

Zanubrutinib is well tolerated and effective in acalabrutinib-intolerant patients with B-cell malignancies: A long-term follow-up

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Introduction: While Bruton tyrosine kinase (BTK) inhibitors are a mainstay of treatment for B-cell malignancies, their use can be limited by adverse events (AEs). In clinical trials, 15%-23% of patients treated with acalabrutinib discontinued treatment due to AEs (Sharman JP, et al. *Blood*. 2023;142(Suppl 1):636; Ghia P, et al. *Hemasphere*. 2022;6(12):e801; Seymour JF, et al. *Blood*. 2023;142(8):687-699). Zanubrutinib is a highly potent and selective next-generation BTK inhibitor designed to maximize BTK occupancy, providing greater efficacy with fewer off-target bindings compared with other BTK inhibitors. Previous data from this phase 2 study (BGB-3111-215; NCT04116437) showed that zanubrutinib was well tolerated in patients with B-cell malignancies intolerant of ibrutinib and/or acalabrutinib (Shadman M, et al. *Lancet Haematol*. 2023;10[1]:e35-e45). Here, we report long-term results, with 3 additional years of follow-up, of the tolerability and efficacy of zanubrutinib in patients intolerant of acalabrutinib (study 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 BTK inhibitor therapy were excluded. Safety and efficacy, including recurrence of acalabrutinib intolerance events, were evaluated by investigators.

Results: As of May 1, 2025, 39 patients intolerant of prior acalabrutinib received zanubrutinib (CLL/SLL, n=30; WM, n=4; MCL, n=3; MZL, n=2). The median age was 71 (range, 51-87) years. Patients received a median of 2 prior therapies (range, 1-6), and 14 patients (36%) were also intolerant to prior ibrutinib. The median duration of prior

acalabrutinib was 5.7 (range, 0.2-68.6) months. At the time of analysis, the median duration of zanubrutinib treatment was 18.2 (range, 0.5-55.8) months, and the median study follow-up was 28.5 (range, 1.9-55.8) months. At the data cut-off, 25 patients (64%) were still on zanubrutinib. Fourteen patients had discontinued zanubrutinib due to AE (n=7; diarrhea [n=2], rash, skin toxicity, neutropenia, fall, myalgia [n=1 each]), physician decision (n=4), progressive disease (n=2), or withdrawal (n=1).

Overall, 55 acalabrutinib intolerance events were reported among the 39 patients. The most common acalabrutinib intolerance events were myalgia (n=8 events), arthralgia and headache (n=7 each), rash and fatigue (n=4 each), and diarrhea and hemorrhage (n=3 each). Of these 39 patients, 24 (62%) did not have any acalabrutinib intolerance events recur on zanubrutinib. Of the 55 acalabrutinib intolerance events, 37 (67%) did not recur with zanubrutinib. Eighteen events (33%) recurred with zanubrutinib (0 at a higher grade than that observed with acalabrutinib, 11 at the same grade, and 7 at a lower grade). Three patients discontinued zanubrutinib due to the same type of event that led to their acalabrutinib discontinuation (myalgia, rash, and diarrhea; all recurred at the same grade as with prior acalabrutinib).

Five patients experienced the same intolerance event with both prior acalabrutinib and ibrutinib treatment. Of these, 4 had either no recurrence with zanubrutinib or only grade 1 recurrence of the same event. One patient had grade 3 diarrhea with all 3 BTK inhibitors.

In 39 efficacy-evaluable patients, the disease control rate was 92.3%, with 22 patients (56.4%) having a response better than stable disease.

Conclusions: These data demonstrate that patients with prior intolerance of acalabrutinib can safely and efficaciously switch to zanubrutinib. Despite longer median treatment duration with zanubrutinib compared with prior acalabrutinib (18.2 vs 5.7 months), 67% of prior acalabrutinib intolerance events did not recur. Furthermore, switching treatment to zanubrutinib resulted in a disease control rate of 92% in efficacy-evaluable patients. In summary, in acalabrutinib-intolerant patients, switching to zanubrutinib may be a well-tolerated and effective treatment option.