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LYMPHOID NEOPLASIA

Early time to relapse as a survival prognosticator in nodal mature T-cell lymphomas: results from the PETAL consortium

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KEY POINTS

- **Patients with nMTCL with TTR12 from initial therapy have worse survival and distinct subsequent therapeutic responses.**
- **Poor OS effect of TTR12 is consistent across sensitivity, validation, and subgroup analyses, including histological and high-risk subgroups.**

We assessed the overall survival (OS) impact of time to relapse (TTR) in multinational cohorts with independent observational and randomized validation. Patients with nMTCL with frontline complete response were assigned to TTR12 (≤12 months) or without TTR12 based on time to progression or next therapy. OS analyses included modified landmark (m-LM), standard landmark (s-LM), and time-dependent Cox (td-Cox), adjusting for age, histology, and prognostic index for T-cell lymphoma (PIT) score. Across 452 patients, 165 (36.5%) had TTR12, 181 (40%) relapsed at ≥12 months, and 106 (23.5%) remained relapse-free. TTR12 conferred worse OS using m-LM (hazard ratio [HR], 2.14; 95% confidence interval [CI], 1.58-2.90; *P* < .001), s-LM (HR, 1.92; 95% CI, 1.39-2.66; *P* < .001); and td-Cox (HR, 5.81; 95% CI, 2.94-11.46; *P* < .001). Results were consistent in the independent validation cohorts. TTR12 consistently conferred worse OS irrespective of frontline stem cell transplantation or PIT score, in peripheral T-cell lymphoma, not otherwise specified (m-LM: HR, 2.32; 95% CI, 1.51-3.55; *P* < .001; s-LM: HR, 2.10; 95% CI, 1.33-3.31; *P* = .001), anaplastic large cell lymphoma (m-LM: HR, 3.34; 95% CI, 1.18-9.50; *P* = .023; s-LM: HR, 2.96; 95% CI, 1.02-8.81; *P* = .046), and angioimmunoblastic T-cell/T follicular helper cell lymphoma (m-LM only: HR, 1.92; 95% CI, 1.15-3.21; *P* = .013). Second-line novel therapies improved OS (second-line start to death) vs chemotherapy in TTR12 only (HR, 0.60; 95% CI, 0.37-0.97; *P* = .038; without TTR12: HR, 0.82; 95% CI, 0.51-1.32; *P* = .407). TTR12 serves as a prognostic and potential OS surrogate marker, supporting stratification of new risk groups and need for their differential treatment.

Introduction

Despite significant differences in pathologic and molecular heterogeneity in nodal mature T-cell lymphomas (nMTCL), they are mostly treated empirically with anthracycline-based first-line (1L) treatments.[1-3] Treatment response and outcomes are diverse, ranging from a 3- to 5-year overall survival (OS) of 30% to 65%.[3-8] Relapsed/refractory (R/R) disease after 1L therapy remains frequent. We, and other investigators, have previously demonstrated that patients with primary refractory lymphoma have a worse prognosis than those with relapsed disease, highlighting additional distinct subgroups within a high-risk population.[3,5,9] Given the heterogeneity of patients with relapsed nMTCL, we hypothesized that it might be important to delineate subsets within the relapsed group at a heightened risk of lymphoma-related death and, hence, in immediate need of innovative treatment strategies.

Time from 1L to disease progression is a significant prognosticator of treatment response and survival in follicular and mantle cell lymphomas, in which progression of disease within 24 months (POD24) of initial therapy confers poor survival in both clinical trial and real-world settings.[10-13] Landmark analyses demonstrated event-free survival at 24 months (EFS24) to have a marked association with OS in patients with peripheral T-cell lymphoma (PTCL).[14] Patients with R/R diffuse large B-cell lymphoma and Hodgkin lymphoma within 12 months after autologous hematopoietic stem cell transplant (auto-HSCT) or 1L therapy have significantly poorer survival than others with later relapse.[15,16] As such, time to relapse (TTR) is an important therapeutic decision-making factor and large clinical trials have shown differential treatment benefit of novel therapeutic agents between refractory or early (≤12 months) vs late (>12 months) relapsing groups.[16,17] These survival disparities are likely due to distinct clinical and biologic differences across lymphoma subpopulations.[18]

We examined whether varying TTR after 1L therapy in patients with nMTCL may affect survival. Given the paucity of data and the critical need to develop tools that drive therapeutic choices in patients with R/R nMTCL, we aimed to better characterize these patients with relapsed disease based on their TTR from up-front therapy and subsequently explore differential 2L (2L) therapy effects based on TTR subgroups.

Methods

Patient eligibility and study design

This was a global retrospective cohort study using data on a total of 1901 patients with nMTCL from multiple international, multicenter cohorts including the PETAL (Peripheral-T-Cell-Lymphoma) consortium and GELL (Latin American Group of Lymphoproliferative Disorders) groups previously described.[3,9,19-21] Screening included patients with a new lymphoma diagnosis between 2010 and 2021 (PETAL) and 2000 and 2023 (GELL) who had received any systemic frontline therapy. Details on patient enrollment are included in Figure 1 CONSORT diagram, and supplemental Table 1, available on the *Blood* website. Two separate, external, independent cohorts were used to validate TTR of ≤12 months from frontline therapy (TTR12) as a prognosticator of survival: (1) an observational cohort from 2 US sites (n = 138), and (2) the phase 3 randomized prospective trial of Ro-CHOP (romidepsin plus cyclophosphamide, doxorubicin, Oncovin [vincristine], and prednisone) vs CHOP, which verified pathology centrally.[22]

Patients with peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma/T follicular helper cell lymphoma (AITL/TFHL), or anaplastic large cell lymphoma (ALCL; anaplastic lymphoma kinase [ALK] positive or negative) with a complete response to systemic frontline therapy were included in the final analysis, consistent with our previous work highlighting that patients with primary refractory disease (defined as not achieving a complete response to frontline therapy) had distinctly poorer OS than those who did achieve a complete response.[3] Patients were excluded if they were missing diagnosis date, date of death, or therapy start dates. Details are included in the CONSORT diagram (Figure 1).

Outcomes and measures

The primary objective was to define the association with OS among patients with nMTCL with a complete response to frontline therapy with TTR12 compared with those without TTR12.[23,24] Patients were assigned into TTR groups based on the time from start of 1L to progression or time to next therapy (TTNT; time from 1L start to 2L start)[25] if radiologic progression information was missing. The TTR cutoff of 12 months was chosen because nearly half of patients in our cohort and previous studies of nMTCL experienced disease relapse within 12 months. (Figure 2),[4,14] however, the association with TTR cutoffs of 6, 18, and 24 months were also investigated. Patients without documented progression and who did not receive 2L were classified as not relapsed and were included in analyses as not having TTR12, and were subsequently excluded for sensitivity analyses consistent with previously described methods.[11,23,26,27] The secondary objective was to compare OS among 2L treatment modalities received (novel agents [NAs] vs cytotoxic chemotherapy [CC]) in those with and without TTR12 to interrogate the need for therapy optimization in the R/R setting.

Statistical and sensitivity analyses

Crude Kaplan-Meier methods and Cox proportional hazards models to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) were used. Median follow-up was estimated using the reverse Kaplan-Meier method.[28] A modified landmark analysis (m-LM) was used as the primary analysis with OS measured from relapse or 2L start (TTR12 group), or starting from 12 months after 1L start (without TTR12 group) to death.[13,14,23,24] Given the potential for immortal time and other bias, sensitivity analyses included a standard 12-month landmark analysis (s-LM), which excluded patients who died or were lost to follow-up before 12 months.[11,27] TTR also displayed a significant time interaction ($P < .001$). Therefore, a time-dependent Cox (td-Cox) model was used as an additional sensitivity analysis (OS measured from 1L start to death). For 2L treatment comparisons, OS was measured from 2L start to death.

