6-13-2023

Impact of diagnosis to treatment interval in patients with newly diagnosed mantle cell lymphoma

Narendranath Epperla

Mary-Kate Malecek

Brad S Kahl

Nancy L Bartlett

et al.

REGULAR ARTICLE

blood advances

Impact of diagnosis to treatment interval in patients with newly diagnosed mantle cell lymphoma

Narendranath Epperla,[1] Jeffrey Switchenko,[2] Veronika Bachanova,[3] James N. Gerson,[4] Stefan K. Barta,[4] Max J. Gordon,[5] Alexey V. Danilov,[6] Natalie S. Grover,[7] Stephanie Mathews,[7] Madelyn Burkart,[8] Reem Karmali,[8] Yazeed Sawalha,[1] Brian T. Hill,[9] Nilanjan Ghosh,[10] Steven I. Park,[10] David A. Bond,[1] Mehdi Hamadani,[11] Timothy S. Fenske,[11] Peter Martin,[12] Mary-Kate Malecek,[13] Brad S. Kahl,[13] Christopher R. Flowers,[5] Brian K. Link,[14] Lawrence D. Kaplan,[15] David J. Inwards,[16] Andrew L. Feldman,[16] Eric D. Hsi,[17] Kami Maddocks,[1] Kristie A. Blum,[2] Nancy L. Bartlett,[13] James R. Cerhan,[16] John P. Leonard,[12] Thomas M. Habermann,[16] Matthew J. Maurer,[16,*] and Jonathon B. Cohen[2,*]

[1]Division of Hematology, Department of Medicine, The Ohio State University, Columbus, OH; [2]Winship Cancer Institute, Emory University, Atlanta, GA; [3]Department of Medicine, University of Minnesota, Minneapolis, MN; [4]Department of Medicine, University of Pennsylvania, Philadelphia, PA; [5]Department of Medicine, MD Anderson Cancer Center, Houston, TX; [6]Department of Medicine, City of Hope, Duarte, CA; [7]Department of Medicine, University of North Carolina, Chapel Hill, NC; [8]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; [9]Cleveland Clinic, Cleveland, OH; [10]Department of Medicine, Levine Cancer Institute, Atrium Health, Charlotte, NC; [11]BMT & Cellular Therapy Program, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [12]Department of Medicine, Weill Cornell Medical College, Manhattan, NY; [13]Department of Medicine, Washington University in St. Louis, St. Louis, MO; [14]Department of Medicine, University of Iowa, Iowa City, IA; [15]Department of Medicine, University of California, San Francisco, CA; [16]Department of Medicine, Mayo Clinic, Rochester, MN; and [17]Department of Medicine, Wake Forest University, Winston-Salem, NC

Key Points

- DTI is strongly associated with adverse clinical factors and inferior survival outcomes in patients with newly diagnosed MCL.
- DTI should be reported in all patients newly diagnosed with MCL enrolling in clinical trials; steps must be taken to avoid selection bias.

The prognostic relevance of diagnosis to treatment interval (DTI) in patients with newly diagnosed mantle cell lymphoma (MCL) is unknown. Hence, we sought to evaluate the impact of DTI on outcomes in MCL using 3 large datasets (1) the University of Iowa/Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource, (2) patients enrolled in the ALL Age Asthma Cohort/CALGB 50403, and (3) a multisitecohort of patients with MCL. Patients were a priori divided into 2 groups, 0 to 14 days (short DTI) and 15 to 60 days (long DTI). The patients in whom observation was deemed appropriate were excluded. One thousand ninety-seven patients newly diagnosed with MCL and available DTI were included in the study. The majority (73%) had long DTI (n=797). Patients with short DTI had worse eastern cooperative oncology group performance status (ECOG PS ≥2), higher lactate dehydrogenase, bone marrow involvement, more frequent B symptoms, higher MCL International Prognostic Index (MIPI ≥6.2), and were less likely to receive intensive induction therapy than long DTI group. The median progression-free survival (2.5 years vs 4.8 years, p<0.0001) and overall survival (7.8 years vs. 11.8 years, p<0.0001) were significantly inferior in the short DTI group than the long DTI cohort and remained significant for progression-free survival and overall survival in multivariable analysis. We show that the DTI is an important prognostic factor in patients newly diagnosed with MCL and is strongly associated with adverse clinical factors and poor outcomes. DTI should be reported in all the patients newly diagnosed with MCL who are enrolling in clinical trials and steps must be taken to ensure selection bias is avoided.

Submitted 24 October 2022; accepted 31 October 2022; prepublished online on *Blood Advances* First Edition 14 December 2022; final version published online 24 May 2023. https://doi.org/10.1182/bloodadvances.2022009225.

*M.J.M. and J.B.C. are co-senior authors.

Data are available on request from the corresponding author, Narendranath Epperla (narendranath.epperla@osumc.edu).

The full-text version of this article contains a data supplement.

Introduction

Mantle cell lymphoma (MCL) is a subtype of B-cell non-Hodgkin lymphoma (NHL) characterized by the translocation t(11;14)(q13;32) resulting in the overexpression of cyclin D1.[1,2] MCL accounts for ~6% to 8% of all NHLs with a median age at diagnosis of >65 years and male predominance.[2,3] Although the survival of patients with MCL has improved in the past decade because of the advent of novel agents,[3] there remains a subset of patients with high-risk features that continue to have poor outcomes, such as those with blastoid or pleomorphic variants and those harboring *TP53* mutation.[4]

The diagnosis to treatment interval (DTI) is an important prognostic factor in patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)[5] in which patients who begin therapy quickly (within 14 days) after diagnosis have an inferior event-free survival than those not requiring such immediate treatment initiation likely reflecting disease aggressiveness[6] in those with shorter DTI. Similarly, a retrospective study that evaluated the impact of DTI on outcomes of patients with aggressive NHLs, including MCL, showed that shorter DTI was associated with unfavorable outcomes.[7] However, the study was limited by lack of details on treatment regimens, prognostic variables, and lymphoma-related endpoints such as progression-free survival (PFS).

Given the paucity of data surrounding the prognostic relevance of DTI in MCL, we sought to evaluate the impact of timing of treatment initiation from diagnosis on outcomes using 3 large datasets (1) the University of Iowa/Mayo Clinic Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (MER), (2) patients enrolled in the ALLIANCE/CALGB 50403, and (3) a multisite cohort of patients with MCL.

Patients and methods

Study design

This is a pooled analysis of 3 large datasets, 2 prospective (SPORE/MER and CALGB/ALLIANCE 50403) and 1 retrospective (MCL retrospective cohort study [MCL-RCS]).

