Impact of Novel Therapies on Real-World Clinical Outcomes of Patients with Relapsed/Refractory Mantle Cell Lymphoma by Race/Ethnicity and *TP53* Mutation Status

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INTRODUCTION

- Advancements in the treatment landscape for relapsed/refractory (R/R) mantle cell lymphoma (MCL) have resulted in a shift away from traditional chemoimmunotherapy (CIT) to innovative novel therapies (NTs), such as Bruton tyrosine kinase (BTK) inhibitors.[1,2] *TP53* mutations are a known poor prognostic marker in MCL;[3] however it is unknown how often *TP53* mutation testing occurs in the real-world (RW) and whether there are different clinical outcomes by *TP53* mutation status with CIT versus NTs
- In a prior US study of all patients (pts) diagnosed with MCL in the National Cancer Database from 2004 to 2013 (during the CIT era prior to NT use), disparities in overall survival (OS) were observed by race/ethnicity.[4] In this study, median OS (95% confidence interval [CI]) for Hispanic pts was 75.2 months (65, 89.6), Non-Hispanic White pts 60.2 months (58.4, 62.1), and Non-Hispanic Black pts 49.2 months (41.4, 62)
- Little is known about current RW treatment patterns and clinical outcomes of pts with R/R MCL in regard to CIT compared with NTs among pts of different race/ethnicity and *TP53* mutation status

METHODS

- This retrospective cohort study included adult pts with R/R MCL who initiated BTK inhibitor therapy as a second-line (2L) or third-line (3L) treatment on January 1, 2018 or later and were followed until loss to follow-up or death using the US Flatiron Health electronic health record-derived de-identified database. The snapshot date used for this analysis was December 2023
- CIT included any MCL treatment regimen using chemotherapy + anti-CD20 antibody, and pts who received CIT as induction and subsequent hematopoietic stem cell transplantation. NTs included BTK inhibitors, B-cell lymphoma-2 (BCL-2) inhibitors, lenalidomide, bortezomib, and chimeric antigen receptor T-cell therapy (CAR-T), or combinations. Concurrent systemic treatments for other cancers, clinical trial drug (for any cancer), and rituximab monotherapy were categorized in "Other"
- RW time to next treatment (rwTTNT) and RW overall survival (rwOS) were estimated based on Kaplan-Meier analyses and adjusted for age and sex. Adjusted rwTTNT and rwOS for time from start of 1L therapy to start of 2L therapy (POD24) (defined as time from start of 1L therapy to start of 2L therapy, greater to, less than or equal to 24 months) is available in supplementary information
- *P* values were calculated using the log-rank test

RESULTS

Baseline Characteristics

- The majority of pts with R/R MCL who received 2L and 3L therapy were Non-Latinx (NL)-White (75%), followed by NL-Asian/Other race (8%), Latinx (6%), then NL-Black (4%) [**Table 1**]
- The overall 2L and 3L population had a median age of 71 years (range 63-78), were mostly male (74%), had a diagnosis of MCL not otherwise specified (NOS) (85%), and had stage IV disease (62%). Sixty-three percent of pts had disease progression within 24 months from first-line (1L) treatment (POD24) before starting 2L therapy
- Black and Asian/Other race pts had more variants of MCL (blastic, leukemic, pleomorphic), less MCL NOS (75% and 81%, respectively), as well as higher rates of Ki67 status score at 2L initiation greater than 50% (32% and 26%, respectively) compared with all other race/ethnicity groups. In contrast, Latinx pts had more MCL NOS (92%) and a lower percentage had a Ki67 status score at 2L initiation greater than 50% (20%)

Table 1. Patient Demographic and Clinical Characteristics Among Pts with R/R MCL Receiving Any 2L or 3L Treatment