All multivariable Cox proportional hazards analyses estimating aHRs and 95% CIs used for primary, sensitivity, and subgroup analyses were adjusted for a priori covariates as

previously described,[3,9] including age at time 0 of the respective methods used (ie, age at relapse or 12 months from initial therapy), histological subtype, and a prognostic index for T-cell lymphoma (PIT) score of ≥2 at diagnosis. Missing data for PIT were imputed using standard multiple imputation procedures.[29,30] Planned subgroup analyses examined the effects of TTR12 across unique histological subtypes, PIT groups, among patients who received 2L HSCT consolidation, and among multinational cohorts. Given that 2L HSCT occurs in the future relative to time 0, the effect of 2L HSCT on OS was examined in patients with and without TTR12 separately with time measured from the start of 2L therapy to death, also adjusting for 2L therapy received in addition to age at time 0, histological subtype, and PIT score.

Comprehensive details on data sets used, definitions, statistical methodology, and sensitivity and exploratory analyses can be found within supplemental Methods. The study was conducted in compliance with the Declaration of Helsinki, and approval was obtained from the institutional review board at the coordinating center (Massachusetts General Hospital, Boston, MA) and at each participating center per institutional standards.

Results

Baseline demographics, clinical characteristics, and covariates

Of 1901 patients screened, 452 were included in the final cohort and for td-Cox sensitivity analysis, 428 were included in the m-LM primary analysis, and 388 were included in the s-LM sensitivity analysis (Figure 1). A distribution of disease relapse over time highlights that approximately half had relapsed disease within 12 months and three-fourths within 2 years of starting 1L (Figure 2; supplemental Figures 1-3). Within the 452 total cohort, 165 (36.5%) had TTR12, 181 (40%) had relapsed disease at ≥12 months, and 106 (23.5%) never had relapsed disease (thus a total of 287 [63.5%] was included in the group without TTR12; Table 1). The median age at diagnosis was 58 years (range, 18-89) and 60 years (range, 15-92) in patients with TTR12 and without TTR12, respectively. PTCL-NOS encompassed 47.3% and 43.2%, AITL/TFHL 35.8% and 32.1%, and ALCL 16.4% and 24.7% of patients with TTR12 and without TTR12, respectively. Frontline anthracycline-based chemotherapy regimens (CHOP or CHOEP/EPOCH [cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone]) were administered to most patients in both cohorts (80.6% with TTR12 vs 80.0% without TTR12), and ~30% received up-front

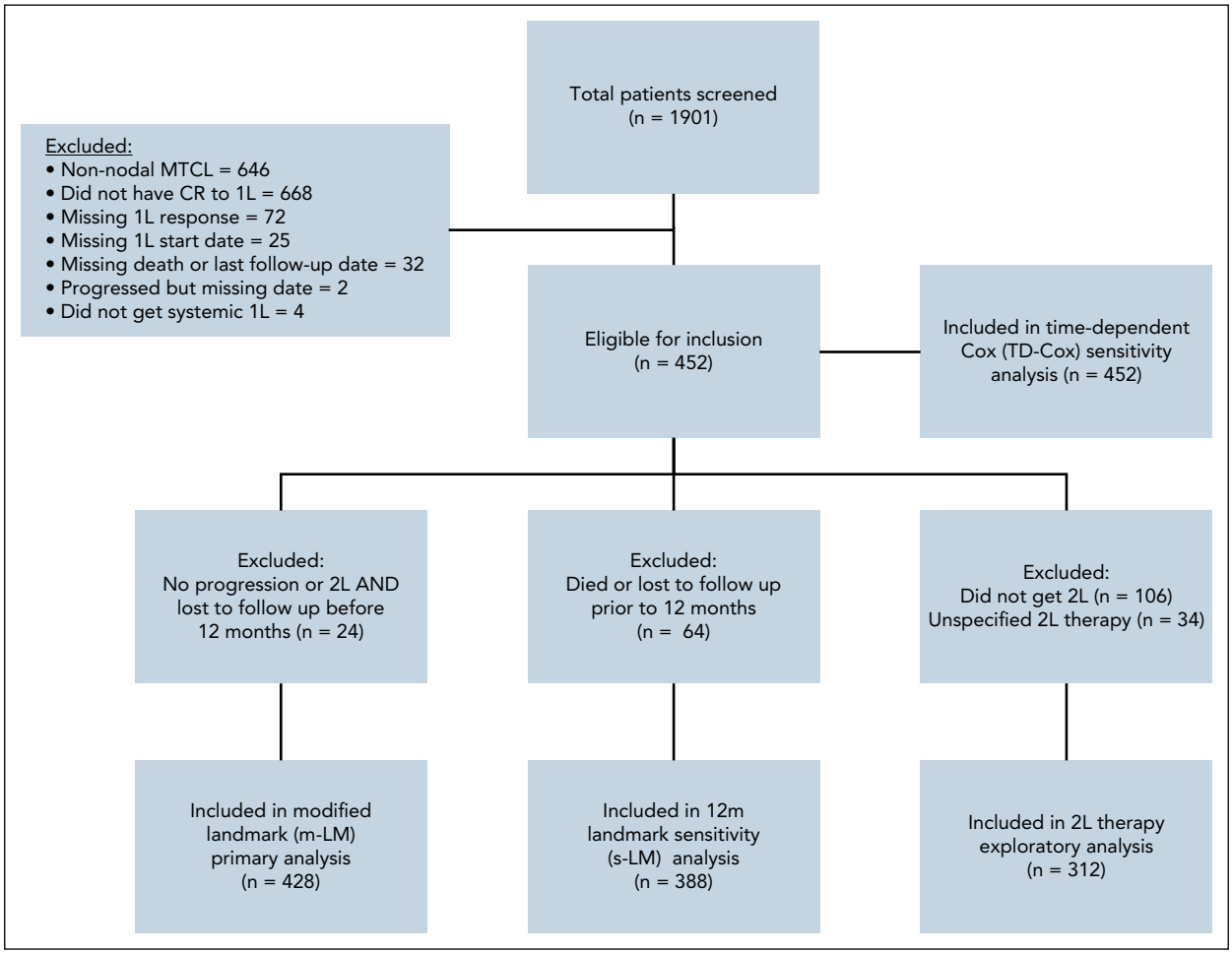


Figure 1. CONSORT diagram for participant selection. A total of 452 patients met the inclusion criteria. Consistent with methods of landmark analyses, patients were included into analyses based on their TTR and when they were lost to follow-up. The m-LM primary analysis included 428 patients, the s-LM sensitivity analysis included 388 patients, and all patients that met the inclusion criteria (n = 452) were included in the sensitivity td-Cox analysis. 1L, first-line; 2L, second-line; CR, complete response.

