Zanubrutinib is well tolerated and effective in acalabrutinib-intolerant patients with B-cell malignancies

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Introduction: Despite higher selectivity of the second-generation Bruton tyrosine kinase inhibitor (BTKi) acalabrutinib compared with the first-generation BTKi ibrutinib, 15%-23% of patients treated with acalabrutinib discontinued treatment due to adverse events (AEs) in clinical trials. The next-generation BTKi zanubrutinib was designed to maximize efficacy with increased potency as well as bioavailability and tolerability by minimizing off-target binding. Previous results from this ongoing phase 2 study (BGB-3111-215; NCT04116437) showed that zanubrutinib was well tolerated in patients intolerant of ibrutinib and/or acalabrutinib. Here, we report the updated results of the tolerability and efficacy of zanubrutinib in patients intolerant of acalabrutinib (cohort 2).

Methods: 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 intolerance of acalabrutinib 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 by investigators.

Results: As of May 1, 2024, 35 patients intolerant of prior acalabrutinib received zanubrutinib (CLL/SLL, n=27; WM, n=4; MCL, n=2; MZL, n=2). Median age was 71 y (range, 51-87 y); median zanubrutinib treatment duration was 14.8 mo (range, 0.1-43.8 mo), with median follow-up of 18.9 mo (range, 0.1-43.8 mo). Median number of prior therapies was 2 (range, 1-6); 14 patients (40%) also received prior ibrutinib. Median cumulative exposure to acalabrutinib was 5.7 mo (range, 0.2-68.6 mo). Eleven patients

discontinued zanubrutinib (AE, n=5; physician decision, n=3; progressive disease, n=2; withdrawal, n=1), and 24 patients remained on treatment. A total of 48 acalabrutinib-intolerance events were reported in 35 patients, most commonly arthralgia (n=7 events); myalgia (n=6); headache (n=5); rash (n=4); and diarrhea, fatigue, and hemorrhage (n=3 each). Thirty-three acalabrutinib-intolerance events (69%) did not recur with zanubrutinib, corresponding to 23 patients (66%) not experiencing any recurrence of acalabrutinib-intolerance events. Fifteen events (31%) recurred (8 at a lower grade, 7 at the same grade, 0 at a higher grade), and 3 patients discontinued due to recurrence (myalgia, rash, and diarrhea; all recurred at the same grade). Of 4 patients who experienced the same intolerance event with prior ibrutinib and acalabrutinib, 2 patients (one experiencing atrial fibrillation and the other hemorrhage) did not have a recurrence of these events with zanubrutinib, and 2 patients (one experiencing diarrhea of grade 3 with ibrutinib and grade 2 with acalabrutinib and the other experiencing pain in extremity of grade 2 with both ibrutinib and acalabrutinib) had a recurrence with zanubrutinib at a lower grade (all grade 1). In the 32 efficacy-evaluable patients, the disease control rate was 93.8%: 13 patients (40.6%) had a best response of stable disease and 17 patients (53.1%) had better response.

Conclusions: Patients with prior intolerance to acalabrutinib are able to safely and effectively switch to treatment with zanubrutinib based on our data. Despite longer median drug exposure duration on zanubrutinib than prior acalabrutinib (14.8 vs 5.7 mo, respectively), the majority of patients (66%) did not experience any recurrence of their prior acalabrutinib-intolerance events. Treatment switch to zanubrutinib maintained or improved efficacy in 93.8%of efficacy-evaluable patients treated with zanubrutinib. These results suggest that switching to zanubrutinib in patients who are intolerant of acalabrutinib is an effective treatment option in such patients. Enrollment and follow-up are ongoing.