Real-World Comparative Effectiveness of Covalent Bruton Tyrosine Kinase Inhibitors Among Patients With Relapsed/Refractory Mantle Cell Lymphoma

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INTRODUCTION

- The recent availability of covalent Bruton tyrosine kinase inhibitors (cBTKis) has contributed to the rapidly evolving treatment landscape for relapsed/refractory (R/R) mantle cell lymphoma (MCL)
- Newer cBTKis (second-generation acalabrutinib and next-generation zanubrutinib) were developed to address concerns with off-target inhibition and side effects, with zanubrutinib being more selective against several off-target kinases than acalabrutinib and ibrutinib
- There is no direct evidence from randomized controlled trials to discern between the efficacy of available cBTKi therapies for R/R MCL, and little is known about their utilization and comparative effectiveness in the real-world (RW) setting

OBJECTIVE

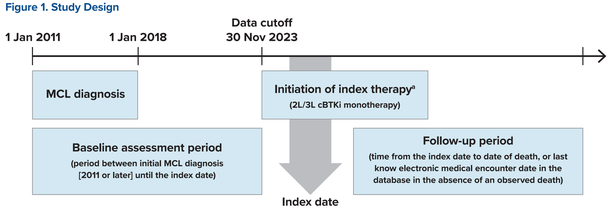
- To describe the RW characteristics and utilization patterns, and evaluate the comparative effectiveness of zanubrutinib, acalabrutinib, and ibrutinib monotherapy in second- or third-line (2L/3L) treatment among patients with R/R MCL in the United States (US)

METHODS

Data Source and Study Design

- This retrospective observational cohort study used the nationwide, longitudinal, electronic health record-derived, Flatiron Health database, comprising de-identified patient-level data originated from ~280 US cancer clinics and curated via technology-enabled abstraction[1,2]
- The study design is shown in **Figure 1**

Figure 1. Study Design



Study Population

- Eligible adults were included from the real-world database
- Inclusion criteria were:
  - International Classification of Disease code for non-Hodgkin lymphoma (NHL), as identified by structured data
  - ≥2 documented clinical visits on different days occurring on or after January 1, 2011
  - Diagnosis of MCL on or after January 1, 2011, as confirmed by a review of unstructured data
  - Received treatment with ≥2 lines of treatment, where 2L treatment for MCL was received on or after January 1, 2018
  - Treated with zanubrutinib, acalabrutinib, or ibrutinib monotherapy in the 2L/3L setting
- Patients were excluded if they were treated with a BTKi prior to their first cBTKi monotherapy in the 2L/3L setting

Study Outcomes

- Patient baseline demographic and clinical characteristics were described
- RW treatment patterns were evaluated, as well as clinical outcomes:
  - RW time to next treatment (rwTTNT), defined as time from index date to the start of the next treatment or death, whichever occurred first
  - RW overall survival (rwOS), defined as time from index date to date of death

Statistical Methods

- For continuous variables, descriptive statistics included medians, interquartile range (IQR), and minimum and maximum values; for categorical variables, frequencies and percentages were reported
- Survival curves were generated using Kaplan-Meier analyses and log-rank test was used to compare the survival distributions across treatment groups
- In unadjusted analyses, rwTTNT and rwOS were compared between 2L/3L cBTKi treatment groups without any covariate adjustment. Median survival estimates, survival probabilities at 1, 3, 6, 9, and 12 months after the index date, and 95% confidence intervals (CIs) were reported
- In adjusted analyses, propensity scores were estimated using multivariable logistic regression models, and inverse probability of treatment weighting was conducted to estimate the average treatment effect
- Cox proportional hazards regression models were used to generate unadjusted or adjusted hazard ratios (HR) for the treatment comparisons with associated 95% CIs and *P* values

RESULTS

Patient Baseline Characteristics

- Of the 1,377 patients with R/R MCL who received any therapy in the 2L+ setting, 602 patients received 2L/3L cBTKi monotherapy for MCL and were included in this study
- Median age at the start of 2L therapy was 74 years (range 34-85), and the majority of patients were male (74%), identified as White (76%), did not identify as Hispanic or Latino (75%), had Stage IV disease (63%) and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0-1 (60%) (**Table 1**)
- Most patients (96%) had undocumented and/or negative tests for *TP53* status

Table 1. Baseline Demographic and Clinical Characteristics of Patients with R/R MCL Who Received 2/3L cBTKi Monotherapy

