Zanubrutinib in Acalabrutinib-Intolerant Patients With B-Cell Malignancies

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Abstract Content: Bruton tyrosine kinase inhibitors (BTKi) are effective treatments for various B-cell malignancies. However, treatment-related adverse events (AEs), potentially due to off-target kinase binding, limit their use. Zanubrutinib, a potent next-generation BTKi, is designed to selectively bind to BTK and maximize tolerability by minimizing off-target kinase binding. Results from the BGB-3111-215 phase 2 study (NCT04116437) showed that zanubrutinib is well tolerated in patients with intolerance to ibrutinib and/or acalabrutinib (*Blood* 2021;138[suppl 1]:1410). Here, we report updated results of the tolerability and efficacy of zanubrutinib in patients intolerant to acalabrutinib (cohort 2).

Eligible patients 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 acalabrutinib intolerance received zanubrutinib 160 mg twice daily or 320 mg once daily. Patients who progressed on prior BTKi therapy were excluded. Safety and efficacy were evaluated. Investigators used parameters at study entry as baseline and assessed responses every 3 cycles based on indication-specific standard response criteria.

As of June 6, 2022, 17 patients in cohort 2 received zanubrutinib (12 CLL/SLL; 3 WM; 1 MCL; 1 MZL). Median age was 74 years (range, 51-87); median treatment duration was 9.2 months (range, 0.5-20.9), median follow-up was 10.4 months (range, 1.1-20.9); median number of prior therapies was 2 (range, 1-6); 9 (53%) patients received prior ibrutinib and acalabrutinib. Five patients discontinued treatment (AEs n=2, withdrawal n=2, progressive disease n=1). A total of 28 acalabrutinib-intolerance events were reported in 17 patients, most commonly arthralgia, myalgia, headache (4 each), hemorrhage, and fatigue (2 each). Twenty-one (75%) acalabrutinib-intolerance events did not recur on zanubrutinib, corresponding to 11 (65%) patients not experiencing any intolerance recurrence. Seven (25%) events recurred (1 lower grade, 6 same grade); 2 patients discontinued owing to recurrence (myalgia and diarrhea same grade). Two patients who experienced the same intolerance events (pain in extremity and atrial fibrillation) on ibrutinib and acalabrutinib did not have a recurrence of either event on zanubrutinib. Among 14 efficacy-evaluable patients on zanubrutinib, 13 (93%) achieved at least stable disease and 9 (64%) achieved a deepening of response.

With a longer median zanubrutinib exposure (9.2 months) compared with acalabrutinib exposure (3.8 months), acalabrutinib intolerances were unlikely to recur, and disease was controlled in 13 (93%) efficacy-evaluable patients treated with zanubrutinib. Our results suggest that switching to zanubrutinib may yield clinical benefit in patients intolerant to other BTKi. Enrollment is ongoing.