	Total R/R MCL (2L/3L) N=1,377	NL-White N=1,028	NL-Black N=53	Latinx N=86	NL-Asian/ Other N=108	Unknown/Not Documented N=102
Age (years) at 2L initiation (continuous)						
Median	71	72	67	67	71	70
IQR	63, 78	64, 79	59, 80	60, 75	65, 79	62, 77
Sex, n (%)						
Male	1,024 (74%)	768 (75%)	41 (77%)	61 (71%)	80 (74%)	74 (73%)
Female	353 (26%)	260 (25%)	12 (23%)	25 (29%)	28 (26%)	28 (27%)
Disease subtype, n (%)						
Blastic MCL (blastoid variant)	93 (6.8%)	69 (6.7%)	9 (17%)	4 (4.7%)	6 (5.6%)	5 (4.9%)
MCL (pleomorphic)	50 (3.6%)	37 (3.6%)	1 (1.9%)	2 (2.3%)	7 (6.5%)	3 (2.9%)
Leukemic MCL	64 (4.6%)	51 (5.0%)	3 (5.7%)	1 (1.2%)	7 (6.5%)	2 (2.0%)
MCL NOS	1,170 (85%)	871 (85%)	40 (75%)	79 (92%)	88 (81%)	92 (90%)
Stage at initial diagnosis, n (%)						
I	27 (2.0%)	22 (2.1%)	0 (0%)	1 (1.2%)	2 (1.9%)	2 (2.0%)
II	60 (4.4%)	47 (4.6%)	4 (7.5%)	2 (2.3%)	6 (5.6%)	1 (1.0%)
III	189 (14%)	146 (14%)	9 (17%)	11 (13%)	15 (14%)	8 (7.8%)
IV	849 (62%)	629 (61%)	35 (66%)	53 (62%)	65 (60%)	67 (66%)
Unknown/not documented	252 (18%)	184 (18%)	5 (9.4%)	19 (22%)	20 (19%)	24 (24%)
Ki67 status at 2L initiation, n (%)						
<10%	73 (5.3%)	53 (5.2%)	3 (5.7%)	5 (5.8%)	8 (7.4%)	4 (3.9%)
11-30%	277 (20%)	192 (19%)	14 (26%)	27 (31%)	25 (23%)	19 (19%)
31-50%	236 (17%)	180 (18%)	6 (11%)	15 (17%)	19 (18%)	16 (16%)
>50%	343 (25%)	258 (25%)	17 (32%)	17 (20%)	28 (26%)	23 (23%)
Unknown/not documented	448 (33%)	345 (34%)	13 (25%)	22 (26%)	28 (26%)	40 (39%)

Table 1. (Continued)

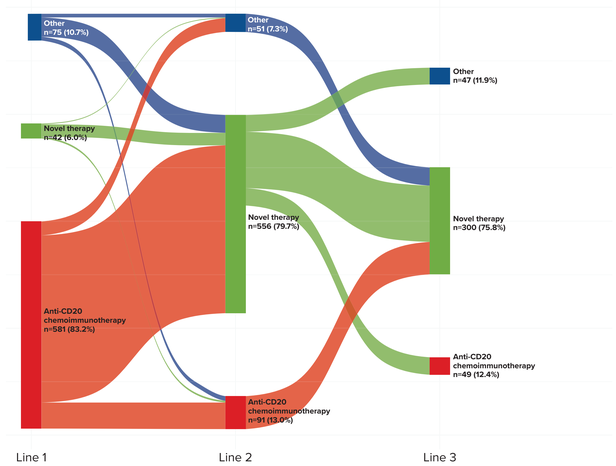
	Total R/R MCL (2L/3L) N=1,377	NL-White N=1,028	NL-Black N=53	Latinx N=86	NL-Asian/ Other N=108	Unknown/Not Documented N=102
Time from 1L initiation to 2L initiation (months)						
Median (IQR)	14 (4, 38)	14 (4, 40)	9 (4, 30)	17 (6, 38)	18 (8, 43)	9 (3, 23)
≤24 months	865 (63%)	630 (61%)	37 (70%)	54 (63%)	66 (61%)	78 (76%)
>24 months	512 (37%)	398 (39%)	16 (30%)	32 (37%)	42 (39%)	24 (24%)

1L, first-line; 2L, second-line; IQR, interquartile range; MCL, mantle cell lymphoma; NL, Non-Latinx; NOS, not otherwise specified; R/R, relapsed/refractory.

