Evaluating Reasons for Differences in Real-World Clinical Outcomes Among Patients with Relapsed/Refractory Mantle Cell Lymphoma on Covalent BTK Inhibitors

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INTRODUCTION

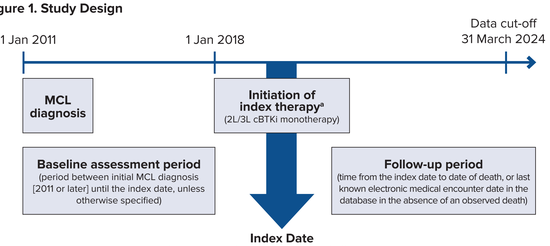
- The use of covalent Bruton tyrosine kinase inhibitors (cBTKis) has contributed to the evolution of the treatment landscape for relapsed/refractory (R/R) mantle cell lymphoma (MCL)
- Second-generation (acalabrutinib) and next-generation (zanubrutinib) cBTKis were developed to address off-target inhibition and side effects seen with ibrutinib, the first-generation cBTKi
- We have previously reported differences in real-world time to next treatment (rwTTNT) and overall survival (rwOS) among patients treated with ibrutinib, acalabrutinib, and zanubrutinib;[1,2] however, reasons for these differences were unknown
- The objective of this study is to further evaluate rwTTNT and rwOS using an updated dataset with 4 additional months of follow-up, assess treatment patterns of cBTKis (including switching), describe reasons for cBTKi discontinuation, and compare the real-world effectiveness of ibrutinib, acalabrutinib, and zanubrutinib monotherapy among patients with R/R MCL in the United States (US)

METHODS

Data Source and Study Design

- This retrospective observational cohort study used the US nationwide, longitudinal, electronic health record (EHR)-derived Flatiron Health database, comprising de-identified patient-level data originated from approximately 280 US cancer clinics (~800 sites of care; primarily community oncology settings) and curated via technology-enabled abstraction[3,4]
- The study design is shown in **Figure 1**

Figure 1. Study Design



[a] Index therapy was defined as the patient's first exposure to 2L/3L zanubrutinib, acalabrutinib, or ibrutinib.
2L, second-line; 3L, third-line; cBTKi, covalent Bruton tyrosine kinase inhibitor; MCL, mantle cell lymphoma.

Study Population

- 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
- Patients were excluded if they were treated with a BTKi prior to their first cBTKi monotherapy in the second- or third-line (2L/3L) setting
- Patients were followed until loss to follow-up or death

Study Outcomes

- Real-world treatment patterns were evaluated
- Real-world clinical outcomes included:
  - rwTTNT, defined as time from index date to the start of the next treatment or death (whichever occurred first), or censored at last EHR activity date
  - rwOS, defined as time from index date to date of death, or censored at last EHR activity date
- Reasons for discontinuation were abstracted from documentation in clinical notes and included non-mutually exclusive categories: Financial, Non-cancer related medical issue, Cancer-related symptoms not due to therapy, Toxic effect of therapy, Progression, Patient request, Other, and Not documented/Unknown

Statistical Analyses

- Patient baseline demographic and clinical characteristics were described
- Descriptive statistics including medians, interquartile range (IQR), and minimum and maximum values were reported for continuous variables and frequencies and percentages were reported for categorical variables
- Survival curves were generated using Kaplan-Meier analyses and the log-rank test was used to compare 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, 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 (IPTW) was conducted to estimate the average treatment effect
  - Adjusted models were: (i) multivariate (Cox model), (ii) IPTW minimally adjusted (which was adjusted for age, sex, time from first-line [1L] to 2L, number of prior lines), and (iii) IPTW fully adjusted (which was adjusted for age, sex, time from 1L to 2L, number of prior lines, Eastern Cooperative Oncology Group score, stage at initial diagnosis, lactose dehydrogenase status, bulky disease status, and Ki67 status)
- 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