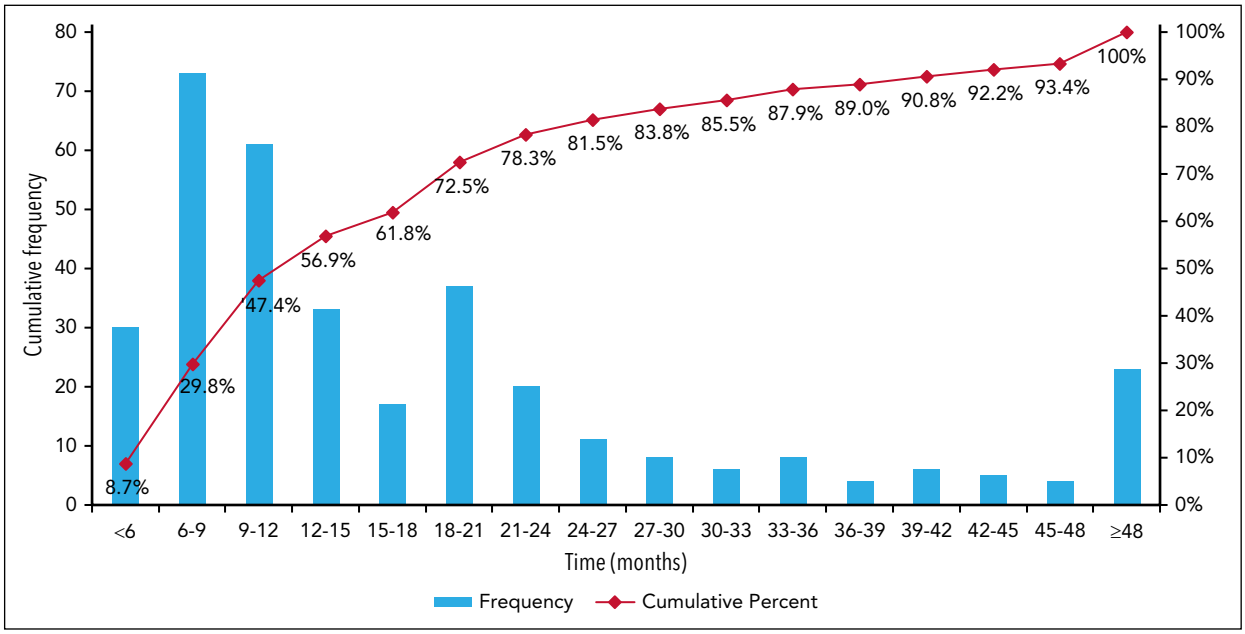


Figure 2. Distribution of disease relapse after initial therapy over time among patients with relapsed nMTCL included in analyses. The distribution and cumulative incidence of relapse among patients with nMTCL with an initial complete response to frontline therapy (n = 346). Patients with complete response to frontline therapy who were included in analyses and did not have disease progression or initiate a 2L therapy during follow-up (n = 106) are not depicted here.

autologous HSCT (30.9% in patients with TTR12% and 29.6% in those without TTR12). Details on patients included within landmark analyses and from each data set are found in supplemental Tables 2-6.

The observational validation cohort included 138 patients, with 30 (21.7%) patients having TTR12, 23 (16.7%) with relapsed disease at ≥12 months, and 85 (61.6%) without relapsed disease before the end of follow-up. Demographics largely mirror the primary cohort (supplemental Table 7). Notable differences include a generally lower rate of patients with PTCL-NOS, particularly in those without TTR12 (36.7% vs 26.9%), and higher rates of ALCL, especially in those without TTR12 (40% vs 48.8%). Details of the patients enrolled on the Ro-CHOP randomized phase 3 study, our second distinct external validation data set, have been described previously and can be found in supplemental Table 8.[22]

TTR as a prognosticator of survival

From the start of frontline therapy, overall median follow-up time was 4.88 years (interquartile range [IQR], 2.22-7.68) and median OS was 5.71 years (95% CI, 4.39-7.04). Median OS for patients with and without TTR12 using m-LM methods was 2.86 (95% CI, 1.71-4.00) and 6.09 (95% CI, 3.57-8.61) years, respectively (log-rank $P < .001$). Among all patients in the m-LM primary analysis, TTR12 was significantly associated with worse OS (aHR, 2.14; 95% CI, 1.58-2.90; $P < .001$; Table 2; Figure 3). The poor prognostic effect of early relapse was retained when examining 18 months (aHR, 2.29; 95% CI, 1.68-3.12; $P < .001$) and 24 months (aHR, 3.09; 95% CI, 2.13-4.47; $P < .001$); however, relapse within 6 months did not meet statistical significance (aHR, 1.85; 95% CI, 0.90-3.80; $P = .095$; supplemental Table 9). Patients with TTR12 consistently had worse OS, irrespective of 1L HSCT consolidation or PIT score, and across prespecified subgroups including each histological subtype (PTCL-NOS: aHR, 2.32; 95% CI, 1.51-3.55; $P < .001$; AITL/TFHL: aHR, 1.92; 95% CI, 1.15-3.21; $P = .013$; and ALCL: aHR, 3.34; 95% CI, 1.18-9.50; $P = .023$; Figure 4; supplemental Figure 4). When excluding patients that did not have relapsed disease, TTR12 retained its significantly poor prognostic association (m-LM: aHR, 1.60; 95% CI, 1.18-2.18; $P = .003$; s-LM: aHR, 1.43; 95% CI, 1.03-1.98; $P = .035$). Details can be found in Table 2.

Results were consistent across sensitivity analyses. Using s-LM and td-Cox, TTR12 was significantly associated with worse OS (s-LM: aHR, 1.92; 95% CI, 1.39-2.66; $P < .001$; td-Cox: aHR, 5.81; 95% CI, 2.94-11.46; $P < .001$; Table 2; Figure 3). Across subgroup analyses, TTR12 was consistently associated with worse survival irrespective of 1L HSCT consolidation or PIT score, and for patients with PTCL-NOS (s-LM: aHR, 2.10; 95% CI, 1.33-3.31; $P = .001$; Figure 5), and ALCL (s-LM: aHR, 2.96; 95% CI, 1.02-8.61; $P = .046$). The OS difference between patients with TTR12 vs without TTR12 in patients with AITL/TFHL histological subtype did not meet statistical significance when using s-LM methods (aHR, 1.64; 95% CI, 0.94-2.87; $P = .081$; Table 2). When assessing the effect of 2L HSCT, allogeneic HSCT significantly improved OS compared with no 2L HSCT in both patients with TTR12 (aHR, 0.31; 95% CI, 0.11-0.89; $P = .030$) and without TTR12 (m-LM: aHR, 0.09; 95% CI, 0.02-0.35; $P < .001$: Table 3). There were no significant OS differences between receiving autologous 2L HSCT and no 2L HSCT in both TTR12 groups (Table 3). In exploratory m-LM analyses, patients with primary refractory disease (ie, no complete response to 1L) had significantly worse OS vs patients with TTR12 (ie, complete response to 1L but relapsed within 12 months; aHR, 1.52; 95% CI, 1.22-1.88; $P < .001$; supplemental Table 10).

Validation of TTR

Median follow-up time was 3.31 years (IQR, 1.53-4.95) in the observational and 6.34 years (IQR, 5.44-6.90) in the

Table 1. Demographic, clinical, and treatment characteristics for included relapsed patients (n = 452)

	With TTR12 (n = 165)	Without TTR12 (n = 287)
Age; median (range)	58 (18-89)	60 (15-92)
Male; n (%)	104 (63.0)	181 (63.1)
ECOG performance status, n (%)		
0 or 1	133 (80.6)	235 (81.9)
≥2	16 (9.7)	33 (11.5)
Missing	16 (9.7)	19 (6.6)
Histology, n (%)		
PTCL-NOS	78 (47.3)	124 (43.2)
AITL/TFHL	59 (35.8)	92 (32.1)
ALCL	27 (16.4)	71 (24.7)
ALK^+	10 (6.1)	22 (7.7)
ALK^-	17 (10.3)	49 (17.1)
PIT score, n (%)		
0 or 1	69 (41.8)	146 (50.9)
≥2	65 (39.4)	95 (33.1)
Missing	31 (18.8)	46 (16.0)
Frontline therapy, n (%)		
CHOP	69 (41.8)	100 (34.8)
CHOEP/EPOCH	64 (38.8)	101 (35.2)
BV-CHP	3 (1.8)	8 (2.8)
Alemtuzumab-containing regimen*	1 (0.6)	6 (2.1)
Other chemotherapy†	13 (7.9)	30 (10.5)
Other†	15 (9.1)	42 (14.6)
1L HSCT consolidation, n (%)		
Autologous	51 (30.9)	85 (29.6)
Allogeneic	7 (4.2)	4 (1.4)
2L HSCT consolidation, n (%)		
Autologous	14 (8.5)	16 (5.6)
Allogeneic	17 (10.3)	24 (8.4)

ALK, anaplastic lymphoma kinase; BV-CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ECOG, Eastern Cooperative Oncology Group.

