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

Superior progression-free survival with zanubrutinib plus rituximab vs bendamustine-rituximab in treatment-naïve mantle cell lymphoma (TN MCL): Primary analysis of a phase 3 study (MANGROVE)

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Character count (limit 4500 characters, including spaces): 4498

Background: MCL affects primarily older adults, who face an inferior prognosis and significant risks from standard chemoimmunotherapy. Recent trials in TN MCL combining Bruton tyrosine kinase inhibitors (BTKi) with bendamustine plus rituximab (BR) show improved progression-free survival (PFS), but a clear increase in toxicity. There remains an unmet need for highly efficacious, less toxic chemotherapy-free strategies. Although chemo-free combinations with BTKi have been reported, no head-to-head comparisons with BR exist and the highly selective, next-generation covalent BTKi zanubrutinib (zanu) is a leading candidate for this approach. We report results of the prespecified primary analysis of MANGROVE (BGB-3111-306; NCT04002297), an international, multicenter, randomized phase 3 study of zanu plus rituximab (ZR) vs BR in patients with TN MCL.

Methods: Previously untreated patients with MCL aged ≥70 years, or aged ≥60 to <70 years unsuitable for autologous stem cell transplant, with ECOG performance status 0-2 and measurable disease, were randomized 1:1 to ZR for 6 cycles followed by zanu monotherapy until disease progression, or BR for 6 cycles followed by observation. Rituximab was given in 6 monthly doses in both arms without maintenance. Disease assessments were performed by CT with contrast and PET per Lugano Classification.

The primary endpoint was PFS by independent review committee (IRC). Secondary endpoints included overall survival (OS), PFS by investigator (INV), overall response rate (ORR), complete response (CR) rate, duration of response (DoR), and safety.

Results: Overall, 510 patients were enrolled (ZR: 257; BR: 253). Median age was 74 years (range, 60-91; 83.1% aged ≥70 years); 50.6% of patients had high-risk MIPI, 10.8% had pleomorphic/blastoid histology, 56.5% (256/453) had Ki-67 ≥30%, and 24.0% (58/242) had *TP53* mutations. Baseline characteristics were generally balanced between arms.

At a median study follow-up of 44.1 months, the primary endpoint of PFS by IRC demonstrated superiority of ZR over BR (HR: 0.57 [95% CI: 0.43-0.76]; 1-sided *P*<.0001). Median PFS was not reached with ZR (95% CI: 56.5-not estimable [NE]) vs 39.2 months (95% CI: 33.5-55.7) with BR. Additionally, 4-year PFS rates were higher with ZR vs BR (62.4% vs 46.2%). PFS benefit with ZR was consistent across all prespecified subgroups, including geographic region and high-risk subgroups (eg, high risk MIPI, pleomorphic/blastoid histology, Ki-67 ≥30%, and *TP53* mutated). PFS by INV was also consistent (HR: 0.54 [95% CI: 0.41-0.71]; 1-sided *P*<.0001).

OS, though immature at this analysis, was numerically superior with ZR over BR (HR: 0.71 [95% CI: 0.51-0.99]; 1-sided *P*=.0222) with 4-year OS rates of 75.1% vs 67.6%, respectively. The observed OS trend favoring ZR over BR was notable, considering that 88.2% of patients in the BR arm who required subsequent anticancer therapy (90/102) received a BTKi. ORR rates were similar (ZR: 89.9%; BR: 88.1%), while CR rates (59.5% vs 52.6%) and DoR favored ZR. Median DoR was not reached with ZR (95% CI: NE-NE) vs 42.9 months with BR (95% CI: 32.0-NE); 4-year DoR rates were 67.1% vs 46.0%, respectively.

During the safety reporting period (ie, from start of treatment until progression or start of new anticancer therapy), grade ≥3 AEs occurred in 75.0% and 73.6%, serious AEs in 56.6% and 46.0%, and AEs leading to death in 9.0% and 8.8% in the ZR and BR arms, respectively. During the 6-month induction period, rates of grade ≥3 AEs (39.8% vs 58.4%) and serious AEs (19.1% vs 23.6%) were lower in the ZR vs BR arm. In the treatment-emergent period, exposure-adjusted incidence rates (per 100 person-months) of most events of interest were lower in the ZR arm vs BR arm, such as infections (4.69 vs 7.80), neutropenia (0.78 vs 9.14), anemia (0.56 vs 4.32), thrombocytopenia (0.38 vs 3.52), AFib/flutter (0.13 vs 0.28), and hypertension (0.61 vs 1.30). The safety profile was consistent with the known profile of zanubrutinib, and no new safety signals were identified.

Conclusions: MANGROVE is the first randomized global phase 3 trial to demonstrate superiority of a chemo-free regimen with zanu plus rituximab over BR in TN MCL. With a median follow-up of 44.1 months, ZR demonstrated a statistically significant and clinically meaningful improvement in PFS vs BR, with a safety profile consistent with previous studies. These findings support ZR as a potential new standard, replacing chemotherapy for patients with TN MCL.

Review category: 623. Mantle Cell, Follicular, Waldenstrom's, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological

Keywords: **Diseases**-Lymphomas-NHL, B-cell lymphoma, indolent lymphoma; **Treatment considerations**-Combination therapy; **Research**- Clinical Research - Clinical Trials