Characteristic	Overall (N=602)	Zanubrutinib (n=107)	Acalabrutinib (n=301)	Ibrutinib (n=194)
Age at 2L start (range), years	74 (34, 85)	74 (46, 85)	74 (34, 85)	72 (38, 85)
Male, n (%)	448 (74%)	79 (74%)	229 (76%)	140 (72%)
Race, n (%)				
White	458 (76%)	82 (77%)	231 (77%)	145 (75%)
Black or African American	21 (3.5%)	≤5	11 (3.7%)	9 (4.6%)
Asian	9 (1.5%)	≤5	7 (2.3%)	≤5
Other race	48 (8.0%)	5 (4.7%)	24 (8.0%)	19 (9.8%)
Unknown/not documented	66 (11%)	17 (16%)	28 (9.3%)	21 (11%)
Ethnicity, n (%)				
Hispanic or Latino	34 (5.6%)	7 (6.5%)	15 (5.0%)	12 (6.2%)
Non-Hispanic or Latino	451 (75%)	80 (75%)	227 (75%)	144 (74%)
Unknown/not documented	117 (19%)	20 (19%)	59 (20%)	38 (20%)
SES index, n (%)				
1 – lowest SES	70 (12%)	9 (8.4%)	29 (9.6%)	32 (16%)
2	97 (16%)	21 (20%)	48 (16%)	28 (14%)
3	118 (20%)	16 (15%)	62 (21%)	40 (21%)
4	143 (24%)	31 (29%)	67 (22%)	45 (23%)
5 – highest SES	112 (19%)	23 (21%)	59 (20%)	30 (15%)
Unknown/not documented	62 (10%)	7 (6.5%)	36 (12%)	19 (9.8%)
Disease subtype, n (%)				
Blastoid MCL	41 (6.8%)	≤5	23 (7.6%)	13 (6.7%)
Pleomorphic MCL	20 (3.3%)	≤5	11 (3.7%)	7 (3.6%)
Leukemic MCL	30 (5.0%)	≤5	17 (5.6%)	8 (4.1%)
MCL, NOS	511 (85%)	95 (89%)	250 (83%)	166 (86%)
Stage at initial diagnosis, n (%)				
I	11 (1.8%)	≤5	6 (2.0%)	≤5
II	18 (3.0%)	≤5	6 (2.0%)	10 (5.2%)
III	68 (11%)	9 (8.4%)	38 (13%)	21 (11%)
IV	381 (63%)	71 (66%)	186 (62%)	124 (64%)
Unknown/not documented	124 (21%)	24 (22%)	65 (22%)	35 (18%)
Bulky disease at initial diagnosis, n (%)				
Yes	105 (17%)	15 (14%)	46 (15%)	44 (23%)
No/unknown	497 (83%)	92 (86%)	255 (85%)	150 (77%)
ECOG PS at index start, n (%)[a]				
0-1	364 (60%)	68 (64%)	185 (61%)	111 (57%)
2-4	60 (10.0%)	9 (8.4%)	33 (11%)	18 (9.3%)
Unknown	178 (30%)	30 (28%)	83 (28%)	65 (34%)
TP53 status at index start, n (%)[b]				
Positive	27 (4.5%)	6 (5.6%)	17 (5.6%)	≤5
Negative or unknown/not documented	575 (96%)	101 (94%)	284 (94%)	190 (98%)
Ki67 status at index start, n (%)[b]				
<10%	27 (4.5%)	7 (6.5%)	11 (3.7%)	9 (4.6%)
11%-30%	122 (20%)	22 (21%)	61 (20%)	39 (20%)
31%-50%	116 (19%)	16 (15%)	59 (20%)	41 (21%)
>50%	159 (26%)	32 (30%)	74 (25%)	53 (27%)
Unknown/not documented	178 (30%)	30 (28%)	96 (32%)	52 (27%)
LDH at index start, n (%)[b]				
<0.67 ULN	111 (18%)	22 (21%)	49 (16%)	40 (21%)
≥1.50 ULN	46 (7.6%)	6 (5.6%)	23 (7.6%)	17 (8.8%)
0.67-0.99 ULN	190 (32%)	33 (31%)	95 (32%)	62 (32%)
1.00-1.49 ULN	79 (13%)	13 (12%)	38 (13%)	28 (14%)
Unknown/not documented	176 (29%)	33 (31%)	96 (32%)	47 (24%)
Number of LOT prior to index, n (%)[c]				
1	487 (81%)	85 (79%)	240 (80%)	162 (84%)
2	115 (19%)	22 (21%)	61 (20%)	32 (16%)
Time from start of 1L to index of first BTKi, median (IQR), months	22 (7, 46)	25 (10, 57)	19 (7, 45)	22 (6, 43)
Patient disposition at data cutoff, n (%)				
Confirmed death	273 (45%)	26 (24%)	145 (48%)	102 (53%)
Still on therapy at data cutoff	135 (22%)	41 (38%)	54 (18%)	40 (21%)

