2026 ASH Annual Meeting and Exposition Dec 12-15, 2026; New Orleans, LA

Long-term efficacy and safety of zanubrutinib in patients with relapsed/refractory mantle cell lymphoma (R/R MCL): up to 9 years of follow-up from BGB-3111-206 and AU-003

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Character count (limit 4500 including spaces): 4430

Background: Zanubrutinib (zanu), a potent and highly selective Bruton tyrosine kinase inhibitor, is approved in the United States and China for the treatment of R/R MCL and has demonstrated durable efficacy. However, long-term outcomes beyond 5 years remain poorly characterized. Here, we present updated efficacy and safety findings from two clinical studies of zanu in R/R MCL, including patients enrolled in a long-term extension study (LTE1), with follow-up extending to 9 years.

Methods: This analysis included patients with R/R MCL enrolled in two zanu monotherapy studies: the phase 1 AU-003 study (NCT02343120) and the phase 2 BGB-3111-206 study (NCT03206970). Patients completing either parent study were eligible to enroll in the LTE1 study for continued zanu therapy or survival follow-up. Patients continuing treatment in LTE1 initiated zanu immediately after their last dose in the parent study. For these patients, long-term follow-up data from LTE1 through April 1, 2026 was combined with parent study data. Efficacy was analyzed separately by parent-study cohort using investigator assessments according to prespecified response criteria; the time origin and endpoint-specific censoring rules from the respective parent study were retained. Safety data were summarized across the combined AU-003, BGB-3111-206, and LTE1 treatment periods. Efficacy endpoints included overall response rate (ORR), complete response rate (CRR), duration of response (DoR), progression-free survival (PFS), and overall survival (OS). Time-to-event endpoints were estimated using the Kaplan-Meier method. Safety was evaluated in all treated patients.

Results: Overall, 118 patients with R/R MCL received zanu across the parent studies and LTE1. Of 118 patients treated, 52 enrolled in LTE1 (12 from AU-003; 40 from BGB-3111-206). Baseline disease characteristics reflected a high-risk population, with stage IV disease in 74.4%-87.5% of patients, extranodal disease in 70.9%-78.1%, and intermediate-/high-risk MIPI (MIPI-b) scores in 71.9%-83.7% of patients.

Mean treatment exposure was 40.5 months, comprising 4774.9 patient-months of cumulative exposure. Overall, 51.7% of patients remained on treatment for >2 years and 38.1% for >4 years. Median relative dose intensity was 99.6%.

In AU-003 (n=32), ORR was 90.6% and CRR was 34.4%, with median time to response of 2.7 months. In the LTE1 study, patients from AU-003 had a median DoR of 31.6 months (95% CI, 12.6-52.0), with estimated DoR rates of 38.6% and 19.3% at 48 and 72 months, respectively. Median PFS was 21.1 months (95% CI, 13.2-50.6), with estimated PFS rates of 34.9% and 21.0% at 48 and 72 months, respectively. Median OS was 58.2 months (95% CI, 26.1-NE), with estimated OS rates of 55.1% and 41.6% at 48 and 72 months, respectively. Median follow-up in the LTE1 for patients from study AU-003 was 96.8, 99.5, and 87.7 months for DoR, PFS, and OS analyses, respectively.

In study 206 (n=86), ORR was 84.9% and CRR was 79.1%, with median time to response of 2.7 months. In the LTE1 study, patients from study 206 had a median DoR of 46.7 months (95% CI, 24.9-67.6) and estimated DoR rates of 43.5% and 34.4% at 48 and 72 months. Median PFS was 33.0 months (95% CI, 19.4-50.4), with estimated PFS rates of 44.6% and 30.4% at 48 and 72 months. Median OS was not reached, with estimated OS rates of 73.2% and 67.7% at 48 and 72 months. Median follow-up in the LTE1 for patients from study 206 was 100.7, 103.4, and 96.0 months for the DoR, PFS, and OS analyses, respectively.

Across the pooled safety population (N=118), grade ≥3 treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to treatment discontinuation, and fatal TEAEs occurred in 64.4%, 48.3%, 18.6%, and 9.3% of patients, respectively. The most common grade ≥3 TEAEs were pneumonia (16.1%) and decreased neutrophil count (16.1%).

Conclusion: With up to 9 years of follow-up, zanu continued to provide durable disease control and sustained survival outcomes in patients with R/R MCL, with no new safety signals observed. Differences in CRR between cohorts should be interpreted in the context of the response assessment criteria prespecified in each parent study, including differences in imaging requirements. These findings represent the longest follow-up reported for zanu in R/R MCL and provide evidence of durable efficacy and established safety profile of zanu in patients with R/R MCL.