Real-world comparative effectiveness of covalent Bruton tyrosine kinase inhibitors (cBTKi) among patients with relapsed/refractory mantle cell lymphoma (R/R MCL)

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ABSTRACT

Objectives: Treatment for R/R MCL has evolved with the use of cBTKi monotherapy, yet little is known about their relative effectiveness or utilization across patient (pt) groups based on race or biomarker status in the real-world (RW) setting. This study aimed to describe characteristics and utilization patterns and compare the RW effectiveness of zanubrutinib (zanu) with acalabrutinib (acala) and ibrutinib (ibru) monotherapy.

Methods: This retrospective cohort study included adult pts diagnosed with R/R MCL who initiated first treatment with a cBTKi in the second line (2L) or third line (3L) on 01/01/2018, or later, and were followed until death or loss to follow-up using the US nationwide Flatiron Health electronic health-record derived deidentified database. Patient characteristics and survival estimates based on Kaplan-Meier (KM) analyses were summarized with descriptive statistics; inverse probability of treatment weighting (IPTW) and multivariable adjustment were used in adjusted Cox models to compare RW time-to-next treatment (rwTTNT) and overall survival (rwOS).

Results: Of the 1377 R/R MCL pts who received 2L+ lines of therapy, 602 had received cBTKi monotherapy in 2L or 3L for MCL and were included in this study. Median age was 74 (range, 34-85 yrs), majority of pts were male (74%), White (White 76%, Black 3.5%, Asian 1.5%, Other race 8%, Unknown 11%), and non-Hispanic/Latino (non-Hispanic/Latino 75%, Hispanic/Latino 5.6%, Unknown 19%). Patients varied by socioeconomic status (SES; from low to high SES index 1 [12%], 2 [16%], 3 [20%], 4 [24%], 5 [19%], Unknown [10%]). Patients also varied by baseline ECOG performance status, Ki67, and LDH. Most pts had stage III/IV at diagnosis (74%). Only 26 (4.3%) pts had a positive documented *TP53* status at 2L/3L index. Among pts who received their first cBTKi at 2L or 3L index therapy, 107 received zanu (2L [79%], 3L [21%]), 301 received acala (2L [80%], 3L [20%]), and 194 received ibru (2L [84%], 3L [16%]). Follow-up times (median [IQR]) from start of 2L for each cBTKi were zanu 17 mo (9, 31), acala 35 mo (20, 51), and ibru 53 mo (35, 62). Among the overall 2L/3L cBTKi monotherapy cohort, median rwTTNT was 11.1 mo (95% CI: 9.2, 12.9) and median rwOS was 29.2 mo (95% CI: 24.3, 36.5). The median rwTTNT for zanu was 16.8 mo (95% CI: 11.8, 23.7), acala 11.5 mo (95% CI: 8.6, 14.6), and ibru 8.6 mo (95% CI: 7.2, 11.3); *P*=0.06. The median rwOS was not reached (NR) for zanu (95% CI: 23.7, NR), acala 27.4 mo (95% CI: 22.7, 36.5), and ibru 29.3 mo (95% CI: 21.1, 40.5); *P*=0.12. The rwTTNT and rwOS trends persisted when comparing each cBTKi at 3, 6, 9, and 12 mo (**Table**). Adjusted, multivariable models showed significantly longer rwTTNT (HR: 0.68 [95% CI: 0.49, 0.94]; *P*=0.02) and rwOS (HR: 0.64 [95% CI: 0.41, 0.99]; *P*=0.04) for zanu when compared to ibru, and longer but non-significant trends in rwTTNT (HR: 0.82 [95% CI: 0.59, 1.12]; *P*=0.20) and rwOS (HR: 0.69 [95% CI: 0.46, 1.06]; *P*=0.09) for zanu compared to acala.

Conclusions: Among RW pts with R/R MCL who received cBTKi monotherapy, zanu had a significantly longer rwTTNT and rwOS compared to ibru, and a trend favoring zanu was observed in rwTTNT and

rwOS when compared to acala. Limited sample size and follow-up with zanu restricted the ability to discern smaller differences in effectiveness as compared to the other cBTKi. Other limitations include the retrospective nature of the study and limited sample size in subgroups. Given low utilization of cBTKi monotherapy among Black, Indigenous, and people of color (BIPOC) pts and potentially low testing of *TP53*, further investigation into RW R/R MCL treatment patterns and outcomes by race/ethnicity and biomarker status is warranted.