[a]Extracted from unstructured documents using natural language processing when ECOG information from structured data were unavailable in the baseline ECOG table. ECOG values represent the score closest to the index date. ECOG values of 5 were transformed to "unknown" for de-identification purposes. Additional information is provided in Flatiron's Knowledge Center.
[b]As documented with dates occurring at any point from initial diagnosis to 30 days after index date (either 2L or 3L start).
[c]Index referred to start of 2L for the total R/R MCL (2L+) cohort, the start of 3L for the 3L subcohort who initiated 3L, and the earliest BTKi monotherapy start date (either 2L or 3L) for the BTKi monotherapy 2L/3L subcohort.
1L, first-line; LDH, lactose dehydrogenase; LOT, line of treatment; MCL, mantle cell lymphoma; NOS, not otherwise specified; ES, socioeconomic status; ULN; upper limit of normal.

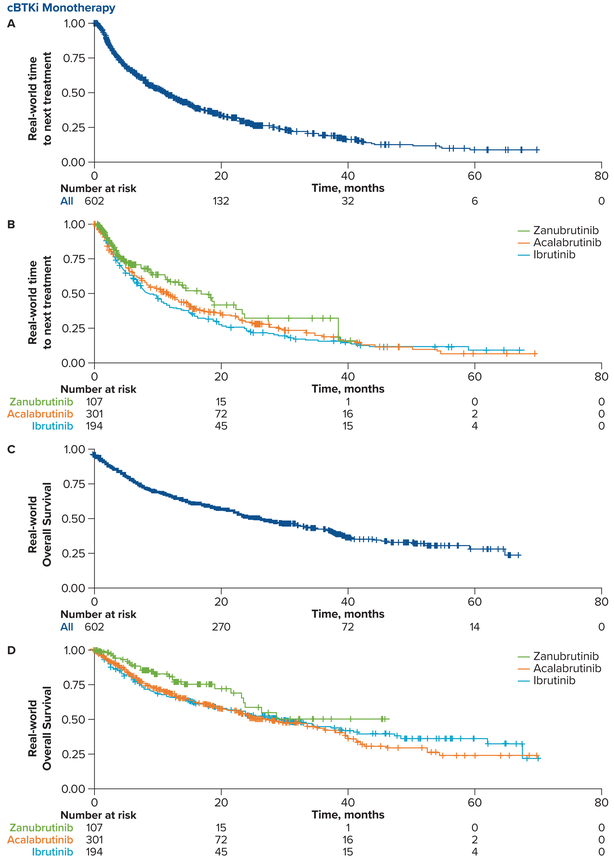
Treatment Patterns (Table 1)

- Among patients who received 2L/3L cBTKi monotherapy, 107 (17.8%), 301 (50.0%) and 194 (32.2%) patients received 2L/3L zanubrutinib, acalabrutinib, and ibrutinib, respectively
- Median (IQR) follow-up from the start of index 2L/3L cBTKi monotherapy was 14 (8-26), 32 (18-48), 51 (31-61) months for zanubrutinib, acalabrutinib, and ibrutinib, respectively

rwTTNT and rwOS

- Among the overall population, unadjusted median rwTTNT and rwOS were 11.1 (95% CI 9.2-12.9) and 29.2 (95% CI 24.3-36.5) months, respectively (**Figure 2**)
- Unadjusted median rwTTNT were 16.8 (95% CI 11.8-23.7) months for 2L/3L zanubrutinib, 11.5 (95% CI 8.6-14.6) months for 2L/3L acalabrutinib, and 8.6 (95% CI 7.2-11.3) months for 2L/3L ibrutinib
- Median rwOS was not reached for 2L/3L zanubrutinib (95% CI 23.7-NR), and the unadjusted median rwOS was 27.4 (95% CI 22.7-36.5) months for 2L/3L acalabrutinib and 29.3 (95% CI 21.1-40.5) months for 2L/3L ibrutinib (**Figure 2**)