Treatment Patterns

- Analysis of treatment patterns for pts with R/R MCL showed that most pts (83%) received CIT as 1L treatment, while only 6% received NTs in the 1L (**Figure 1**). In contrast, 80% of pts at 2L and 76% of pts at 3L received NTs, with the percentage of pts receiving CIT reducing to 13% and 12%, respectively

Figure 1. Sankey Diagram Illustrating the 1L, 2L, and 3L Treatments Received by Pts with R/R MCL



1L, first-line; 2L, second-line; 3L, third-line; MCL, mantle cell lymphoma; pts, patients; R/R, relapsed/refractory.

- In the overall pt cohort, the most common 1L treatments received by pts with R/R MCL were CITs: bendamustine plus rituximab (BR, 54%) and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP, 18%) (**Table 2**)
- Conversely, the most common 2L and 3L treatments in the overall cohort were NTs
  - For 2L treatment, the most common NTs were acalabrutinib (31%) and ibrutinib (21%), while the most common 3L NTs were acalabrutinib (21%) and zanubrutinib (12%)
- Transplantation rates before 2L and CAR-T use in 3L was highest among White pts

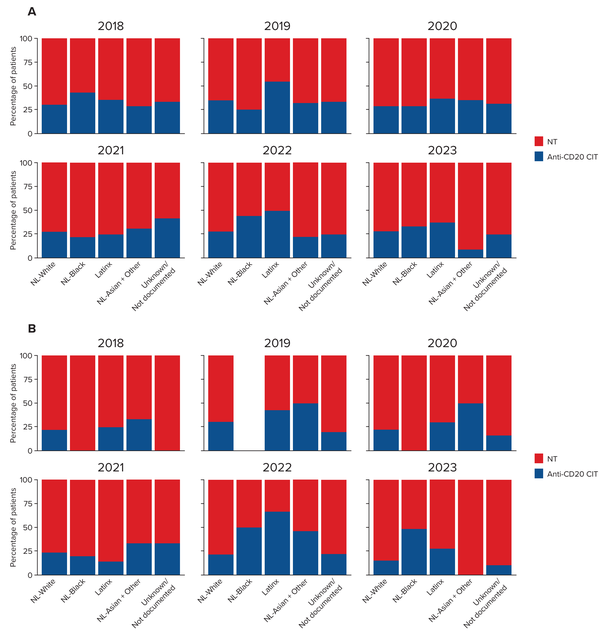
Table 2. Most Common NTs and CITs Received by R/R MCL Pts in the 1L, 2L, and 3L of Treatment

R/R MCL (2L/3L) Cohort Overall, n (%)			
Top 2 most common novel treatments in 1L		**Top 3 most common CIT treatments in 1L**	
Lenalidomide + rituximab	42 (47%)	BR	577 (54%)
Bortezomib + R-CHOP	24 (27%)	R-CHOP	191 (18%)
		R-CHOP alternating with R-DHAP	42 (3.9%)
Top 3 most common novel treatments in 2L		**Top 3 most common CIT treatments in 2L**	
Acalabrutinib	240 (31%)	BR	105 (32%)
Ibrutinib	162 (21%)	R-CHOP	37 (11%)
Zanubrutinib	85 (11%)	R-DHAP	25 (7.5%)
Top 3 most common novel treatments in 3L		**Top 3 most common CIT treatments in 3L**	
Acalabrutinib	76 (21%)	BR	41 (34%)
Zanubrutinib	42 (12%)	R-CHOP	11 (9.2%)
Ibrutinib	38 (10%)	R-DHAP	5 (4.2%)

1L, first-line; 2L, second-line; 3L, third-line; BR, bendamustine + rituximab; CIT, chemoimmunotherapy; pts, patients; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, cisplatin, cytarabine, and prednisone.

