Zanubrutinib in acalabrutinib-intolerant patients with B-cell malignancies

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ABSTRACT

Introduction: Adverse events (AEs) may limit use of Bruton tyrosine kinase inhibitors (BTKis) in patients with B-cell malignancies. The next-generation BTKi zanubrutinib was designed to maximize tolerability by minimizing off-target binding. Results from the ongoing phase 2 study BGB-3111-215 (NCT04116437) showed that zanubrutinib was well tolerated in patients intolerant of ibrutinib and/or acalabrutinib. Here, updated tolerability and efficacy results in the acalabrutinib-intolerant population are reported.

Methods: Eligible patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), mantle cell lymphoma (MCL), or marginal zone lymphoma (MZL) with protocol-defined acalabrutinib intolerance received zanubrutinib 160 mg twice daily or 320 mg once daily. Patients whose disease progressed with prior BTKi therapy were excluded. Safety and efficacy, including recurrence of acalabrutinib-intolerance events, were evaluated.

Results: As of May 15, 2023, 27 patients had received zanubrutinib (CLL/SLL, n=19; WM, n=4; MCL, n=2; MZL, n=2). Median age was 73 years (range, 51-87), median treatment duration was 11.4 months (range, 0.5-32.2), and median follow-up was 12.4 months (range, 1.6-32.2). Median number of prior therapies was 2 (range, 1-6), and 13 patients (48%) had received prior ibrutinib and acalabrutinib. Median cumulative acalabrutinib exposure was 5.4 months (range, 0.5-33.7). Seven patients discontinued zanubrutinib (AE, n=2; physician decision, n=2; withdrawal by patient, n=2; progressive disease, n=1); 20 remained on treatment. Forty acalabrutinib-intolerance events occurred in 27 patients, most commonly arthralgia (n=6 events), headache (n=5), myalgia (n=5), diarrhea (n=3), and rash (n=3). Twenty-eight acalabrutinib-intolerance events (70%) in 17 patients (63%) did not recur with zanubrutinib. Twelve events (30%) recurred (lower grade, n=5; same grade, n=7; higher grade, n=0). Two patients discontinued due to recurrence (myalgia and diarrhea; both same grade). Of 3 patients who experienced the same intolerance event with ibrutinib and acalabrutinib, 2 (atrial fibrillation, n=1; pain in extremity, n=1) did not experience recurrence with zanubrutinib, and 1 (diarrhea: grade 3 [ibrutinib]; grade 2 [acalabrutinib]) experienced grade 1 recurrence with zanubrutinib. Of 25 efficacy-evaluable patients receiving zanubrutinib, 24 (96%) maintained or improved responses from baseline, with 16 (64%) achieving a minor response or better.

Conclusions: With a median zanubrutinib exposure 6 months longer than the cumulative acalabrutinib exposure before discontinuation (11.4 months vs 5.4 months, respectively), 17 patients (63%) did not experience recurrence of acalabrutinib-intolerance events, and disease was controlled in 24 of 25 efficacy-evaluable patients, suggesting that acalabrutinib-intolerant patients may maintain or improve on the clinical benefit by switching to zanubrutinib. Enrollment and follow-up are ongoing.