Patients

- Of the 1,377 patients with R/R MCL who received any therapy in the 2L+ setting, 698 patients received 2L/3L cBTKi monotherapy for MCL and were included in this study (**Table 1**)
- In 96% of patients, *TP53* testing was negative or not documented (**Table 1**)

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

Characteristic	Overall (N=698)	Zanubrutinib (n=135)	Acalabrutinib (n=342)	Ibrutinib (n=221)
Age (years) at index, median (range)	73 (34, 85)	74 (45, 85)	74 (34, 85)	71 (38, 85)
Male, n (%)	520 (74%)	102 (76%)	259 (76%)	159 (72%)
Race, n (%)				
White	541 (78%)	109 (81%)	266 (78%)	166 (75%)
Black or African American	22 (3.2%)	<5	11 (3.2%)	10 (4.5%)
Asian	9 (1.3%)	<5	7 (2.0%)	0
Other Race	53 (7.6%)	5 (3.7%)	25 (7.3%)	23 (10%)
Unknown/not documented	73 (10%)	18 (13%)	33 (9.6%)	22 (10.0%)
Ethnicity, n (%)				
Hispanic or Latino	42 (6.0%)	8 (5.9%)	19 (5.6%)	15 (6.8%)
Not Hispanic or Latino	518 (74%)	97 (72%)	258 (75%)	163 (74%)
Unknown/not documented	138 (20%)	30 (22%)	65 (19%)	43 (19%)
Bulky disease at initial diagnosis, n (%)				
Yes	127 (18%)	21 (16%)	53 (15%)	53 (24%)
No/unknown	571 (82%)	114 (84%)	289 (85%)	168 (76%)
ECOG at index start, n (%)[a]				
0-1	424 (61%)	93 (69%)	208 (61%)	123 (56%)
2-4	66 (9.5%)	9 (6.7%)	35 (10%)	22 (10.0%)
Unknown	208 (30%)	33 (24%)	99 (29%)	76 (34%)
TP53 mutation status at index start, n (%)				
No documented *TP53* test available	613 (88%)	115 (85%)	286 (84%)	212 (96%)
Has documented *TP53* test available	85 (12%)	20 (15%)	56 (16%)	9 (4%)
TP53 mutation status among patients with available *TP53* result				
Positive	30 (35%)	6 (30%)	20 (36%)	<5
Negative	53 (62%)	13 (65%)	35 (63%)	5 (56%)
Unknown/inconclusive	<5	<5	<5	0
Ki67 status at index start, n (%)[b]				
<10%	31 (4.4%)	7 (5.2%)	12 (3.5%)	12 (5.4%)
11%-30%	144 (21%)	30 (22%)	72 (21%)	42 (19%)
31%-50%	139 (20%)	24 (18%)	69 (20%)	46 (21%)
>50%	180 (26%)	42 (31%)	79 (23%)	59 (27%)
Unknown/not documented	204 (29%)	32 (24%)	110 (32%)	62 (28%)
LDH at index start, n (%)[b]				
<0.67 ULN	130 (19%)	28 (21%)	58 (17%)	44 (20%)
0.67-0.99 ULN	227 (33%)	42 (31%)	113 (33%)	72 (33%)
1.00-1.49 ULN	88 (13%)	16 (12%)	41 (12%)	31 (14%)
≥1.50 ULN	54 (7.7%)	9 (6.7%)	25 (7.3%)	20 (9.0%)
Unknown/not documented	199 (29%)	40 (30%)	105 (31%)	54 (24%)
Number of LOT prior to index, n (%)[c]				
1	532 (76%)	107 (79%)	260 (76%)	165 (75%)
2	166 (24%)	28 (21%)	82 (24%)	56 (25%)
Time from start of 1L to index of first cBTKi, months, median (IQR)	23 (8, 51)	26 (10, 67)	21 (7, 50)	23 (7, 47)
Patient disposition at data cutoff, n (%)				
Confirmed death	329 (47%)	36 (27%)	170 (50%)	123 (56%)
Still on therapy at data cut off	154 (22%)	46 (34%)	68 (20%)	40 (18%)

