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

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ABSTRACT

Introduction: Despite higher selectivity of second-generation BTK inhibitor (BTKi) acalabrutinib vs first-generation BTKi ibrutinib, 15%-23% of patients (pts) discontinued acalabrutinib due to AEs in clinical trials. Zanubrutinib is a potent, selective, next-generation BTKi designed to maximize tolerability by minimizing off-target binding. In the ongoing phase 2 BGB-3111-215 study (NCT04116437), zanubrutinib was well tolerated in pts intolerant of ibrutinib and/or acalabrutinib. Here, updated tolerability and efficacy in pts intolerant of acalabrutinib are reported.

Methods: Eligible pts 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. Pts with progressive disease (PD) on a prior BTKi were excluded. Safety, efficacy, and recurrence of acalabrutinib-intolerance events were evaluated.

Results: As of May 1, 2024, 35 acalabrutinib-intolerant pts 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 exposure was 14.8 mo (range, 0.1-43.8 mo); median follow-up was 18.9 mo (range, 0.1-43.8 mo). Median number of prior therapies was 2 (range, 1-6); 14 pts (40%) also received prior ibrutinib. Median cumulative acalabrutinib exposure was 5.7 mo (range, 0.2-68.6 mo). Eleven pts discontinued zanubrutinib (AE, n=5; physician decision, n=3; PD, n=2; withdrawal, n=1), and 24 remained on treatment. In 35 pts, 23 pts (66%) did not experience any recurrence of the prior acalabrutinib-intolerance events. Most acalabrutinib-intolerance events (69%) did not recur at any grade with zanubrutinib. Of the 15 events, none recurred at a higher severity (8 at a lower grade, 7 at the same grade); 3 pts discontinued due to recurrence (myalgia, rash, diarrhea; all at the same grade). Of 4 pts who had the same intolerance event with prior ibrutinib and acalabrutinib, 2 (atrial fibrillation and hemorrhage) did not have recurrence with zanubrutinib, and 2 (diarrhea: grade 3 with ibrutinib, grade 2 with acalabrutinib; pain in extremity: grade 2 with ibrutinib and acalabrutinib) had recurrence at grade 1 with zanubrutinib. In 32 efficacy-evaluable pts, disease control rate was 93.8%: 13 (40.6%) had stable disease and 17 (53.1%) had a better response.

Conclusions: Zanubrutinib was well-tolerated and provided a clinically meaningful efficacy benefit, as measured by a disease control rate of 94% in pts with prior acalabrutinib intolerance. Switching to zanubrutinib may be an excellent treatment option for acalabrutinib-intolerant pts. Enrollment and follow-up are ongoing.