts received prior ibr and acala. Five pts discontinued treatment (2 AE, 2 withdrawal, 1 progressive disease). Seventeen pts reported 28 acala intolerance events (arthralgia, myalgia, headache [4 each], hemorrhage and fatigue [2 each]). Twenty-one (75%) acala intolerance events did not recur on zanu, corresponding to 11 (65%) pts not experiencing any intolerance recurrence. Seven (25%) events recurred (1 lower grade, 6 same grade, 0 higher grade); 2 pts discontinued owing to recurrence (myalgia and diarrhea same grade). Two pts who experienced the same intolerance event (pain in extremity and atrial fibrillation) on ibr and acala did not have a recurrence of either event on zanu. Among 14 efficacy-evaluable pts on zanu, 13 (93%) achieved at least stable disease and 9 (64%) achieved a deepening of response. With a longer median zanu exposure (zanu 9.2 mo vs acala 3.8 mo), acala intolerances were still unlikely to recur on zanu; disease was controlled in 93% of efficacy-evaluable pts with zanu.

Conclusion: Results suggest that switching to zanu may yield clinical benefit in pts intolerant to other BTKi. Enrollment is ongoing.