The details on the MER cohort have been previously reported.[8] Briefly, adult patients newly diagnosed with MCL were prospectively enrolled in the MER from 2002 to 2015. All patients were within 9 months of initial diagnosis at the time of enrollment and all diagnoses were confirmed by a study hematopathologist. Baseline clinical, laboratory, and treatment data were abstracted from medical records using a standard protocol. CALGB (now ALLIANCE) 50403 is a phase II randomized study wherein patients newly diagnosed with MCL received aggressive immunochemotherapy induction followed by high-dose cytarabine–based stem cell mobilization, autologous stem cell transplant, and posttransplant rituximab. Patients were then randomized to 2 different doses and schedules of posttransplant bortezomib.[9] The MCL-RCS included adult patients (≥18 years) with MCL treated from 2000 through 2017 at 12 participating US medical centers. The patients from the sites in the MCL-RCS that enrolled on CALGB 50403 were excluded. The details of the cohort are described elsewhere.[10,11] The study was institutional review board approved at all the participating sites and was conducted in accordance with the Declaration of Helsinki.

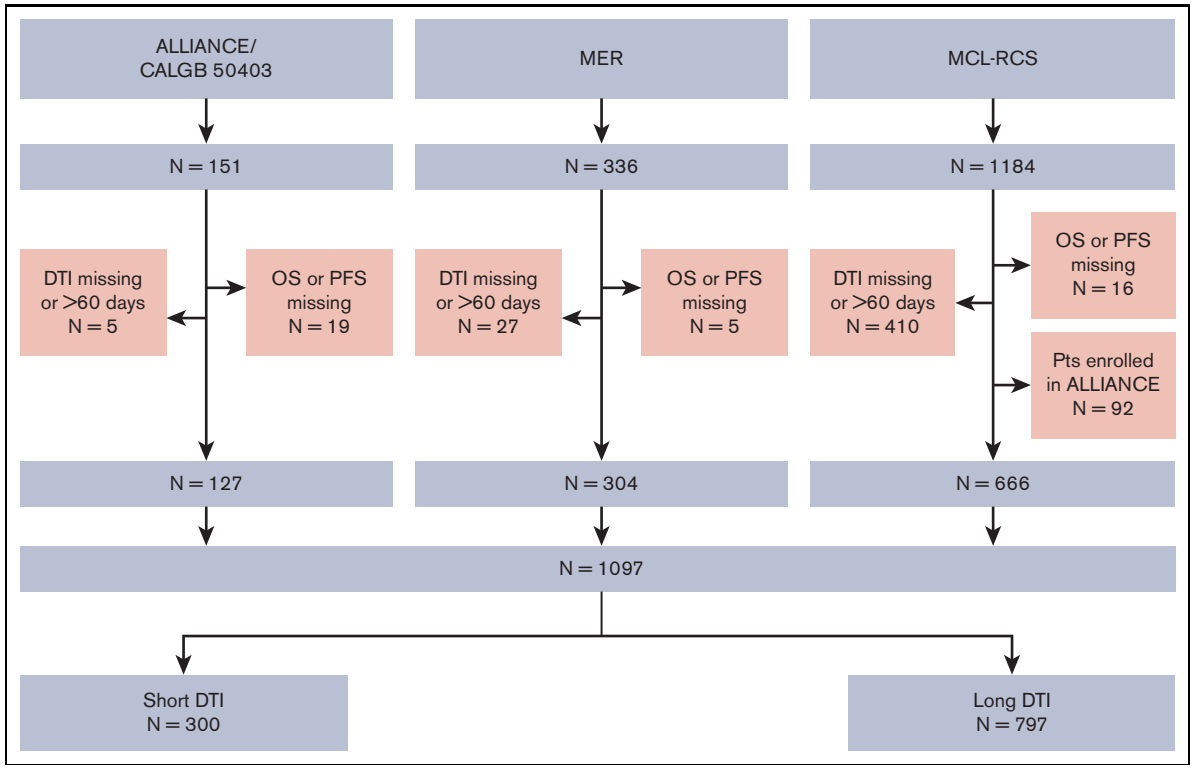


Figure 1. CONSORT diagram.

Table 1. Patient characteristics

Covariate	Datasets			
	ALLIANCE N = 127, n (%)	MER N = 304, n (%)	MCL-RCS N = 666, n (%)	All N = 1097, n (%)
Time to first treatment				
0-14 d	13 (10)	107 (35)	180 (27)	300 (27)
15-60 d	114 (90)	197 (65)	486 (73)	797 (73)
Age at diagnosis, y				
Median	60	64	62	63
Range	29-69	32-96	29-88	29-96
Sex				
Female	29 (23)	69 (23)	158 (24)	256 (23)
Male	98 (77)	235 (77)	507 (76)	840 (77)
Race				
White	116 (96)	278 (99)	576 (89)	970 (92)
Black	4 (3)	0 (0)	36 (5)	40 (4)
Others	1 (1)	2 (1)	37 (6)	40 (4)
ECOG PS				
0	82 (65)	188 (62)	331 (58)	601 (60)
1	41 (32)	86 (28)	208 (36)	335 (33)
≥2	4 (3)	30 (10)	33 (6)	67 (7)
Ann Arbor stage				
1-3	19 (15)	49 (16)	84 (13)	152 (14)
4	108 (85)	255 (84)	571 (87)	934 (86)
LDH				
Normal	83 (65)	168 (66)	263 (56)	514 (61)
Elevated	44 (35)	85 (34)	203 (44)	332 (39)
BM involvement				
Yes	106 (83)	229 (80)	467 (84)	802 (83)
No	21 (17)	56 (20)	88 (16)	165 (17)
B symptoms				
Yes	39 (31)	62 (21)	208 (33)	309 (29)
No	87 (69)	238 (79)	413 (67)	738 (71)
MIPI*				
<5.7	104 (82)	85 (34)	150 (37)	339 (43)
≥5.7 <6.2	15 (12)	77 (31)	128 (31)	220 (28)
≥6.2	8 (6)	88 (35)	132 (32)	228 (29)
Intensive induction therapy				
Yes	127 (100)	45 (15)	305 (46)	477 (44)
No	0 (0)	259 (85)	358 (54)	617 (56)
Auto-HCT in CR1				
Yes	104 (82)	86 (28)	316 (51)	506 (48)
No	23 (18)	218 (72)	310 (49)	551 (52)
Ki-67 percentage				
≤30%	62 (84)	-	162 (52)	224 (58)
>30%	12 (16)	-	149 (48)	161 (42)
Median f/up in years	8.5	8.0	3.5	5.0

Of note, the data on blastoid histology were only available in the MCL-RCS data set. Among the patients with available data (n = 534), only 15% (n = 81) had blastoid histology.
auto-HCT, autologous hematopoietic cell transplantation; CR1, first complete remission; f/up, follow-up.
*The MIPI score from the ALLIANCE data set was generated from the integer value of 0 to 8 giving us the distribution as outlined in the Table. This is different from what is reported in the ALLIANCE publications which used 0 to 3, 4 to 5, and 6 to 8 as low, intermediate, and high risk, respectively.