Figure 2. Kaplan-Meier Curves Reflecting rwTTNT for (A) cBTKi Overall, (B) by cBTKi Therapy, and rwOS for (C) cBTKi Overall, (D) by cBTKi Therapy, Among Patients with R/R MCL Who Received 2L/3L cBTKi Monotherapy



CONCLUSIONS

- Among patients with R/R MCL treated with cBTKi monotherapies in the US, patients who received 2L/3L zanubrutinib had significantly longer rwTTNT and rwOS compared with 2L/3L ibrutinib, and there was a trend favoring improved clinical outcomes for 2L/3L zanubrutinib compared with 2L/3L acalabrutinib
- Future research into identifying factors influencing utilization of cBTKis, and reasons for differences in rwTTNT and rwOS across cBTKis are warranted

- Adjusted models showed significantly longer rwTTNT and rwOS for 2L/3L zanubrutinib vs 2L/3L ibrutinib and trends for improved outcomes for 2L/3L zanubrutinib over 2L/3L acalabrutinib (**Table 2**)
  - In the fully adjusted model, rwTTNT (HR 0.64, 95% CI 0.44-0.93, *P*=.02) and rwOS (HR 0.56, 95% CI 0.35-0.91, *P*=.02) was significantly improved with 2L/3L zanubrutinib vs 2L/3L ibrutinib
  - Fully adjusted HRs for rwTTNT and rwOS for 2L/3L zanubrutinib vs 2L/3L acalabrutinib were 0.84 (95% CI 0.61-1.17; *P*=.30) and 0.74 (95% CI 0.48-1.13; *P*=.20), respectively

Table 2. Unadjusted, Multivariate, and Propensity-Score Adjusted Hazard Ratios for rwTTNT and rwOS Comparing 2L/3L cBTKi Monotherapy Among Patients with R/R MCL

	Zanubrutinib vs Acalabrutinib		Zanubrutinib vs Ibrutinib	
Outcome[a]	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
rwTTNT				
Unadjusted	0.77 (0.56-1.06)	.11	0.66 (0.48-0.92)	.01
Multivariate (Cox model)	0.82 (0.59-1.12)	.20	0.68 (0.49-0.94)	.02
IPTW minimally adjusted[b]	0.81 (0.59-1.11)	.20	0.67 (0.48-0.94)	.02
IPTW fully adjusted[c]	0.84 (0.61-1.17)	.30	0.64 (0.44-0.93)	.02
rwOS				
Unadjusted	0.66 (0.44-1.01)	.06	0.66 (0.43-1.02)	.06
Multivariate (Cox model)	0.69 (0.46-1.06)	.09	0.64 (0.41-0.99)	.04
IPTW minimally adjusted[b]	0.69 (0.45-1.05)	.08	0.61 (0.40-0.95)	.03
IPTW fully adjusted[c]	0.74 (0.48-1.13)	.20	0.56 (0.35-0.91)	.02

[a]Reference treatment was acalabrutinib for zanubrutinib vs acalabrutinib, and ibrutinib for zanubrutinib vs ibrutinib.
[b]The minimally adjusted model adjusted for: age, sex, time from 1L to 2L, time from 2L to 3L; absolute SMDs post-IPTW were <0.2, indicating that balance between cohorts was achieved.
[c]The IPTW fully adjusted model adjusted for: age, sex, time from 1L to 2L, time from 2L to 3L, ECOG stage at initial diagnosis, LDH status, bulky disease status, and Ki67 status; absolute SMDs post-IPTW were <0.2, indicating that balance between cohorts was achieved.
IPTW, inverse probability of treatment weighting; LDH, lactose dehydrogenase; MCL, mantle cell lymphoma; SMD, standardized mean difference.

LIMITATIONS

- The limited sample size and follow-up period with 2L/3L zanubrutinib restricted the ability to discern smaller differences in effectiveness compared with the other evaluated cBTKis
- The included oncology practices may not have represented all practice sites within the US
- Lack of certain data (eg, specific variables, loss to follow-up) could have introduced bias

REFERENCES

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DISCLOSURES

TP: Consultant: BeiGene. **TAM, JW, AP:** Employment, Flatiron Health, Inc., an independent member of the Roche Group, and stock ownership in Roche. **GAM, EKS:** Employment and may hold stock: BeiGene.

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