Zanubrutinib switch in patients with previously treated B-cell malignancies intolerant to previous Bruton tyrosine kinase inhibitors: Final results of a phase 2, open-label, single-arm study

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Introduction: B-cell malignancies, such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), marginal zone lymphoma (MZL), and mantle cell lymphoma (MCL), are commonly treated with Bruton tyrosine kinase inhibitors (BTKis) due to their efficacy in targeting the B-cell receptor signaling pathway. However, a notable proportion of patients experience intolerance to first-generation BTKis, with adverse events (AEs) that contribute to treatment discontinuation. The next-generation BTKi, zanubrutinib (zanu), was designed to maximize efficacy with increased potency as well as bioavailability and tolerability by minimizing off-target binding. Previous results from this phase 2 study (BGB-3111-215; NCT04116437) showed that zanu was well tolerated in patients intolerant of ibrutinib (ibru) and/or acalabrutinib (acala). Here, we report results from the final analysis of this trial.

Methods: BGB-3111-215 is a phase 2, open-label, single-arm, multicenter trial designed to evaluate the safety and efficacy of zanu in adults in the United States with previously treated CLL/SLL, WM, MCL, or MZL intolerant to prior BTKi therapy. Patients intolerant to ibru and not acala were assigned to Cohort 1. Patients intolerant to acala, regardless of ibru intolerance status, were assigned to Cohort 2. Patients received oral zanu monotherapy at 160 mg BID or 320 mg QD, based on investigator and patient preference. Zanu was administered until disease progression, unacceptable toxicity, withdrawal, or until study termination by sponsor. The primary endpoint was recurrence and change in severity of prior BTKi intolerance AEs. Secondary outcomes included overall response rate (ORR), disease control rate (DCR; proportion of patients achieving best overall response of stable disease or better before initiating subsequent anticancer therapy), and progression-free survival (PFS).

Results: As of 9 Jan 2026, 96 patients were enrolled (Cohort 1: n=57; Cohort 2: n=39 [14 intolerant to both ibru and acala]). Median treatment duration for prior BTKi was 9.8 months for Cohort 1 (ibru) and 6.3 months for Cohort 2 (acala). Median zanu treatment duration was 44.4 months for Cohort 1 and 22.1 months for Cohort 2. The majority of patients ended study treatment due to sponsor-initiated study termination (Cohort 1: 52.6%; Cohort 2: 61.5%). In both cohorts, 62% of prior intolerance events (Cohort 1: 78/125; Cohort 2: 34/55) did not recur on zanu. In Cohort 1, 68.1% (32/47) prior intolerance events occurred at a lower severity on zanu; in Cohort 2, 38.1% (8/21) occurred at a lower severity. No events recurred at a higher severity. Over half of patients (Cohort 1: 52%, 36/69; Cohort 2: 54%, 21/39) did not experience recurrence.

Ibru intolerance events occurring in ≥5 patients during prior ibru treatment that reoccurred during zanu treatment (rate ≥50%) were hemorrhage (5/6), fatigue (9/14), arthralgia (5/10), and rash (5/10); low rates of recurrence were observed for atrial fibrillation/flutter (1/11), stomatitis (1/6), and muscle spasms (1/5). Acala intolerance events occurring in ≥2 patients during prior acala treatment that reoccurred during zanu treatment (rate ≥50%) were diarrhea (3/3), hemorrhage (3/3), rash (3/4), myalgia (5/8), and fatigue (2/4); a low rate of recurrence was observed for headache (1/7) and no events of atrial fibrillation/flutter or asthenia recurred in this cohort (0/2 each). Overall, seven patients discontinued zanu due to recurrence of prior intolerance events (from ibru: stomatitis, lymphoedema, hemorrhage; from acala: rash [n=2], myalgia; from both ibru and acala: diarrhea). Safety data were consistent with the known profile of zanu. Across B-cell malignancies, the ORR was 66.7% and DCR was 93.8%. With a median

follow-up of 44.2 months, median PFS was not reached, and the estimated event-free rate at 48 months was 71.6%.

Conclusion: Despite longer treatment exposure with zanu, 62% of intolerance events associated with prior ibru or acala therapy did not recur following the switch to zanu. Only 1 of 13 prior atrial fibrillation/flutter intolerance events recurred following transition to zanu. Disease control was maintained or improved in 94% of patients. These results demonstrate that switching to zanu is an effective approach to sustain disease control while minimizing recurrence of prior BTKi intolerance events.