Table 2. Patient characteristics by time from diagnosis to first treatment

Covariate	Time to first treatment		*P* value
	0-14 d, N = 300, n (%)	15-60 d, N = 797, n (%)	
Data set			
MER	107 (36)	197 (25)	
ALLIANCE	13 (4)	114 (14)	
MCL-RCS	180 (60)	486 (61)	
Age at diagnosis, y			.70
Median	63	62	
Range	32-95	29-96	
Sex			.85
Female	71 (24)	185 (23)	
Male	228 (76)	612 (77)	
Race			.09
White	273 (94)	697 (91)	
Black	5 (2)	35 (5)	
Others	11 (4)	29 (4)	
ECOG PS			**<.001**
0	134 (50)	467 (63)	
1	96 (36)	239 (33)	
≥2	37 (14)	30 (4)	
Ann Arbor stage			**.009**
1-3	28 (9)	124 (16)	
4	267 (91)	667 (84)	
LDH			**<.001**
Normal	107 (50)	407 (64)	
Elevated	106 (50)	226 (36)	
BM involvement			**.005**
No	30 (11)	135 (19)	
Yes	231 (89)	571 (81)	
B symptoms			**.02**
No	180 (65)	558 (72)	
Yes	97 (35)	212 (28)	
MIPI			**<.001**
<5.7	62 (31)	277 (47)	
≥5.7 <6.2	50 (25)	170 (29)	
≥6.2	88 (44)	140 (24)	
Intensive induction therapy			**.001**
No	192 (64)	425 (53)	
Yes	107 (36)	370 (47)	
Ki-67 percentage			**.007**
≤30%	37 (45)	187 (62)	
>30%	45 (55)	116 (38)	

Boldface value signifies statistically significant value.

Patients initially managed with observation were excluded. DTI was defined as the time in days from the date of diagnosis to the initiation of therapy. The date of diagnosis was the date of the first biopsy that confirmed a diagnosis of MCL. Patients were stratified into 2 groups, 0 to 14 days (short DTI) and 15 to 60 days (long DTI). Patients who initiated therapy >60 days after diagnosis were excluded based on prior work highlighting an excellent prognosis for patients where initial therapy is deferred.[12-14]

Study end points and definitions

The primary end point for outcome analysis was overall survival (OS), whereas the secondary end point was PFS. OS was defined as the time from first treatment to death or last follow-up. Patients not experiencing an event were censored at their last known follow-up. PFS was defined as the time from first treatment to progression or death; the MER study included initiation of second line therapy as an event for PFS. supplemental Table 1 shows the breakdown of the intensive induction therapies among the 3 cohorts.

