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Title: A real-world comparison of treatment and survival outcomes with zanubrutinib (zanu) and acalabrutinib (acala) monotherapy among patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) in the United States

Background: MCL is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma that remains incurable. Bruton tyrosine kinase (BTK) inhibitors are an established standard of care for R/R MCL. However, comparative effectiveness data for different BTK inhibitors for R/R MCL are limited. This study evaluated the real-world effectiveness of zanu and acala in US patients with R/R MCL based on overall survival (OS) and time to next treatment (TTNT).

Methods: A retrospective cohort study was conducted using Komodo health administrative claims data. Eligible patients were adults (aged ≥18 years) with ≥2 MCL diagnoses and continuous enrollment or activities within 1 year prior to and 3 months following the index date. Patients were required to initiate monotherapy with zanu (index period: November 2019 to August 2025) or acala (index period: October 2017 to August 2025) as a second-line or later (2L+) treatment, with index date defined as the first observed claim for zanu or acala. Patients with evidence of clinical trial participation, end stage renal disease or prior stem cell transplant were excluded. Outcomes included OS (time from index date to all-cause mortality) and TTNT (time from index date to subsequent therapy with an allowable gap of 120 days). If an outcome was not observed, patients were censored at the date of last activity or enrollment end date. Survival analyses were conducted using Kaplan-Meier estimates and Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) was adjusted for age, sex, US region, treatment initiation year and Charlson Comorbidity Index (CCI).

Results: In total, 2219 patients (zanu, n=931; acala, n=1288) were eligible and included in the study. The mean age was higher in the zanu (72.3 years; SD, 9.4) vs acala cohort (71.4 years; SD, 9.7). Most patients were male (zanu, 71%; acala, 75%), non-Hispanic white (zanu, 73%; acala, 74%), and the mean CCI was 3.5 (SD, 3.2) and 3.6 (SD, 3.1) in the zanu and acala cohorts, respectively. Median follow-up was 14.8 and 18.2 months in zanu and acala cohorts, respectively. Median TTNT was 26.7 months for zanu and 20.8 months for acala. Median OS was not reached for zanu and was 60.6 months for acala. In the unadjusted model, zanu had a longer TTNT (HR, 0.86; 95% CI, 0.76-0.97; *P*=.012) and OS (HR, 0.74; 95% CI, 0.62-0.88; *P*<.001). After IPTW adjustment, TTNT and OS favored zanu treatment (TTNT: IPTW-adjusted HR, 0.86; 95% CI, 0.76-0.98; *P*=.025; OS: IPTW-adjusted HR, 0.81; 95% CI, 0.68-0.98; *P*=.03).

Conclusions: In this real-world analysis of US health claims data, zanu monotherapy demonstrated significantly longer TTNT and improved OS compared with acala in patients receiving 2L+ therapy for MCL. These findings support zanu as an effective BTK inhibitor for R/R MCL.

Conflict of Interests:

YW: Research funding (to institution): Incyte, InnoCare Pharma, Lilly, MorphoSys, Novartis, Genentech, Genmab, AbbVie, BeOne Medicines, Ltd, Merck, AstraZeneca, Bristol Myers Squibb; Advisory board (compensation to institution): Lilly, TG Therapeutics, Incyte, InnoCare Pharma, Kite Pharma, Janssen, BeOne Medicines, Ltd, AstraZeneca, Genmab, AbbVie; Consultancy (compensation to institution): InnoCare Pharma, AbbVie; Honorarium (to institution): Kite Pharma. **GAM**: Employment: BeOne Medicines, Ltd; Stock or other ownership: BeOne Medicines, Ltd, Gilead, Amgen, CRISPR Therapeutics; Consulting or advisory role: CRISPR Therapeutics, BeOne Medicines, Ltd; Travel, accommodations, expenses: BeOne Medicines, Ltd, CRISPR Therapeutics. **EKS**: Employment: BeOne Medicines, Ltd; Stock or other ownership: BeOne Medicines, Ltd, Roche. **DN**, **RK**, **NJ**: Employee of ZS Associates and serve as paid consultants for BeOne Medicines, Ltd. **JM:** Consulting: Pharmacyclics/AbbVie, Bayer, Gilead/Kite, BeOne Medicines, Ltd, Pfizer, Janssen, Celgene/BMS, Kyowa, Alexion, Fosunkite, Seattle Genetics, Karyopharm, Aurobindo, Verastem, Genmab, Genzyme, Genentech/Roche, ADC Therapeutics, Epizyme, Novartis, Morphosys/Incyte, MEI, TG Therapeutics, AstraZeneca, Lilly; Research funding: Bayer, Gilead/Kite, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium, Novartis, BeOne Medicines, Ltd, E.R. Squibb & Sons; Honoraria: Targeted Oncology, OncView, Curio, Aptitude Health, Physicians' Education Resource. **MS, MH, RW**: Employment and may own stock: BeOne Medicines, Ltd.