- Over a 6-year assessment period between 2018 and 2023, a greater proportion of pts with R/R MCL received NTs compared with CIT in the 2L (**Figure 2A**) and 3L (**Figure 2B**)

Figure 2. The Annual Percentage of Pts with R/R MCL Receiving NT vs CIT Grouped by Race/Ethnicity in the 2L (A) and 3L (B)



2L, second-line; 3L, third-line; CIT, chemoimmunotherapy; MCL, mantle cell lymphoma; NL, Non-Latinx; NT, novel therapy; R/R, relapsed/refractory.

Clinical Outcomes

- Among all pts, median rwTTNT (mrwTNNT) (months [95% CI]) was longer with 2L NT (11.9 [10.6, 14.5]) than CIT (9.9 [8.1, 12.9]) [**Table 3**]. NL-White, NL-Black, and NL-Asian/Other race pts had longer mrwTTNT with NT (11.9 [10.5, 14.6], 12.9 [7.6, not reported [NR]], and 14.6 [8.5, 21.4], respectively) than CIT (9.9 [7.6, 12.9], 9.7 [3.0, NR], and 6.0 [3.2, 21.2]). Latinx pts had longer mrwTTNT with CIT (14.9 [11.8, NR]) than NT (9.0 [3.8, 24.2])
- Among all pts, median rwOS (mrwOS) (months [95% CI]) was longer with 2L CIT (43.0 [34.1, 56.5]) than NT (35.6 [29.9, 41.2]). White and Latinx pts had longer mrwOS with CIT (47.3 [33.9, NR] and NR [33.3, NR], respectively) than NT (35.0 [28.8, 48.4] and 42.3 [31.0, NR]). Black and Asian/Other race pts had longer mrwOS with NT (41.2 [32.8, NR] and 38.8 [23.5, NR], respectively) than CIT (34.8 [9.7, NR] and 13.5 [8.3, NR])
- Among all pts on 3L treatment, mrwTTNT (months [95% CI]) improved when using NTs (7.9 [6.8, 10.3]) versus CIT (4.4 [3.5, 6.9]) [**Table 4**]. NTs demonstrated better mrwTTNT than CIT in all race/ethnic groups except Latinx pts. For all race/ethnic groups, mrwOS was improved with NTs (32.5 [24.7, 42.6]) versus CIT (19.5 [13.7, 47.3])
- For pts with *TP53* mutations, mrwTTNT and mrwOS (mo [95% CI]) were longer for 2L NTs (3.3 [2.2, 6.4] and 18.3 [9.0, NR], respectively) than CIT (3.0 [1.9, 7.6] and 15.0 [7.2, NR]) [**Table 5**]. Less than 5% of pts were positive for the presence of a *TP53* mutation; however, only 15% were tested for a *TP53* mutation in the whole cohort

Table 3. Adjusted rwTTNT and rwOS for NT or CIT in 2L by Race/Ethnicity

	Overall NT n=766 CIT n=333		NL-White NT n=569 CIT n=240		NL-Black NT n=28 CIT n=14		Latinx NT n=44 CIT n=27		Asian/Other Race NT n=66 CIT n=26	
Median rwTTNT (95% CI) in months										
NTs	11.9 (10.6, 14.5)	*P*=.6	11.9 (10.5, 14.6)	*P*=.7	12.9 (7.6, NR)	*P*=.8	9.0 (3.8, 24.2)	*P*=.5	14.6 (8.5, 21.4)	*P*=.4
CIT	9.9 (8.1, 12.9)		9.9 (7.6, 12.9)		9.7 (3.0, NR)		14.9 (11.8, NR)		6.0 (3.2, 21.2)	
Median rwOS (95% CI) in months										
NTs	35.6 (29.9, 41.2)	*P*=.003	35.0 (28.8, 48.4)	*P*=.012	41.2 (32.8, NR)	*P*=.7	42.3 (31.0, NR)	*P*=.2	38.8 (23.5, NR)	*P*=.8
CIT	43.0 (34.1, 56.5)		47.3 (33.9, NR)		34.8 (9.7, NR)		NR (33.3, NR)		13.5 (8.3, NR)	

2L, second-line; CI, confidence interval; CIT, chemoimmunotherapy; NL, Non-Latinx; NR, not reached; NT, novel therapy; rwOS, real-world overall survival; rwTTNT, real-world time to next treatment.