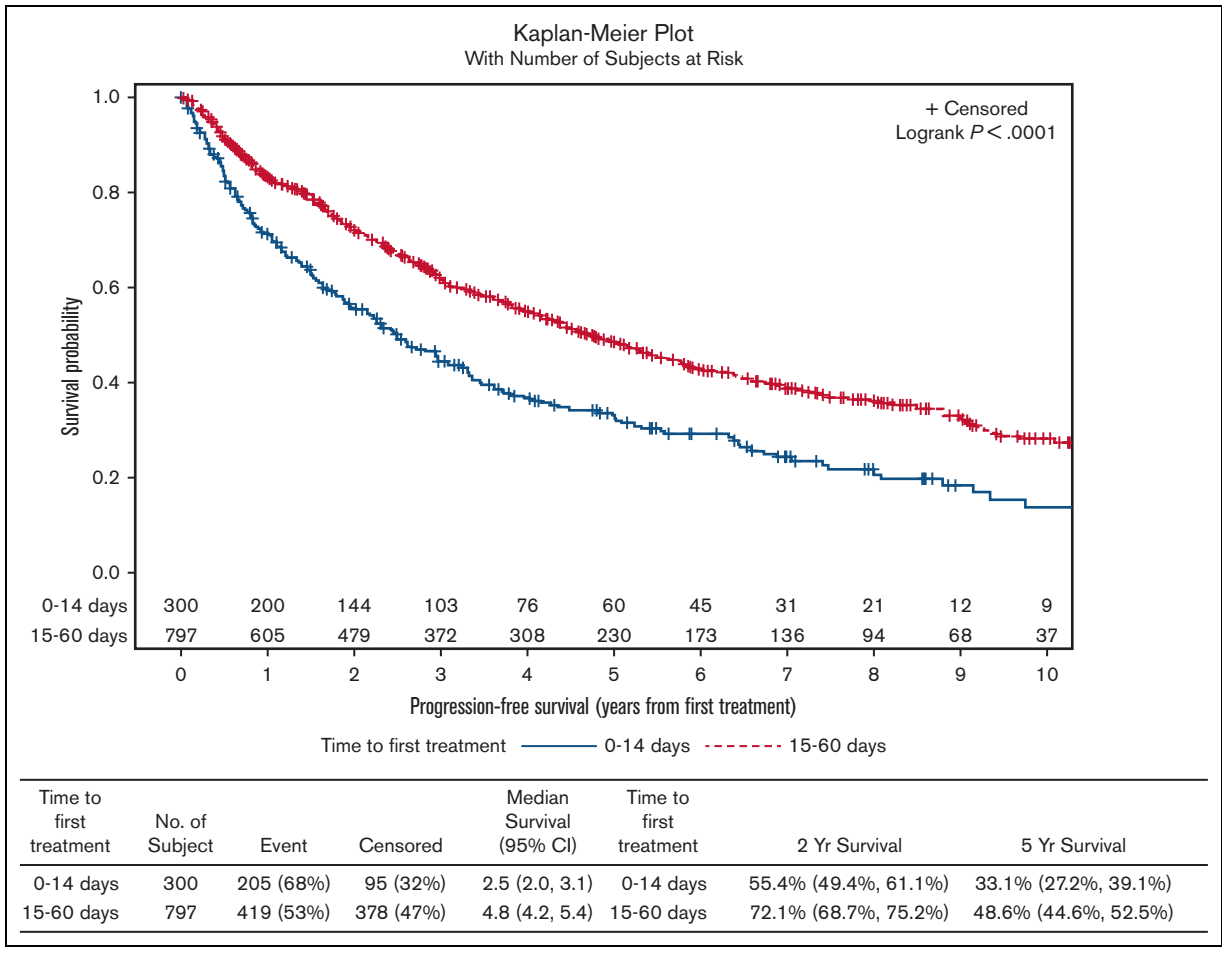
Statistical considerations

Descriptive statistics were generated for categorical variables using frequencies and percentages, and for continuous variables using mean, median, standard deviation, and range. DTI groups were compared using analysis of variance for continuous variables and using χ^2 or Fisher exact tests for categorical variables. OS and PFS were estimated from the start of first treatment using the Kaplan-Meier method and were compared using log-rank tests. Univariate Cox proportional hazards models were fit for OS and PFS as a function of the DTI group, and other relevant patient and treatment characteristics. Multivariable Cox models were fit as a function of DTI group, sex, stage, bone marrow (BM) involvement, B symptoms, MCL International Prognostic Index (MIPI), and intensive induction therapy. For multivariable models, a complete case analysis was utilized, such that patients missing 1 model covariate were excluded from the model. Model assumptions were assessed and verified. Adjusted Kaplan-Meier plots were created, by reweighting observations by the propensity of receipt of short DTI. In addition, as a sensitivity analysis, DTI was converted into a weekly variable (0-6 days, 7-13 days, etc), and placed into multivariable Cox models as a continuous variable with MIPI and intensive induction therapy. Of note, a restricted quadratic spline was fit for time from diagnosis to first treatment (in days) as a function of the relative hazard of death, using knots assessed at the 20th, 40th, 60th, and 80th percentiles.[15] This was performed to verify the use of the predefined clinical cut-off point of 14 days for the time from diagnosis to first treatment. Statistical analysis was conducted using SAS 9.4 (SAS Institute Inc, Cary, NC), and statistical significance was assessed at the 0.05 level.

Results

Patient characteristics

A total of 1097 patients newly diagnosed with MCL and available DTI were included in the study (see CONSORT, Figure 1). 27% (n = 300) had short DTI, whereas 73% (n = 797) had long DTI. Median DTI was 8 days (interquartile range [IQR], 5-12 days) for the short DTI group vs 31 days for the longer DTI group (IQR, 23-42 days). Table 1 shows



Time to first treatment	No. of Subject	Event	Censored	Median Survival (95% CI)	Time to first treatment	2 Yr Survival	5 Yr Survival
0-14 days	300	205 (68%)	95 (32%)	2.5 (2.0, 3.1)	0-14 days	55.4% (49.4%, 61.1%)	33.1% (27.2%, 39.1%)
15-60 days	797	419 (53%)	378 (47%)	4.8 (4.2, 5.4)	15-60 days	72.1% (68.7%, 75.2%)	48.6% (44.6%, 52.5%)

Figure 2. PFS of short vs long DTI in patients with MCL.

the baseline characteristics stratified by the 3 datasets (MER, ALLIANCE, and MCL-RCS). The median age at diagnosis was 63 years (range, 29-96 years), the majority sex was male (77%), and the majority race was White (92%). Most patients had stage IV disease (86%). MIPI was low, intermediate, and high in 43%, 28%, and 29%, respectively. The median follow-up was 8 years, 8.5 years, and 3.5 years in the MER, ALLIANCE, and MCL-RCS cohorts, respectively.

Association of short DTI with prognostic factors at diagnosis

Short DTI was associated with several adverse prognostic factors at diagnosis (see Table 2). Compared with patients who initiated treatment 15 to 60 days after diagnosis, patients who started treatment within 14 days had worse eastern cooperative oncology group performance status (ECOG PS ≥2; 14% vs 4%; $P < .01$), more frequently elevated lactate dehydrogenase (LDH) levels (elevated LDH levels, 50% vs 36%; $P < .01$), and higher MIPI (MIPI ≥6.2; 44% vs 24%; $P < .001$), with more modest differences observed for bone marrow (BM) involvement (89% vs 81%; $P = .005$), B symptoms (35% vs 28%; $P = .02$), stage IV disease (91% vs 84%; $P = .009$), and lack of receipt of intensive induction therapy (64% vs 53%; $P = .001$).

Association of short DTI with survival

The median PFS was 2.5 years (95% confidence interval [CI], 2.0-3.1) for patients with short DTI and 4.8 years (95% CI, 4.2-5.4) for patients with longer DTI (Figure 2, log-rank $P < .0001$). A similar trend was seen when the analysis was restricted to the recipients of intensive induction therapy (short vs long DTI, median PFS was 3.3 years vs 6.3 years, respectively; $P < .001$; supplemental Figure 1). In the univariate analysis, short DTI was associated with significantly inferior PFS (hazard ratio [HR], 1.69; 95% CI, 1.43-2.00; $P < .001$). Other factors that showed significant association with PFS are shown in supplemental Table 2. After adjusting for covariates (sex, stage, BM involvement, B symptoms, MIPI score, and intensive induction therapy, supplemental Table 3) that were significant in the univariate analysis, short DTI remained associated with significantly inferior PFS than long DTI (HR, 1.50; 95% CI, 1.20-1.87; $P < .001$) in the multivariable analysis (see adjusted PFS in supplemental Figure 2). Other factors that were associated with inferior PFS in the multivariable analysis (Table 3) included male sex (HR, 1.39; 95% CI, 1.08-1.80; $P = .01$) and higher MIPI (MIPI ≥6.2; HR, 1.65; 95% CI, 1.27-2.15; $P < .001$), whereas recipients of intensive induction therapy had longer PFS (HR, 0.69; 95% CI, 0.56-0.86; $P = .001$).

The median OS was 7.8 years (95% CI, 6.7-9.1) for the short DTI group and 11.8 years (95% CI, 9.9-14.3) for the longer DTI group (Figure 3, log-rank $P < .0001$). A similar trend was seen when the analysis was restricted to the recipients of intensive induction therapy (short vs long DTI, median OS was 8.8 years vs not reached, respectively; $P = .008$; supplemental Figure 3). In the univariate analysis, short DTI was associated with significantly inferior OS (HR, 1.66; 95% CI, 1.34-2.06; $P < .001$). Other factors that were significantly associated with OS are shown in supplemental Table 4. After adjusting for covariates (sex, stage, BM involvement, B symptoms, MIPI score, and intensive induction therapy; Table 4) that were significant in the univariate analysis, short DTI remained associated with significantly inferior OS than long DTI (HR, 1.57; 95% CI, 1.20-2.06; $P < .001$) in the multivariable analysis (see adjusted OS in supplemental Figure 4). Other factors that were associated with inferior OS in the multivariable analysis (Table 4) included male sex (HR, 1.60; 95% CI, 1.15-2.23; $P = .005$) and higher MIPI (MIPI ≥6.2; HR, 2.50; 95% CI, 1.81-3.46; $P < .001$).