*One patient in the relapse disease within 12 months arm with PTCL-NOS received initial therapy with alemtuzumab and pentostatin. A total of 6 patients without TTR12 received initial therapy with alemtuzumab monotherapy, 4 with PTCL-NOS and 2 with AITL/TFHL.

†Other regimens included chemotherapy with maintenance strategies, nonchemotherapy, and unspecified initial treatment. All details at 1L and 2L of treatment are included in supplemental Table 12.

randomized phase 3 validation cohorts. In the observational validation cohort, TTR12 was significantly associated with worse OS across m-LM primary analyses in both univariable (HR, 3.72; 95% CI, 1.85-7.46; $P < .001$) and adjusting for covariates with multivariable models (aHR, 3.60; 95% CI, 1.77-7.34; $P < .001$; Table 2; supplemental Figure 5). There was a significantly worse OS with TTR12 using sensitivity s-LM and td-Cox univariable (s-LM: HR, 2.60; 95% CI, 1.12-6.01; $P = .026$; and td-Cox: HR, 2.70; 95% CI, 1.39-5.27; $P = .004$) and multivariable (s-LM: aHR, 2.90; 95% CI, 1.22-6.90; $P = .016$; and td-Cox: aHR, 2.10; 95% CI, 1.03-4.29; $P = .041$) analyses (Table 2). Results were consistent in the phase 3 randomized validation cohort, with significantly poorer OS among patients with TTR12 using m-LM methods in univariable (HR, 3.04; 95% CI, 1.81-5.12; $P < .001$) and multivariable models (aHR, 3.71; 95% CI, 2.17-6.32; $P < .001$; Table 2; supplemental Figure 6), as well as across s-LM and td-Cox sensitivity univariable (s-LM: HR, 2.94; 95% CI, 1.72-5.06; $P < .001$; and td-Cox: HR, 2.39; 95% CI, 1.60-3.56; $P < .001$) and multivariable (s-LM: aHR, 3.58; 95% CI, 2.05-6.25; $P < .001$; and td-Cox: aHR, 2.50; 95% CI, 1.67-3.75; $P < .001$) analyses (Table 2). TTR12 was also associated with PIT score, with patients who had TTR12 and those with PIT of ≥2 exhibiting worst survival (supplemental Figure 7). Patients with PIT score of 4 were at a significantly higher odds of developing TTR12 (odds ratio, 3.64; 95% CI, 1.07-12.38; $P = .038$; supplemental Table 11).

Table 2. OS subgroup and validation analyses of TTR12 using primary and sensitivity analyses

	N	OS estimates for TTR12		3-y OS		5-y OS		Log-rank *P* value
		HR (95% CI)	*P* value	TTR12	No TTR12	TTR12	No TTR12	
m-LM								
Overall cohort	428	2.14 (1.58-2.90)	<.001	49.4%	71.2%	38.8%	55.7%	<.001
PTCL-NOS	196	2.32 (1.51-3.55)	<.001	43.3%	63.4%	37.2%	50.4%	<.001
AITL/TFHL	145	1.92 (1.15-3.21)	.013	54.5%	70.6%	35.2%	51.3%	.008
ALCL (adjusted for ALK^+/ALK^-)	87	3.34 (1.18-9.50)	.023	56.9%	87.7%	49.8%	71.9%	.072
PIT score 0 or 1	206	2.52 (1.56-4.07)	<.001	49.8%	79.0%	41.0%	64.0%	<.001
PIT score ≥2	153	2.70 (1.63-4.45)	<.001	40.5%	61.7%	27.7%	46.1%	.002
Any 1L HSCT (auto or allo)	143	1.96 (1.17-3.29)	.010	50.7%	67.5%	45.1%	53.6%	.014
No 1L HSCT	285	2.41 (1.65-3.53)	<.001	47.8%	73.1%	33.4%	57.2%	<.001
Patients without relapse excluded	346	1.60 (1.18-2.18)	.003	49.4%	62.5%	38.8%	44.4%	.007
PETAL cohort	350	2.09 (1.50-2.91)	<.001	48.5%	69.7%	38.6%	53.4%	<.001
GELL/CUIMC cohorts	78	2.37 (0.94-5.86)	.068	59.2%	75.4%	39.5%	62.7%	.043
Obs validation, univariable*	115	3.72 (1.85-7.46)	<.001	39.4%	78.3%	39.4%	66.7%	<.001
Obs validation, multivariable		3.60 (1.77-7.34)	<.001					
RCT validation, univariable*	124	3.04 (1.81-5.12)	<.001	40%	82%	29%	65%	<.001
RCT validation, multivariable		3.71 (2.17-6.32)	<.001					
s-LM								
Overall cohort	388	1.92 (1.39-2.66)	<.001	50.4%	71.2%	42.8%	55.7%	<.001
PTCL-NOS	179	2.10 (1.33-3.31)	.001	47.7%	63.4%	40.8%	50.4%	.003
AITL/TFHL	130	1.64 (0.94-2.87)	.081	48.8%	70.6%	39.9%	51.3%	.050
ALCL (adjusted for ALK^+/ALK^-)	79	2.96 (1.02-8.61)	.046	58.6%	87.7%	51.3%	71.9%	.091
PIT score 0 or 1	190	2.22 (1.32-3.75)	.003	52.1%	79.0%	45.2%	64.0%	<.001
PIT score ≥2	134	2.35 (1.37-4.01)	.002	41.7%	61.7%	31.8%	46.1%	.010
Any 1L HSCT (auto or allo)	133	1.79 (1.04-3.09)	.036	54.1%	67.5%	48.1%	52.6%	.049
No 1L HSCT	255	2.11 (1.40-3.18)	<.001	46.5%	73.1%	38.2%	57.2%	<.001
Patients without relapse excluded	306	1.43 (1.03-1.98)	.035	50.4%	62.5%	42.8%	44.4%	.051
PETAL	312	1.82 (1.27-2.60)	.001	49.4%	69.7%	42.9%	53.4%	<.001
GELL/CUIMC	76	2.24 (0.84-6.01)	.108	63.6%	75.4%	42.4%	62.7%	.067
Obs validation, univariable*	105	2.60 (1.12-6.01)	.026	54.0%	81.0%	54.0%	71.9%	.021
Obs validation, multivariable		2.90 (1.22-6.90)	.016					
RCT validation, univariable*	119	2.94 (1.72-5.06)	<.001	41.5%	81.7%	32.0%	64.5%	<.001
RCT validation, multivariable		3.58 (2.05-6.25)	<.001					
td-Cox								
Overall cohort	452	5.81 (2.94-11.46)	<.001	53.9%	77.2%	38.0%	61.8%	<.001
Obs validation, univariable*	138	2.70 (1.39-5.27)	.004	44.7%	83.5%	39.1%	67.1%	<.001
Obs validation, multivariable		2.10 (1.03-4.29)	.041					
RCT validation, univariable*	128	2.39 (1.60-3.56)	<.001	42.6%	89.4%	32.0%	77.2%	<.001
RCT validation, multivariable		2.50 (1.67-3.75)	<.001					

ALK, anaplastic lymphoma kinase; allo, allogeneic; auto, autologous; CUIMC, Columbia University Irving Medical Center; GELL, Grupo de Estudio Latinoamericano de Linfoproliferativos; PETAL, Peripheral T-Cell Lymphoma; Obs, observational, RCT, randomized controlled trial.