CONCLUSIONS

- High-risk features, treatment patterns, and clinical outcomes for NTs versus CITs in R/R MCL differed by race/ethnicity
- Analysis of the treatment patterns of pts with R/R MCL revealed that most pts received CIT as 1L treatment, while NTs, the majority being BTK inhibitors, were more commonly used in the 2L and 3L
- Use of 2L+ NTs was associated with a trend towards improved mrwTTNT and mrwOS among NL-Black and Asian/Other race pts. NT use in 3L numerically improved mrwTTNT and mrwOS for most pts versus CIT
- *TP53* mutation testing is low in the RW, emphasizing a need to increase standard of care testing to consider non-CIT therapies for this unmet need population

Table 4. Adjusted rwTTNT and rwOS for NT or CIT in 3L by Race/Ethnicity

	Overall NT n=364 CIT n=119		NL-White NT n=265 CIT n=77		NL-Black NT n=13 CIT n=4		Latinx NT n=26 CIT n=12		Asian/Other Race NT n=28 CIT n=18	
Median rwTTNT (95% CI) in months										
NTs	7.9 (6.8, 10.3)	*P*<.001	7.8 (6.5, 10.8)	*P*<.001	5.7 (2.0, NR)	*P*=.5	14.0 (9.7, NR)	*P*=.5	9.6 (3.8, NR)	*P*=.6
CIT	4.4 (3.5, 6.9)		4.4 (3.2, 6.9)		NA		16.6 (3.1, NR)		5.0 (2.9, 19.4)	
Median rwOS (95% CI) in months										
NTs	32.5 (24.7, 42.6)	*P*=.023	32.5 (20.0, 50.8)	*P*=.053	36.4 (28.7, NR)	*P*>.9	42.2 (23.2, NR)	*P*=.2	35.2 (21.3, NR)	*P*=.3
CIT	19.5 (13.7, 47.3)		20.5 (8.7, 54.1)		NA		16.6 (3.1, NR)		30.1 (5.0, NR)	

3L, third-line; CI, confidence interval; CIT, chemoimmunotherapy; NA, not available; NL, Non-Latinx; NR, not reached; NT, novel therapy; rwOS, real-world overall survival; rwTTNT, real-world time to next treatment.

Table 5. Adjusted rwTTNT and rwOS in Pts with MCL and *TP53* Mutation in 2L

	Overall NT n=42 CIT n=16	
Median rwTTNT (95% CI) in months		
NTs	3.3 (2.2, 6.4)	*P*=.4
CIT	3.0 (1.9, 7.6)	
Median rwOS (95% CI) in months		
NTs	18.3 (9.0, NR)	*P*>.9
CIT	15.0 (7.2, NR)	

2L, second-line; CI, confidence interval; CIT, chemoimmunotherapy; MCL, mantle cell lymphoma; NR, not reached; NT, novel therapy; pts, patients; rwOS, real-world overall survival; rwTTNT, real-world time to next treatment.

DISCUSSION

- The results of this study indicated that there are differences by race/ethnicity in high-risk features (including *TP53* mutation status), treatment patterns, and clinical outcomes for patients with R/R MCL receiving NTs vs CITs
- Future research evaluating the reasons for the differences between pts of different race/ethnicity and *TP53* mutation testing and status is warranted

Study limitations

- The limited sample size per race/ethnicity restricted the ability to discern differences between the subgroups in effectiveness of NTs vs CIT in R/R MCL
- The oncology practices included may not have represented all practice sites within the US and the lack of certain data (eg, specific variables and loss to follow-up) could have introduced bias

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This QR code links to further adjusting of rwTTNT and rwOS results by POD24.

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