Sensitivity analysis

On analyzing the DTI as a continuous variable, we noted that there was an improvement in PFS (HR, 0.86; 95% CI, 0.82-0.91; $P < .001$; supplemental Table 4) and OS (HR, 0.91; 95% CI, 0.85-0.98; $P = .009$; supplemental Table 5) for every week beyond diagnosis after adjusting for other significant covariates in the multivariable analysis. supplemental Figures 5 and 6 show KM curves for DTI per week. We also analyzed DTI in a nonlinear way (spline curves). The spline curve indicates that survival starts to improve significantly after the 14-day mark for time from diagnosis to first treatment (supplemental Figure 7). Because a greater proportion of patients in the ALLIANCE were in the longer DTI group (~90%), additional analysis was performed excluding the ALLIANCE patient population. The results remained in line with the main analysis with inferior PFS (HR, 1.44; 95% CI, 1.13-1.82; $P = .003$; supplemental Table 6) and OS (HR, 1.62; 95% CI, 1.21-2.16; $P = .001$, supplemental Table 7) in the short DTI cohort compared with those in the longer DTI group after adjusting for other covariates in the multivariable analysis.

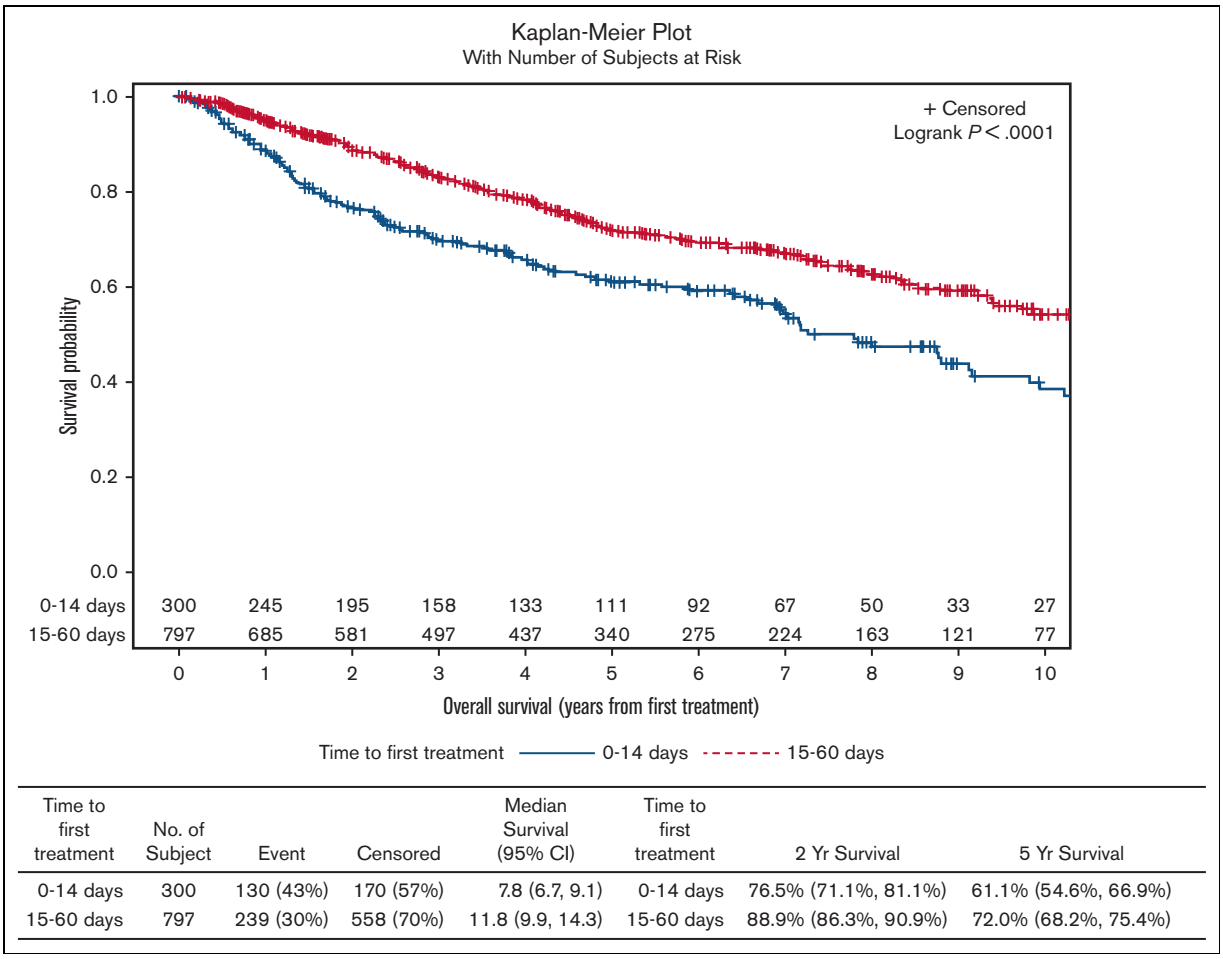
Subgroup analysis

To understand the clinical trial enrollment in the real-world setting, we evaluated the patients in the MCL-RCS. Among the 666 patients in

Table 3. Multivariable analysis of PFS

Covariate	HR (95% CI)	*P* value
Time to first treatment		
15-60 d	Referent	
0-14 d	1.50 (1.20-1.87)	**<.001**
Sex		
Female	Referent	
Male	1.39 (1.08-1.80)	**.01**
Ann Arbor stage		
1-3	Referent	
4	0.90 (0.58-1.39)	.63
BM involvement		
No	Referent	
Yes	1.40 (0.92-2.14)	.12
B symptoms		
No	Referent	
Yes	1.20 (0.95-1.51)	.12
MIPI		
<5.7	Referent	
≥5.7 <6.2	1.23 (0.95-1.58)	.12
≥6.2	1.65 (1.27-2.15)	**<.001**
Intensive induction therapy		
No	Referent	
Yes	0.69 (0.56-0.86)	**.001**

Boldface value signifies statistically significant value.