*All HRs and 95% CIs were adjusted for age, PIT score, and histology, in a multivariable Cox model including in the randomized validation and the observational validation cohort. Additionally, a univariable model without any covariates was used in the validation cohorts to confirm TTR12 as an independent prognosticator of poor prognosis.

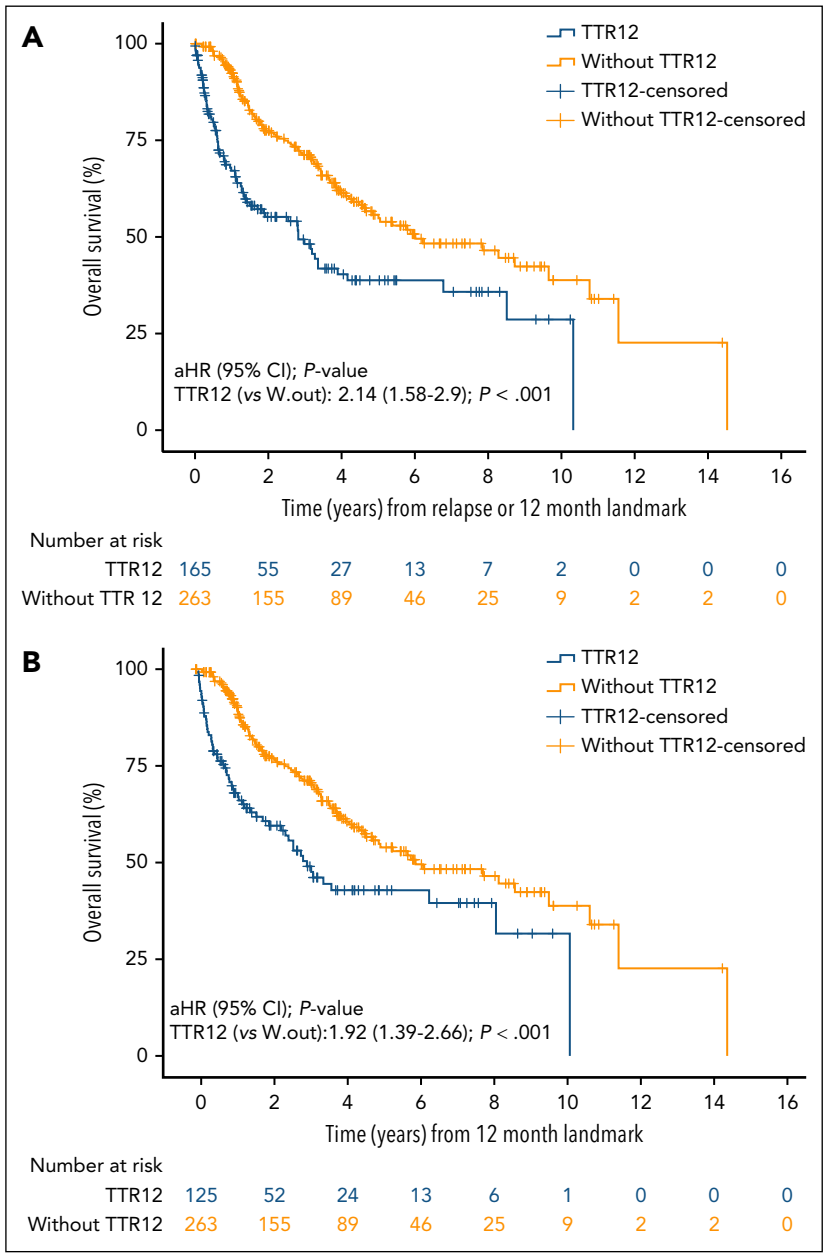


Figure 3. OS for all patients based on TTR. Kaplan-Meier curves of patients with TTR12 compared with those without TTR12, using an m-LM (n = 428) (A) or an s-LM (n = 388) (B) analysis. W.out, without.

2L therapy effects across TTR groups

In patients with TTR12, 72 (49%) received a 2L NA and 75 (51%) received 2L CC. In patients without TTR12, 70 (42%) received a 2L NA and 95 (58%) received 2L CC. The most common 2L NAs included histone deacetylase inhibitors, brentuximab vedotin, phosphatidylinositol 3-kinase inhibitors, and immunomodulatory imide drugs. The most common 2L CC agents included regimens containing ifosfamide, gemcitabine, or platinum chemotherapy. Details on all therapies received are in supplemental Table 12 and have been previously reported.[3,9] In patients with TTR12, 2L NAs significantly improved OS vs CC (aHR, 0.60; 95% CI, 0.37-0.97; P = .038; supplemental Figure 8; supplemental Table 13). In those without TTR12 who received 2L, there were no significant differences in OS with NAs vs CC (aHR, 0.82; 95% CI, 0.51-1.32; P = .407; supplemental Figure 8). Interestingly, patients with TTR12 had numerically lower 3- and 5-year OS rates with CC than patients without TTR12 (40% and 29.8% vs 45.8% and 32.6%, respectively; supplemental Figure 8; supplemental Table 13).

Discussion

In this study using multiple, global, real-world data sets; independent multi-institutional cohorts; and a clinical trial validation cohort of patients with nMTCL, we identified TTR12 as a significant prognosticator of poor survival across primary and sensitivity analyses. Patients with TTR12 consistently had a substantially increased risk of death within 5 years from 1L, and significantly worse OS compared with those without TTR12, irrespective of 1L HSCT consolidation or PIT score, and was observed among