[a] Extracted from unstructured documents using natural language processing when ECOG information from structured data is unavailable in the baseline ECOG table. ECOG values represent the score closest to the index date. ECOG values of 5 are transformed to "Unknown" for de-identification purposes. Additional information can be found on Flatiron's Knowledge Center.
[b] As documented with dates occurring at any point from initial diagnosis to 30 days after index date.
[c] Index here refers to start of earliest cBTKi monotherapy start date (either 2L or 3L).
1L, first-line; 2L, second-line; 3L, third-line; cBTKi, covalent Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactose dehydrogenase; LOT, line of treatment; NOS, not otherwise specified; R/R MCL, relapsed/refractory mantle cell lymphoma; ULN; upper limit of normal.

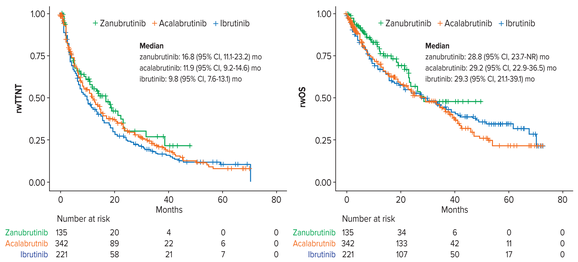
Treatment Patterns

- Median (range) length of follow-up from the start of index 2L/3L cBTKi monotherapy was 36 (19–56) months in the overall cohort, 15 (10–25) months in the zanubrutinib cohort, 36 (20–52) months in the acalabrutinib cohort, and 57 (35–67) months in the ibrutinib cohort (**Table 1**)

rwTTNT and rwOS

- Trends in rwTTNT and rwOS favoring zanubrutinib over acalabrutinib and ibrutinib are observed in **Figure 2**
- The fully adjusted multivariate model (**Table 2**) showed:
  - A longer rwTTNT with zanubrutinib compared with ibrutinib (HR 0.75 [95% CI 0.55–1.04; *P*=.08]) and acalabrutinib (HR 0.91 [95% CI 0.68–1.22; *P*=.50])
  - Significantly longer rwOS for zanubrutinib compared with ibrutinib (HR 0.63 [95% CI 0.42–0.96; *P*=.03])
  - A nonsignificant difference in rwOS for zanubrutinib compared with acalabrutinib (HR 0.77 [95% CI 0.53–1.11; *P*=.20])
- When stratifying patients who received cBTKi monotherapy in 2L by whether they received R-maintenance therapy in their 1L (n=145) or not (n=387), there was no difference in median rwOS for R-maintenance (37.4 [95% CI 29.2–54.5] months) vs no maintenance (25.4 [95% CI 22.9–34.7] months; *P*=.4)

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



2L, second-line; 3L, third-line; cBTKi, covalent Bruton tyrosine kinase inhibitor; mo, months; R/R MCL, relapsed/refractory mantle cell lymphoma; rwOS, real-world overall survival; rwTTNT, real-world time to next treatment.

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	0.86 (0.66–1.14)	.30	0.75 (0.57–1.00)	.05
Multivariate (Cox model)	0.88 (0.67–1.16)	.40	0.76 (0.57–1.01)	.06
IPTW minimally adjusted	0.88 (0.67–1.17)	.40	0.74 (0.55–1.00)	.05
IPTW fully adjusted	0.91 (0.68–1.22)	.50	0.75 (0.55–1.04)	.08
rwOS				
Unadjusted	0.71 (0.50–1.03)	.07	0.71 (0.49–1.04)	.08
Multivariate (Cox model)	0.73 (0.51–1.05)	.09	0.67 (0.46–0.98)	.04
IPTW minimally adjusted	0.73 (0.51–1.05)	.09	0.65 (0.44–0.95)	.03
IPTW fully adjusted	0.77 (0.53–1.11)	.20	0.63 (0.42–0.96)	.03

[a] Reference treatment was acalabrutinib for zanubrutinib vs acalabrutinib, and ibrutinib for zanubrutinib vs ibrutinib.
2L, second-line; 3L, third-line; cBTKi, covalent Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; R/R MCL, relapsed/refractory mantle cell lymphoma; rwOS, real-world overall survival; rwTTNT, real-world time to next treatment.