Time to first treatment	No. of Subject	Event	Censored	Median Survival (95% CI)	Time to first treatment	2 Yr Survival	5 Yr Survival
0-14 days	300	130 (43%)	170 (57%)	7.8 (6.7, 9.1)	0-14 days	76.5% (71.1%, 81.1%)	61.1% (54.6%, 66.9%)
15-60 days	797	239 (30%)	558 (70%)	11.8 (9.9, 14.3)	15-60 days	88.9% (86.3%, 90.9%)	72.0% (68.2%, 75.4%)

Figure 3. OS of short vs long DTI in patients with MCL.

the MCL-RCS, 39 had missing data on the clinical trial enrollment leaving 627 evaluable patients. Among the 163 patients with short DTI, only 13% (n = 21) were treated on a clinical trial in contrast to 20% (n = 94) of patients in the longer DTI (n = 464) cohort, which was significantly different between the 2 groups ($P = .03$).

Information on Ki-67 percentage score was available in 428 patients (ALLIANCE and MCL-RCS) with 94 in the short DTI group and 334 in the long DTI group. Ki-67 was >30% in 45 of 82 (55%) patients in the short DTI group and in 116 of 303 (38%) in the long DTI group ($P = .007$). The data on complex karyotype (defined as >3 cytogenetic abnormalities) were available in 280 patients (all in MCL-RCS) with 78 in the short DTI group and 202 in the long DTI group. Complex karyotype was present in 22 of 78 (28%) patients in the short DTI group and in 29 of 202 (14%) in the long DTI group ($P = .007$). *TP53* mutation data were available only in 90 patients (all in the MCL-RCS) with 29 in the short DTI group and 61 in the long DTI group. *TP53* mutation was present in 13 of 29 (45%) patients in the short DTI group and in 27 of 61 (44%) in the long DTI group ($P = .96$).

Discussion

In this pooled analysis of 3 large datasets, we found that DTI is a simple yet important variable that has a significant association with outcomes in patients newly diagnosed with MCL and make several important observations. Firstly, patients with short DTI have significantly inferior survival (both PFS and OS) relative to long DTI in patients with newly diagnosed MCL. Secondly, short DTI ranged from modest to strongly associated with several adverse disease related prognostic factors, most notably for poor ECOG PS, elevated LDH, and high MIPI. Thirdly, the prognostic value of DTI remained after adjustment for MIPI. And lastly, the effect between DTI and outcomes appears to be continuous.

The association of short DTI with inferior survival in our study is similar to what has been shown in the DLBCL literature,[5] in which the patients with short DTI had worse EFS24 than those with longer DTI. The prognostic relevance of MIPI score[16] is well known in MCL. In our study, we found that the prognostic impact of DTI in newly diagnosed MCL was independent of the MIPI, similar to the prognostic value of DTI independent of IPI in DLBCL.[5] The prognostic relevance of Ki-67 with a cut-off of 30% has been well validated in patients with MCL.[17,18] Hence, we evaluated the impact of Ki-67 >30% on DTI and found that a significantly higher proportion of patients with short DTI had Ki-67 >30% than those with long DTI (55% vs 38%; $P = .007$). Other molecular characteristics such as *TP53* mutation and complex karyotype at diagnosis have also been shown to be associated with worse outcomes.[4,19] Therefore, we looked at these variables in our study.

Table 4. Multivariable analysis of OS

Covariate	HR (95% CI)	*P* value
Time to first treatment		
15-60 d	Referent	
0-14 d	1.57 (1.20-2.06)	**<.001**
Sex		
Female	Referent	
Male	1.60 (1.15-2.23)	**.005**
Ann Arbor stage		
1-3	Referent	
4	1.02 (0.56-1.87)	.94
BM involvement		
No	Referent	
Yes	1.25 (0.71-2.21)	.44
B symptoms		
No	Referent	
Yes	1.13 (0.85-1.51)	.38
MIPI		
<5.7	Referent	
≥5.7 <6.2	1.28 (0.92-1.79)	.14
≥6.2	2.50 (1.81-3.46)	**<.001**
Intensive induction therapy		
No	Referent	
Yes	0.77 (0.59-1.01)	.06

Boldface value signifies statistically significant value.

Although we found no significant association between DTI and *TP53* mutation status ($P = .96$), patients with short DTI had a significantly greater proportion complex karyotypes than those with long DTI (28% vs 14%; $P = .007$). The findings noted in the current study have important consequences for clinical trial design and interpretation in MCL. For instance, in the ALLIANCE trial, 90% of the patients who were newly diagnosed, received first-line therapy beyond 14 days. A similar pattern was noted in those receiving first-line therapy on a clinical trial in MCL-RCS. Also, the prognostic relevance of short DTI persisted even after subsetting to more aggressive therapy (recipients of intensive induction therapy only), likely reflecting a function of disease aggressiveness and needs to be factored in while designing clinical trials in MCL. As the DTI has an independent association with outcomes beyond established clinico-biological prognostic factors, the current inclusion criteria for a clinical trial are not sufficient for patient selection in a non-biased manner. In addition, the clinical trials should be able to facilitate enrollment of patients requiring urgent therapy, including potentially permitting a cycle of off-study treatment to manage symptoms while a patient is screened and enrolled. The strengths of the study include large sample size and inclusion of patients from 2 prospective cohorts and a large multisite retrospective cohort providing a good mix of patients and a better perspective on the scope of the problem. Although we looked at the association of DTI with molecular characteristics such as complex karyotype and *TP53* mutation, these results need to be interpreted with caution given the small sample size and the selected subset of the data. In conclusion, we show that DTI is an important prognostic factor in patients newly diagnosed with MCL and is strongly associated with adverse clinical factors and poor outcomes. DTI should be reported in all the patients newly diagnosed with MCL who are enrolling in clinical trials and steps must be taken to ensure selection bias because of treatment delays in these patients is avoided.

Acknowledgments

Research reported in this publication was supported in part by the Biostatistics Shared Resource of Winship Cancer Institute of Emory University and National Institutes of Health/National Cancer Institute under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

This study was funded by MER (P50 CA97274 and U01 CA195568).

Authorship

Contribution: N.E., M.J.M., and J.B.C. contributed to the concept and study design; N.E. prepared the first draft of the manuscript; and all authors analyzed and interpreted data, reviewed the first draft of manuscript, provided critical scientific input, gave final approval for manuscript, and were accountable for all aspects of the work.

