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Unanchored matching-adjusted indirect comparisons of control and treatment arms from MANGROVE and ECHO trials in first-line mantle cell lymphoma

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Background: MANGROVE (NCT04002297) is a randomized phase 3 study evaluating zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, plus rituximab (ZR) followed by continuous zanubrutinib as first-line therapy for patients with mantle cell lymphoma (MCL). Acalabrutinib + bendamustine + rituximab (ABR) is approved in several countries for the treatment of treatment-naïve (TN) MCL based on results from the ECHO study (NCT02972840). Given the differences in the control regimen between trials, particularly the inclusion of rituximab maintenance in the ECHO bendamustine + rituximab (BR) arm but not the MANGROVE-BR arm, we indirectly compared both control arms. Additionally, in the absence of a randomized prospective trial comparing ZR and ABR, an indirect comparison was performed. Based on these objectives, we conducted an unanchored matching-adjusted indirect comparison (MAIC) using individual patient data from MANGROVE and published aggregate data from ECHO.
Methods: Two independent, unanchored MAICs were performed by reweighting MANGROVE individual patient data to match the reported baseline effect modifiers and prognostic factors of the corresponding ECHO arms. The model matched all reported baseline covariates considered clinically relevant, including sex, geographic region, Ann

Arbor stage, bulky disease, blastoid/pleomorphic histology, simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI), extranodal disease, TP53 status, Ki-67, and time since diagnosis. Outcomes included independent review committee (IRC)–assessed progression-free survival (PFS) and overall survival (OS). Time-to-event endpoints were analyzed using weighted Cox proportional hazards models, and response was analyzed using weighted logistic models. Additional sensitivity models evaluated robustness to alternative matching variable specifications.

Results: Compared with ECHO, MANGROVE enrolled an older, higher-risk population, with more patients aged ≥70 years and high-risk sMIPI scores, whereas ECHO included slightly more patients with extranodal disease. In the control-arm comparison, the effective sample size after matching was 137 (56%), indicating retention of more than half of the original analytic information after adjustment for between-trial differences. MANGROVE-BR and ECHO-BR showed comparable IRC-assessed PFS (hazard ratio [HR], 0.90; 95% CI, 0.66-1.22), while OS statistically supported MANGROVE-BR (HR, 0.70; 95% CI, 0.49-0.99). These findings suggest that the MANGROVE-BR control arm was comparable to ECHO-BR despite the difference in rituximab maintenance use. In the treatment-arm comparison, the effective sample size after matching was 118 (48%). After adjustment for observed differences in baseline covariates, ZR was associated with improved IRC-assessed PFS compared with ABR (HR, 0.70; 95% CI, 0.50-0.99) and a numerically lower risk of death (HR, 0.69; 95% CI, 0.45-1.05). The direction and magnitude of the treatment effects were generally consistent across the sensitivity models, supporting the robustness of the base-case findings.

Conclusions: In this unanchored MAIC, outcomes with MANGROVE-BR were at least comparable to those with ECHO-BR, despite the absence of rituximab maintenance. These results support the interpretability of the treatment-arm comparison in MANGROVE. However, these results should not be broadly interpreted as evidence that R maintenance is not beneficial in certain patient populations or within certain combinations. After adjustment for observed differences in prognostic factors between trial populations, the chemotherapy-free ZR regimen demonstrated favorable IRC-assessed PFS and OS vs the chemoimmunotherapy triplet ABR in patients with TN MCL. Although unanchored indirect comparisons are inherently limited by potential

residual confounding factors, these exploratory findings support the clinical benefit of ZR within the current treatment landscape.