Reasons for Discontinuation

- Reasons for discontinuation were documented in 408 (58.4%) of patients in the overall cohort; among these patients, the most documented reasons for discontinuation were progression (30.1%) and toxicity (11.5%) (**Table 3**)
- A total of 44 (6.3%) patients who received 2L/3L cBTKi monotherapy switched to another cBTKi (**Table 4**); median (IQR) time to next cBTKi among these patients was 8 (4–21) months
  - Among the 31 (4.4%) patients who switched from ibrutinib to acalabrutinib/zanubrutinib, the most documented reasons for discontinuation were toxicity (61.3%), and progression (19.3%) (**Table 4**)
  - Among the 12 (1.7%) patients who switched from acalabrutinib to zanubrutinib, the most documented reason for discontinuation was toxicity (58.3%) (**Table 4**)

CONCLUSIONS

- Among patients with R/R MCL who received 2L/3L cBTKi monotherapy, zanubrutinib was associated with significantly improved rwOS compared with ibrutinib
- Trends in rwTTNT and rwOS favoring zanubrutinib over acalabrutinib and ibrutinib were observed
- 88% of patients included in this study did not have documentation of *TP53* testing, suggesting that *TP53* testing is underutilized in the real world
- For patients who switched cBTKi monotherapies, 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

Table 3. Reasons for Discontinuation Among Patients Receiving 2L/3L cBTKi Monotherapy

Reason for Discontinuation, n (%)[a]	Overall[b] (N=698)	Zanubrutinib (n=135)	Acalabrutinib (n=342)	Ibrutinib (n=221)
Progression	210 (30.1%)	33 (24.4%)	119 (34.8%)	58 (26.2%)
Toxic effect of therapy	80 (11.5%)	9 (6.7%)	33 (9.6%)	38 (17.2%)
Other	65 (9.3%)	7 (5.2%)	32 (9.4%)	26 (11.8%)
Non-cancer related medical issue	27 (3.9%)	5 (3.7%)	9 (2.6%)	13 (5.9%)
Cancer-related symptoms not due to therapy	11 (1.6%)	<5	<5	5 (2.3%)
Patient request	8 (1.1%)	<5	<5	<5
Financial	7 (1.0%)	0	5 (1.5%)	<5
Not documented/Unknown	277 (39.7%)	74 (54.8%)	131 (38.3%)	72 (32.6%)

[a] Reasons for discontinuation are not mutually exclusive and patients could have ≥1 reason for discontinuation.
[b] The categories 'Completed treatment (n=16)' and 'No evidence of disease (n=8)' are not included.
2L, second-line; 3L, third-line; cBTKi, covalent Bruton tyrosine kinase inhibitor.

Table 4. Reasons for Discontinuation Among Subgroup of Patients Who Switched to Another cBTKi Monotherapy

Reason for Discontinuation, n (%)[a]	Switched from Ibrutinib to Another cBTKi Monotherapy (n=31)	Switched from Acalabrutinib to Zanubrutinib (n=12)
Toxic effect of therapy	19 (61.3%)	7 (58.3%)
Progression	6 (19.3%)	<5
Non-cancer related medical issue	<5	0
Patient request	<5	0
Other	<5	0
Financial	0	<5
Cancer-related symptoms not due to therapy	0	0
Not documented/Unknown	0	0

[a] Reasons for discontinuation are not mutually exclusive and patients could have ≥1 reason for discontinuation.
cBTKi; covalent Bruton tyrosine kinase inhibitor.

LIMITATIONS

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

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