Conflict-of-interest disclosure: N.E. received research funding from BeiGene; is a member on the speakers bureau for Incyte; and receives honoraria from and is a consultant for advisory boards for TG Therapeutics, Pharmacyclics, BeiGene, Seattle Genetics, and Novartis. V.B. receives research funding from Incyte, Gamida Cell, and Citius Pharmaceuticals; is a member on safety monitoring committee for Celgene; and is a member on the advisory board for Bristol Meyers Squibb, Fate Therapeutics, Karyopharm, ADC Therapeutics, and AstraZeneca. J.N.G. is a member on the advisory board for AbbVie and Genentech and reports research funding from LOXO. S.K.B. provides consultancy for Monsanto and receives honoraria from Atara, Seattle Genetics, Janssen, and Pfizer. A.V.D. reports consulting fees from AbbVie, AstraZeneca, Bayer Oncology, BeiGene, Bristol Meyers Squibb, Genentech, Genmab, Incyte, Lilly Oncology, Nurix Therapeutics, Oncovalent, Pharmacyclics, and TG Therapeutics, and has ongoing research funding from AbbVie, AstraZeneca, Bayer Oncology, Bristol Meyers Squibb, Cyclacel, MEI Pharma, Nurix Therapeutics, and Takeda Oncology. A.V.D. is an LLS Scholar in clinical research. N.S.G. provides consulting for Tessa and Novartis; is a member on advisory board for ADC Therapeutics and Kite; and receives research funding from Genentech. R.K. is a member on advisory board for Celgene Corporation, Gilead Sciences, Juno Therapeutics, Kite Pharma, Janssen, Karyopharm, Pharmacyclics, Morphosys, Epizyme, Genentech/Roche, EUSA, and Calithera; reports grants/research support from Celgene Corporation/Juno Therapeutics/Bristol Meyers Squibb, Takeda, BeiGene, and Gilead Sciences/Kite; and is a member on speakers bureau for AstraZeneca, BeiGene, and MorphoSys. Y.S. receives research funding from Bristol Meyers Squibb, Celgene, TG Therapeutics, and BeiGene and provides consultation/advisory for TG Therapeutics and Epizyme. B.T.H. receives honoraria from Pharmacyclics, Gilead Sciences, Genentech, AbbVie, Bayer, AstraZeneca, Novartis, Pfizer, Celgene, Karyopharm Therapeutics, Epizyme, BeiGene, and MorphoSys; provides consulting or advisory role for Novartis, Genentech, AbbVie, Gilead Sciences, Karyopharm Therapeutics, AstraZeneca,

Epizyme, MorphoSys, and BeiGene; and reports research funding from AbbVie (to institution), Karyopharm Therapeutics (to institution), Celgene (to institution), Takeda (to institution), Amgen (to institution), Genentech (to institution), Kite/Gilead (to institution), and TG Therapeutics (to institution). N.G. has received consulting fees from Seagen, TG Therapeutics, AstraZeneca, Phamacyclics, Janssen, Bristol Myers Squibb, Gilead Sciences, BeiGene, Incyte, Karyopharm, Roche/Genentech, Novartis, Loxo Oncology, Genmab, Adaptive Biotech, and ADC Therapeutics; previously served on speaker's bureau for Gilead, AstraZeneca, Bristol Myers Squibb, Phamacyclics, Janssen, and Epizyme; and has received research funding from TG Therapeutics, Genentech/Roche, Bristol Myers Squibb, Gilead, MorphoSys, and AbbVie. S.I.P. is a consultant for BMS, G1 Therapeutics, and Teva; is a member on advisory boards for Rafael Pharma and Takeda; and receives research funding from Bristol Meyers Squibb, Teva, Seattle Genetics, and Takeda. D.A.B. is a consultant and receives honoraria from Kite/Gilead and Seagen and receives research funding from Novartis and Nurix Therapeutics. M.H. provides consultancy for Incyte Corporation, ADC Therapeutics, Pharmacyclics, Omeros, Genmab, MorphoSys, Kadmon, Kite, Novartis, AbbVie, Legend, Gamida Cell, and Seagen and is a member on speaker's bureaus for Sanofi Genzyme, AstraZeneca, BeiGene, and ADC Therapeutics. T.S.F. reports funding from AstraZeneca (speaking), BeiGene (speaking), Kile/Gilead (speaking and consulting), Seagen (speaking and consulting), and TG Therapeutics (speaking). P.M. provides a consulting or advisory role for Janssen, BeiGene, Karyopharm Therapeutics, Kite/Gilead, Verastem, ADC Therapeutics, Bristol Myers Squibb/Celgene, Epizyme, Merck, MorphoSys, and Takeda and receives research funding from Karyopharm Therapeutics (to institution). B.S.K. provides consulting or advisory role for Celgene, AbbVie, Pharmacyclics, Acerta Pharma, ADC Therapeutics, Genentech, Roche, AstraZeneca, BeiGene, Bayer, MEI Pharma, Kite/Gilead, MorphoSys, Janssen, Bristol Myers Squibb, Incyte, and Genmab, and receives research funding from Genentech (to institution), Acerta Pharma (to institution), ADC Therapeutics (to institution), and Celgene (to institution). C.R.F. is a consultant for AstraZeneca, Bayer, BeiGene, BioAscend, Bristol Myers Squibb, Celgene, Curio Sciences, Denovo Biopharma, Epizyme/Incyte, Foresight Diagnostics, Genentech/Roche, Genmab, MEI Pharmaceuticals, MorphoSys AG, Pharmacyclics/Janssen, and Seagen, and receives research funding from 4D, AbbVie, Acerta, Adaptimmune, Allogene, Amgen, Bayer, Celgene, Cellectis, Emanuel Merck, Darmstadt, Gilead, Genentech/Roche, Guardant, Iovance, Janssen Pharmaceutical, Kite, Morphosys, Nektar, Novartis, Pfizer, Pharmacyclics, Sanofi, Takeda, TG Therapeutics, Xencor, Ziopharm, Burroughs Wellcome Fund, Eastern Cooperative Oncology Group, National Cancer Institute, V Foundation, and Cancer Prevention and Research Institute of Texas: CPRIT Scholar in Cancer Research. B.K.L. provides compensated consulting and is a member on data and safety monitoring board for MEI Inc. and receives research support form Janssen and Genmab. A.L.F. receives research funding from Seattle Genetic; is an inventor on unlicensed patents held by Mayo Clinic; and has intellectual property licensed to Zeno Pharmaceuticals. E.D.H. has sponsored research support (institution) from Eli Lilly and Virtuoso Therapeutics and provides consultancy for CytomX, Astellas, Novartis, and Abcon Therapeutics. K.M. receives research funding from Pharmacyclics, Pfizer, and BMS; provides consulting/advisory role for AbbVie, ADC, Acerta, AstraZeneca, BeiGene, Bristol Meyers Squibb, Celgene, Genmab, Genentech, Gilead, Incyte, Janssen, Kite, Lilly, MorphoSys, and Pharmacyclics. N.L.B. receives research funding from ADC Therapeutics, Autolus, Bristol Meyers Squibb, Celgene, Forty-Seven, Genentech, Immune Design, Janssen, Merck, Millennium, Pharmacyclics, Affirmed Therapeutics, Dynavax, Gilead, MedImmune, and Novartis; provides consulting/advisory board for Kite Pharma, Pfizer, ADC Therapeutics, Roche/Genentech, Seattle Genetics, BTG, and Acerta. G.S. receives honoraria from Kite Pharmaceuticals and BeiGene. J.R.C. receives grant funding from Bristol Meyers Squibb and Genmab; receives grant funding and is member on the scientific advisory board for Genentech; and is a member on the safety monitoring committee for Protagonist Therapeutics, unrelated to this project. T.M.H. is a member on data monitoring committees for Seagen and Tess Therapeutics; is a member on scientific advisory board for Eli Lilly & Co., Morphosys, Incyte, BeiGene, and Loxo Oncology; and reports research support grants from Genentech. M.J.M. receives research funding from Bristol Meyers Squibb, Genentech/Roche, Morphosys, and Genmab, and is a member on advisory boards for Genmab and Adaptive Biotechnologies. J.B.C. provides consulting or advisory role for AbbVie, Janssen, Loxo, Kite/Gilead, AstraZeneca, Aptitude Medical, Adicet Bio, and Adaptive Biotechnologies and receives research funding from Bristol Myers Squibb (to institution), Janssen (to institution), Novartis (to institution), Takeda (to institution), AI Therapeutics (to institution), Genentech (to institution), ASH (to institution), Lymphoma Research Foundation (to institution), Loxo (to institution), BioInvent (to institution), and AstraZeneca (to institution). The remaining authors declare no competing financial interests.