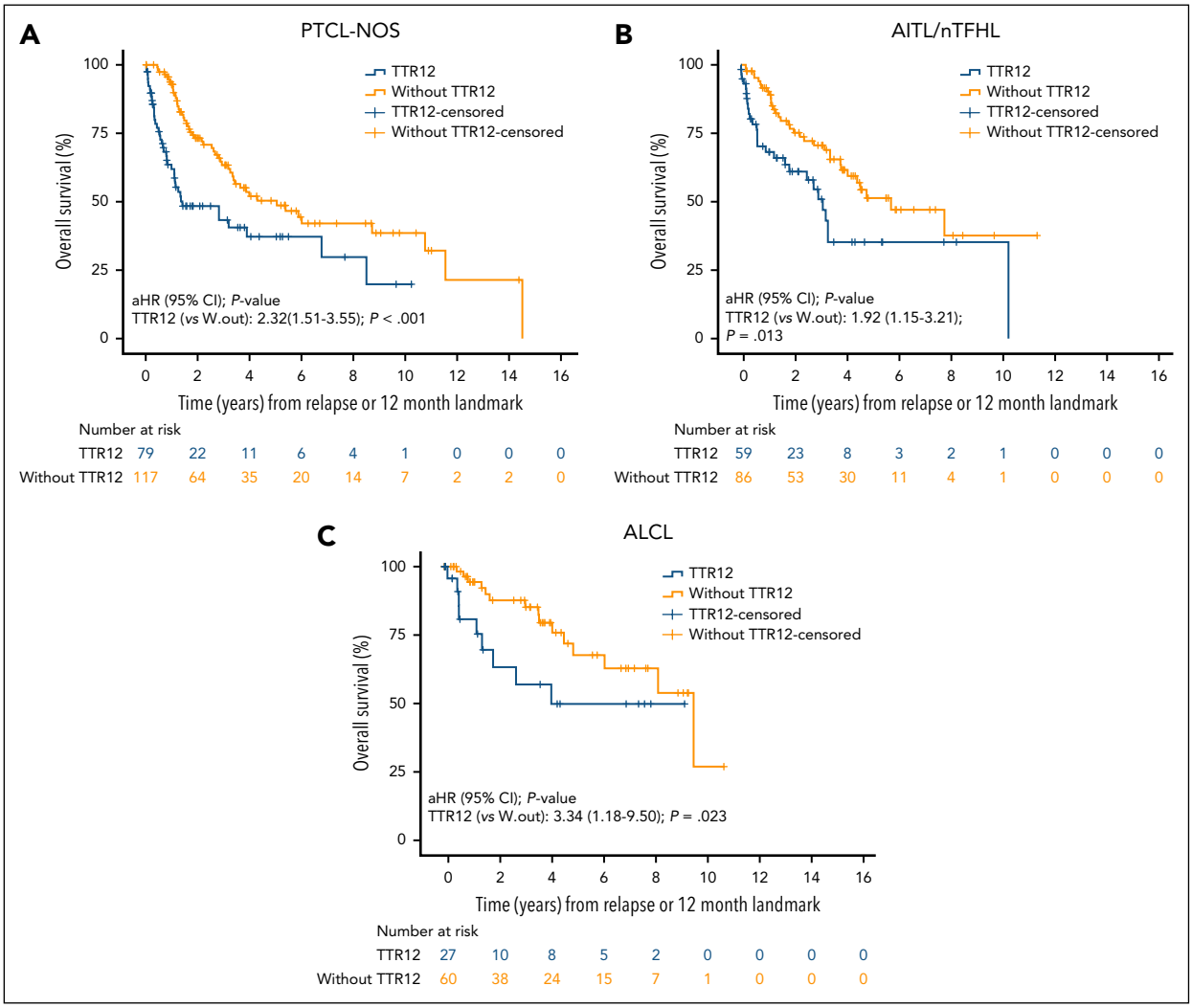


Figure 4. OS across histological subtypes based on TTR using a m-LM analysis. Kaplan-Meier curves of patients with TTR12 compared with those without TTR12, using an m-LM analysis among patients with PTCL-NOS (A), AITL/nTFHL (B), and ALCL (C). nTFHL, nodal TFHL; W.out, without.

prespecified subgroups, particularly those with PTCL-NOS and ALCL. Although time to progression is a well-described prognostic and potential surrogate marker for survival in other lymphomas,[10-13,16-18,23,24] the optimal time that serves as a clinically meaningful, prognostic, and therapeutic decision-making end point is relatively unknown in nMTCL. Our robust prototypical yet representative sample of diverse populations and predominantly treated with anthracycline-based frontline regimens allowed for a critical evaluation of TTR distribution, highlighting that nearly half of all patients with nMTCL experience disease relapse ≤12 months from 1L start. Patients with TTR12 retained a worse prognosis throughout primary and multiple sensitivity analyses, in 2 independent validation cohorts encompassing contemporary real-world and clinical trial settings. To the best of our knowledge, this is the first study to establish that early relapse after 1L anthracycline-based regimens with or without HSCT consolidation is prognostic of poor survival in patients with nMTCL alongside validation in 2 independent cohorts.

The clinical implications of TTR12 are directly relevant to future clinical trial design for nMTCL. The knowledge that early relapse may prognosticate poor survival fills a gap that can assist clinicians in discussions of prognosis and in selection of subsequent treatments. Although intuition suggests that patients with nMTCL who experience relapse earlier may have more aggressive disease, our findings clearly quantify this relationship and the subsequent effects on survival. This study also serves as a potential definition for chemotherapy-sensitive disease in patients without TTR12 and suggests that developing alternative strategies can provide meaningful benefit for the many patients with nMTCL with TTR12, given the high incidence observed in our global data sets. Furthermore, we highlight potential differences in 2L therapeutic effects based on TTR12 status. Thus, we underscore a new patient risk group in dire need of biomarker-driven innovative treatments, both in 1L and relapsed settings, given that distinct biological mechanisms likely drive lack of response to available treatments.

Current tools for risk assessment and prognostication in newly diagnosed nMTCL incorporate clinical and laboratory features applicable to use in frontline settings. We recently developed a risk stratification model at relapse, which required incorporation of new clinical and laboratory features at the time of diagnosis. Given our findings, early relapse after 1L

