Evaluating reasons for differences in real-world (RW) clinical outcomes among patients with relapsed/refractory mantle cell lymphoma (R/R MCL) on covalent BTK inhibitors (cBTKis)

Tycel Phillips,[1] Mengyang Di,[2] Taavy A. Miller,[3] Jingru Wang,[3] Amy Pierre,[3] Gregory A. Maglinte,[4] Erlene K. Seymour,[4] Yucai Wang[5]

[1]City of Hope, Duarte, CA; [2]Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Flatiron Health, New York, NY; [4]BeiGene, San Mateo, CA; [5]Mayo Clinic, Rochester, MN

Introduction: Treatment for R/R MCL has evolved with the use of cBTKi monotherapy. Previously, we reported differences in RW time to next treatment (rwTTNT) and overall survival (rwOS) among patients (pts) treated with ibrutinib (ibr), acalabrutinib (acala), and zanubrutinib (zanu), but reasons for the differences were unknown (Phillips et al. EHA 2024). Our objectives were to re-evaluate trends in rwTTNT and rwOS; assess treatment patterns of cBTKis, including switching; describe reasons for cBTKi discontinuation; and compare RW effectiveness of ibr, acala, and zanu monotherapy.

Methods: This retrospective cohort study included adult pts diagnosed with R/R MCL who initiated second-line (2L) or third-line (3L) first cBTKi treatment 01/2018-11/2023 and were followed until loss to follow-up or death using the US nationwide Flatiron Health EHR deidentified database. Patient characteristics and survival estimates based on Kaplan-Meier (KM) analyses were summarized. Adjusted analysis using a multivariate Cox model was applied to assess rwTTNT and rwOS. Key model variables were age, sex, POD24 (2L start ≤24 mo from first-line start), and number of prior lines of therapy. Reasons for discontinuation were abstracted from documentation in notes and included non-mutually exclusive categories.

Results: This study included 698 pts who received cBTKi monotherapy in 2L or 3L for MCL. The median age at cBTKi start was 73 (range, 34-85 yrs); the majority of pts were male (74%) and White (White 78%, Black 3.2%, Asian 1.3%, Other Race 7.6%, Unknown 10%) and non-Hispanic/Latino (non-Hispanic/Latino 74%, Hispanic/Latino 6.0%, Unknown 20%). Patients varied by socioeconomic status (Yost index 1 [12%], 2 [16%], 3 [19%], 4 [24%], 5 [19%], Unknown [10%]). Patients also varied by baseline ECOG performance status, Ki67, comorbidities, and LDH. Most pts had stage III/IV at diagnosis (75%).

Among pts who received a cBTKi at 2L or 3L index therapy, 135 received zanu (2L [79%], 3L [21%]), 342 received acala (2L [76%], 3L [24%]), and 221 received ibr (2L [75%], 3L [25%]). Follow-up time (median [IQR]) from start of 2L/3L for each cBTKi were zanu 15 mo (10, 25), acala 36 mo (20, 52), and ibr 57 mo (35, 67).

Among the overall 2L/3L cBTKi monotherapy cohort, median rwTTNT was 11.5 mo (95% CI 10.0, 13.5) and median rwOS was 30.4 mo (24.7, 36.1). For each cBTKi therapy in unadjusted KM analyses, median rwTTNT for zanu was 16.8 mo (95% CI 11.1, 23.2), acala 11.9 mo (9.2, 14.6), and ibr 9.8 mo (7.6, 13.1); median rwOS was 28.8 for zanu (95% CI 23.7, not reached), acala 29.2 mo (22.9, 36.5), and ibr 29.3 mo (21.2, 39.1). Adjusted multivariate model showed a trend of longer rwTTNT with zanu compared to ibr (HR 0.76 [95% CI 0.57, 1.01]; *P*=.06) and acala (0.88 [0.67, 1.16]; *P*=.40), and significantly longer rwOS for zanu compared to ibr (0.67 [0.46, 0.98]; *P*=.04) but a nonsignificant trend in rwOS favoring zanu compared to acala (0.73 [0.51, 1.05]; *P*=.09).

Forty-seven pts (6.7%) who received cBTKi monotherapy in 2L or 3L switched to another cBTKi; 31 (4.4%) switched from ibr to acala or zanu, 12 (1.7%) from acala to zanu, and <5 (0.1%) from zanu to acala.

Reasons for discontinuation (~60% documented in cohort) varied by cBTKi monotherapy use. The most common documented reasons for discontinuation were disease progression (30% overall; zanu [24%], acala [35%], ibr [26%]) and toxicity (11% overall; zanu [7%], acala [10%], ibr [17%]). Among pts who switched from one cBTKi to another, the most documented reason for discontinuation was toxicity for ibr to acala or zanu (61%) and for acala to zanu (58%). Other reasons included financial (1%), non–cancer-related medical issue (4%), cancer-related symptoms not due to therapy (2%), and pt request (1%).

Conclusions: Among RW pts with R/R MCL who received cBTKi monotherapy, zanu had a longer rwOS compared to ibr, and a trend of longer rwTTNT and rwOS compared to acala. Reasons for discontinuation were most commonly disease progression and toxicity. Among pts who switched cBTKis, the most common reason for switching was toxicity, which provides a broader scope of reasons for differences in rwTTNT that are not exclusive to disease progression.