ORCID profiles: N.E., 0000-0002-8216-3457; J.S., 0000-0002-5563-9325; N.S.G., 0000-0002-1346-3157; M.B., 0000-0002-5105-0564; R.K., 0000-0003-0984-4376; Y.S., 0000-0001-6355-3671; N.G., 0000-0002-3848-6136; S.I.P., 0000-0001-5674-6408; D.A.B., 0000-0003-0773-1829; M.H., 0000-0001-5372-510X; B.S.K., 0000-0003-0459-6609; B.K.L., 0000-0001-5084-0698; A.L.F., 0000-0001-5009-4808; E.D.H., 0000-0001-8623-4067; N.L.B., 0000-0001-8470-394X; J.R.C., 0000-0002-7482-178X; M.J.M., 0000-0002-1867-0526; J.B.C., 0000-0002-2723-6481.

Correspondence: Narendranath Epperla, The Ohio State University Comprehensive Cancer Center, 1110E Lincoln Tower, 1800 Cannon Dr, Columbus, OH 43210; email: narendranath.epperla@osumc.edu.

References

1. Perez-Galan P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood*. 2011;117(1):26-38.

2. Zhou Y, Wang H, Fang W, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. *Cancer*. 2008;113(4):791-798.
3. Epperla N, Hamadani M, Fenske TS, Costa LJ. Incidence and survival trends in mantle cell lymphoma. *Br J Haematol*. 2018;181(5):703-706.
4. Eskelund CW, Dahl C, Hansen JW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood*. 2017;130(17):1903-1910.
5. Maurer MJ, Ghesquières H, Link BK, et al. Diagnosis-to-treatment interval is an important clinical factor in newly diagnosed diffuse large B-cell lymphoma and has implication for bias in clinical trials. *J Clin Oncol*. 2018;36(16):1603-1610.
6. Alig S, Macaulay CW, Kurtz DM, et al. Short diagnosis-to-treatment interval is associated with higher circulating tumor DNA levels in diffuse large B-cell lymphoma. *J Clin Oncol*. 2021;39(23):2605-2616.
7. Olszewski AJ, Ollila T, Reagan JL. Time to treatment is an independent prognostic factor in aggressive non-Hodgkin lymphomas. *Br J Haematol*. 2018;181(4):495-504.
8. Cerhan JR, Link BK, Habermann TM, et al. Cohort Profile: the lymphoma specialized program of research excellence (SPORE) molecular epidemiology resource (MER) cohort study. *Int J Epidemiol*. 2017;46(6):1753-1754i.
9. Kaplan LD, Maurer MJ, Stock W, et al. Bortezomib consolidation or maintenance following immunochemotherapy and autologous stem cell transplantation for mantle cell lymphoma: CALGB/Alliance 50403. *Am J Hematol*. 2020;95(6):583-593.
10. Shanmugasundaram K, Goyal S, Switchenko J, et al. Intensive induction regimens after deferring initial therapy for mantle cell lymphoma are not associated with improved survival. *Eur J Haematol*. 2021;107(3):301-310.
11. Bond DA, Switchenko JM, Villa D, et al. Early relapse identifies MCL patients with inferior survival after intensive or less intensive frontline therapy. *Blood Adv*. 2021;5(23):5179-5189.
12. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol*. 2009;27(8):1209-1213.
13. Cohen JB, Han X, Jemal A, Ward EM, Flowers CR. Deferred therapy is associated with improved overall survival in patients with newly diagnosed mantle cell lymphoma. *Cancer*. 2016;122(15):2356-2363.
14. Abrisqueta P, Scott DW, Slack GW, et al. Observation as the initial management strategy in patients with mantle cell lymphoma. *Ann Oncol*. 2017;28(10):2489-2495.
15. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ Jr. Splines for trend analysis and continuous confounder control. *Epidemiology*. 2011;22(6):874-875.
16. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. 2008;111(2):558-565.
17. Determann O, Hoster E, Ott G, et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. *Blood*. 2008;111(4):2385-2387.
18. Hoster E, Rosenwald A, Berger F, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomized trials of the european mantle cell lymphoma network. *J Clin Oncol*. 2016;34(12):1386-1394.
19. Greenwell IB, Staton AD, Lee MJ, et al. Complex karyotype in patients with mantle cell lymphoma predicts inferior survival and poor response to intensive induction therapy. *Cancer*. 2018;124(11):2306-2315.