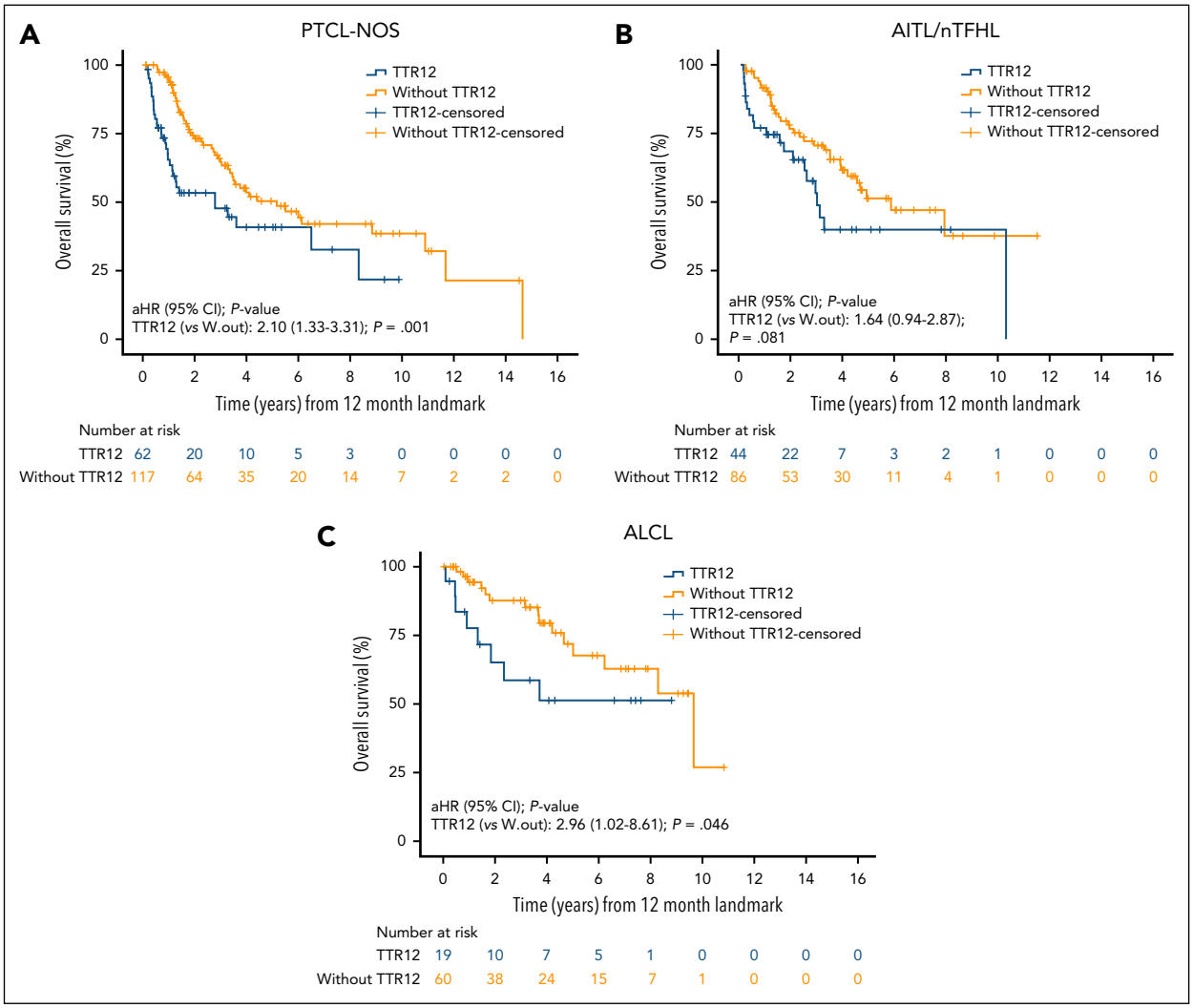


Figure 5. OS across histological subtypes based on TTR using an s-LM analysis. Kaplan-Meier curves of patients with TTR12 compared with those without TTR12, using an s-LM analysis among patients with PTCL-NOS (A), AITL/nTFHL (B), and ALCL (C). nTFHL, nodal TFHL; W.out, without.

Table 3. OS subgroup analyses of 2L HSCT among patients with and without TTR12

TTR12 groups	2L HSCT	N	OS from 2L* estimates		3-y OS	5-y OS	Log-rank *P* value
			HR (95% CI)†	*P* value			
Patients with TTR12	None	133	Reference		45.2%	32.0%	Reference
	Auto	14	0.93 (0.39-2.24)	.870	49.9%	37.4%	.477
	Allo	17	0.31 (0.11-0.89)	.030	79.1%	79.1%	.005
	Any (auto or allo)	31	0.53 (0.26-1.07)	.075	67.4%	62.6%	.009
Patients without TTR12	None	145	Reference		35.9%	25.6%	Reference
	Auto	11	1.18 (0.54-2.58)	.687	45.0%	0%	.939
	Allo	24	0.09 (0.02-0.35)	<.001	86.4%	86.4%	<.001
	Any (auto or allo)	35	0.33 (0.17-0.66)	.001	72.4%	56.7%	<.001

Any HSCT includes patients who received either auto-HSCT or allo-HSCT.

allo, allogeneic; auto, autologous.

*OS is measured from the start of 2L therapy as therapy with subsequent transplant consolidation can be considered as a single interventional course.

†HRs and 95% CIs were adjusted for age at time 0, histological subtype, PIT score, and treatment type at 2L therapy.

chemotherapy could be an additional powerful prognostic indicator of survival and should be incorporated to stratify the risk of patients in studies of nMTCL. This will be a part of the ongoing efforts of the PETAL Consortium to identify novel high-risk groups and their biological features early and develop personalized approaches commensurate with their tumor and microenvironment heterogeneity.

We, and others, have shown that there are significant prognostic differences in patients with nMTCL refractory to 1L and those who respond.[3,5,8,9] However, it is unclear whether there are survival differences in patients with initial response with then early or late relapse. Both EFS24 and POD24 have been described as a potential prognostic markers in nMTCL,[4,14] although this study, as well as multiple large analyses in nMTCL, have demonstrated median OS of less than 2 to 3 years from 1L,[1,4,7,19] limiting the utility of EFS24 or POD24 as clinical markers and decision-making tools. Furthermore, Maurer et al found that nearly two-thirds of patients with nMTCL progressed within 24 months, underscoring the importance of earlier identification of high-risk patients.[14] We identified that nearly half of patients who experience disease relapse after initial treatment will do so within the first year, with the cumulative relapse rate quickly tapering off beyond 12 months, consistent with the aggressive nature of nMTCL. Therefore, our findings granularly dissect the previously identified high-risk populations and enhance application universally in clinical practice and clinical trials. Our findings are also particularly promising because the definition of TTR12 used in this study was uniquely flexible, allowing the use of TTNT, a validated real-world measure,[25] or time-to-progression, tracked in clinical practice and applicable in closely monitored settings such as prospective trials. We also identified that patients with initial response to 1L then subsequently relapse within 12 months (ie, TTR12) have better survival than patients without initial response (ie, primary refractory disease), consistent with our previous findings.[3,9] Taken together, TTR12 should be further validated in the context of prospective randomized clinical trials as a potential surrogate end point of progression-free survival or OS in patients with nMTCL treated with 1L anthracycline-based chemotherapy and novel combinations.

The poor prognostic effect of TTR12 in subgroups mirrored the overall cohorts with both unadjusted 3- and 5-year OS rates, and adjusted HRs highlighting worse OS in those with TTR12, irrespective of 1L HSCT consolidation or PIT score, especially for those with PTCL-NOS and ALCL. In patients with AITL/TFHL, unadjusted mortality estimates were significantly worse with TTR12 but did not meet statistical significance in sensitivity analyses, potentially because AITL/TFHL is generally less responsive to chemotherapy, which is still the most commonly use treatment strategy globally in the relapsed setting.[3,9] With the growing development of frontline therapeutic strategies incorporating NAs (eg, brentuximab vedotin–CHP[2]), TTR12 would need further validation as a clinically significant end point, although may still retain significance given the aggressive relapsing nature of nMTCL. It may be possible that a later clinical time point, such as 18 or 24 months, become more relevant with availability of more novel treatments associated with improved response rates, duration of response, as well as survival outcomes. Interestingly, 2L allogeneic HSCT significantly improved OS in both patients with and without TTR12 compared with no 2L HSCT. This may represent a population with relatively high fitness and potential to receive multiple lines of therapy and thus a longer OS or, more likely, the potential direct survival benefit of allogeneic HSCT because patients who received 2L allogeneic HSCT had much higher 3- and 5-year survival rates than the rest of the population. However, the ability to receive 2L HSCT is also contingent upon responding to 2L therapy, which this study was not designed to assess, therefore more work is needed to define the role of 2L HSCT after early or late relapse. Importantly, TTR12 was significantly associated with PIT score, a validated prognostic score for nMTCL. Patients with TTR12 and high PIT scores represented both parallel and compounding risk groups, and very high PIT at diagnosis may inform developing TTR12.

This study incorporated multiple analyses to better understand the effect of TTR12 on nMTCL. Primary m-LM analyses measured survival time from relapse or 12 months from 1L, consistent with methods assessing EFS24 in nMTCL and POD24 in B-cell lymphomas.[11,13,14,23] The primary benefit of this method is to account for immortal time bias that may arise from defining cohorts using a time-based event.[27] Additionally, the measurement of time from relapse allows for inclusion of patients who both progressed and died or were lost to follow-up within 12 months, thereby more accurately reflecting the heterogeneity in disease kinetics and aggressiveness seen in nMTCL. There is a potential for exacerbating an immortal time bias because those with TTR12 may have survival-time start sooner than those who experience relapsed disease at ≥12 months. As such, a 12-month s-LM sensitivity analysis was used that excluded patients who died or were lost to follow-up within 12 months. This may normalize time 0, however, may also induce a selection bias favoring patients without TTR12 because those with early aggressive relapse and subsequent death would be excluded. The risk of relapse also exhibited time dependency so relapse was modeled as a step-function to adjust for each patient's unique time to progression[31] in a td-Cox sensitivity analysis, allowing for more representative modeling of clinical practice (ie, survival time measured from treatment or study enrollment). At the start of initial therapy in clinical practice (eg, prospective settings), it is impossible to predict the time in which disease relapse will occur. Before relapse, the disease theoretically exists in multiple paths: early relapse, late relapse, or no relapse. Because clinical studies observe patients only for a finite period, it is unknown whether a patient who did not experience disease relapse during study follow-up will not experience disease relapse after the study end. Therefore, patients who did not experience disease relapse were included in analyses to more accurately model the clinical environment because excluding them may illicit a selection bias by excluding patients who may go on to have disease relapse after study follow-up. This is consistent with methods in studies evaluating POD24 and EFS24 in non-Hodgkin lymphomas.[11,13,14,23] However, nMTCL is potentially curable and including these patients may also create a nonrepresentative comparator group to assess the effects of TTR12. As such, analyses were repeated after excluding those without relapse and confirmed the poor prognostic association with TTR12. Given that the poor prognostic effect of TTR12

was observed across all analyses, it is less likely to be attributable to any bias. This supports TTR12 as a significant poor prognostic marker and potentially a relevant surrogate for OS.

A major limitation is the retrospective observational nature, which included patients treated in the last 2 decades and its associated systematic drawbacks. The pathobiological understanding and classification of these patients have evolved and may have resulted in histological misclassification. However, TTR12 consistently was a poor prognostic marker overall and across each histologic subtype. Results were also validated in a more contemporary observational cohort of patients treated at referral academic medical centers in univariable and multivariable models accounting for histology, and in a rigorous randomized phase 3 clinical trial setting in which pathology was centrally reviewed. Therefore, the retrospective observational and historical aspects of the primary analyses are less likely to have skewed the results. We have also designed the ongoing prospective global study of the PETAL Consortium (ClinicalTrials.gov identifier: NCT06067347) to fully elucidate the effects of TTR12 as a prognostic and surrogate marker encompassing a wider spectrum of disease subtypes in conjunction with correlative novel genomics, including noninvasive monitoring of residual disease with circulating tumor-derived DNA. Additionally, response assessment and imaging practices vary across sites and countries, however this is unlikely to have affected the results significantly due to our use of TTNT to define TTR, which is an objective event that can easily be applied to observational cohorts and results were validated with a randomized phase 3 clinical trial data set in which response and imaging assessment is rigorously assessed. Cause of death could not be reliably attained across all multinational datasets. As such, we were unable to attribute any proportion of death to disease progression or treatment mortality. However, this would have unlikely skewed the results as frontline regimens were generally consistent across groups and disease aggressiveness is not directly related to patient physical fitness (ie, the likelihood of having high treatment-related mortality). Lastly, any immortal time bias was unlikely to be fully negated with landmark analyses given the varied responses (eg, early, late, and no relapse) and natural disease course in nMTCL. This is unlikely to have affected the results because the use of both m-LM and s-LM standard methodology was able to better discern the poor prognostic effects attributable to TTR12 by assessing different relative time 0 for patients. The use of td-Cox also may allow for more representative assessment by limiting selection bias. Lastly, the sample size in some subgroups may have limited statistical power and ability to fully examine effects in those populations. Given the rarity and heterogeneity of nMTCL and our sample size, this is one of the largest retrospective studies integrating patients from varied clinical and geographic backgrounds and, as such, our study fills this critical knowledge gap.

In conclusion, patients with TTR12 exhibited significantly worse OS than those without TTR12, thereby defining a novel unique risk group of patients with nMTCL treated predominantly with anthracycline-based chemotherapy regimens. Advancing scientific understanding of the mechanisms responsible for this through serial molecular profiling of the coevolving tumor and its microenvironment would be critical to improving the outcome of this group and for generation of tailored therapies. This novel high-risk group of patients warrant distinct attention in prospective clinical trials in both frontline and relapsed settings to overcome mechanism of resistance to the most used treatments globally. We hypothesize that TTR12 may be a practical and clinically meaningful end point for clinical trials in nMTCL but requires prospective validation.

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Authorship

Contribution: M.N.S., K.N.A., E.B., M.M.L., and S.J. designed the research; M.N.S., K.N.A, M.M.L., E.J., E.B., and S.J. analyzed the data; M.N.S., K.N.A., E.B., K.N., M.I., K.M.K., O.A., D.M., K.C., A.L., and S.J. wrote the manuscript; and all authors contributed to patient screening enrollment in the cohort, data collection and cleanup, and organization for enrolled patients, and reviewed and supervised the research and the manuscript.

Conflict-of-interest disclosure: M.N.S. reports research funding from Secura Bio and Daiichi Sankyo and reports honoraria from Genmab. C.C. reports honoraria from Roche, AbbVie, Janssen, AstraZeneca, Lylli, and Takeda and reports a consultancy role with Roche, AbbVie, Janssen, AstraZeneca, Lylli, and Takeda. P.L.Z. reports membership on the board of directors or advisory committees with Servier, Sandoz, Celltrion, Gilead, Secura Bio, Janssen-Cilag, Bristol Myers Squibb (BMS), Novartis, ADC Therapeutics, Incyte, Merck Sharp and Dohme (MSD), AstraZeneca, Takeda, Roche, Eusa Pharma, Kyowa Kirin, and BeiGene; reports speakers bureau participation with Servier, Celltrion, Gilead, Janssen-Cilag, BMS, Novartis, Incyte, MSD, AstraZeneca, Takeda, Roche, Eusa Pharma, Kyowa Kirin, and BeiGene; and reports a consultancy role with Novartis, MSD, and Eusa Pharma. W.-S.K. reports research funding from Sanofi, BeiGene, Boryong, Roche, Kyowa-Kirin, and Donga. C.S. reports current employment with Biogen Digital Health. S.J. reports a consultancy role with Mersana Therapeutics, Myeloid Therapeutics, SIRPant Immunotherapeutics, and Abcuro Inc; reports membership on the board of directors or advisory committees with Mersana Therapeutics, Myeloid Therapeutics, Abcuro Inc, SecuraBio, SIRPant Immunotherapeutics, Daiichi Sankyo, and CRISPR Therapeutics; and reports research funding from SIRPant Immunotherapeutics, Abcuro Inc, Daiichi Sankyo, and Acrotech LLC. H.J. reports research funding from ImmunoACT, Zydus Pharmaceuticals, and Intas Pharmaceuticals; reports honoraria from Merck, Daiichi, BMS, and Bayer; and reports patents with, and royalties from, UpToDate. C.V.D.W. has been employed by Cartherics Pty Ltd in the past 24 months; reports speakers bureau participation with Prince, Takeda, Merck, Mallinkrodt, Mundipharma, Seagen, Acrotech, Casadei, Kite-Gilead, AbbVie, Janssen, Novartis, Lilly, and Roche; reports honoraria from Foss, SecuraBio, Daiichi Sankyo, Kyowa, Conjupro, and Astex; and reports membership on the board of directors or advisory committees with Cartherics Pty Ltd, Casadei, Kite-Gilead, AbbVie, Janssen, Celgene-BMS, BeiGene, and Takeda. V.C. reports research funding from AbbVie, AstraZeneca, Incyte, and Ideogen and reports honoraria from AbbVie,

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Footnotes

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Data are available from corresponding author Salvia Jain (salvia.jain@mgh.harvard.edu) on request. Outcomes from patients in the Peripheral T-Cell Lymphoma Consortium and Columbia University Irving Medical Center data sets used in this work have been presented in previous analyses (https://doi.org/10.1182/bloodadvances.2024014674; https://doi.org/10.1111/bjh.20063). Patient data in the Grupo de Estudio Latinoamericano de Linfoproliferativos data set have also been presented previously (https://doi.org/10.1016/S2352-3026(2500011-0)).

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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