

## **The CNS Relapse in T-Cell Lymphoma Index Predicts CNS Relapse in Patients with T- and NK-Cell Lymphomas**

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**Supplementary Table S1. Contribution of cases by institution to CNS relapse cohort.**

<b>Institution</b>	<b>Final cases included for review</b>
Memorial Sloan Kettering Cancer Center	36
University of Pennsylvania	12
Mayo Clinic	11
H. Lee Moffitt Cancer Center and Research Institute	10
Washington University in St. Louis	9
Winship Cancer Institute at Emory University	6
City of Hope	8
The Ohio State University Comprehensive Cancer Center	7
Brown University	6
University of Texas MD Anderson Cancer Center	6
Thomas Jefferson University	6
Atrium Health/Levine Cancer Institute	3
University of Colorado Cancer Center	3
University of Chicago	3
Roswell Park Comprehensive Cancer Center	2
University of California San Diego Moores Cancer Center	2
Cleveland Clinic	2
University of Minnesota	2
Northwell Health Cancer Institute	1
<b>Total</b>	<b>135</b>

**Supplementary Table S2. Characteristics of CNS relapse in CNS relapse cohort.**

<b>CNS relapse characteristics (N=135)</b>	
	<b>N (%)</b>
<b>Systemic relapse/progression prior to CNS involvement</b>	
Yes	60 (44)
No	75 (56)
<b>Concurrent CNS and systemic disease</b>	
Yes	92 (68)
No	43 (32)
<b>CNS symptoms</b>	
Yes	97 (72)
No	28 (21)
Missing	10 (7)
<b>Method of CNS detection</b>	
Radiographic only	20 (15)
Flow cytometry/Cytology/Biopsy	54 (40)
Both	61 (45)
<b>Pattern of CNS Relapse</b>	
Leptomeningeal	70 (52)
Parenchymal	38 (28)
Mixed	25 (19)
Missing	2 (1)
<b>Cause of death</b>	
Systemic lymphoma	26 (26)
CNS lymphoma	16 (16)
Both CNS/systemic lymphoma	36 (36)
Treatment-related	4 (4)
Other/Unknown	19 (19)

**Supplementary Table S3. Frontline treatment for CNS relapse cohort.**

<b>Treatment characteristics (N=135)</b>	
	<b>Median (range)</b>
<b>Lines of therapy prior to CNS relapse</b>	1 (1-7)
	<b>N (%)</b>
<b>Response to frontline therapy<sup>2</sup></b>	
CR	49 (36)
PR	32 (24)
SD	4 (3)
PD	39 (29)
NE	2 (1)
Missing	9 (7)
<b>CR ever achieved prior to CNS relapse</b>	
Yes	64 (47)
No	61 (45)
NE	1 (1)
Missing	9 (7)
<b>Frontline regimens<sup>3</sup></b>	
CHOP alone	35 (26)
CHOEP/EPOCH alone	38 (28)
CHOP + Duvelisib	1 (1)
CHOP + Belinostat	1 (1)
CHO(E)P + Lenalidomide	6 (4)
EPOCH + Nivolumab	1 (1)
BV-CH(E)P	7 (5)
HyperCVAD + MTX/AraC	6 (4)
(m)SMILE	6 (4)
Newcastle regimen	3 (2)
Platinum-based intensive chemotherapy	6 (4)
Alemtuzumab-based regimen	3 (2)
AZT/IF	3 (2)
Romidepsin	1 (1)
Bexarotene-based therapy	2 (1)
Steroids	3 (2)
Other non-intensive therapy	3 (2)
Skin-based therapy for MF	9 (7)
Observation	3 (2)
Radiation (excl. TSEB)	9 (7)
Surgery	1 (1)
Use of frontline anthracycline	94 (70)
Use of frontline BV	7 (5)
Use of frontline etoposide	51 (38)
Use of frontline oral targeted agent	9 (7)
<b>Frontline CNS prophylaxis</b>	
Yes, IT MTX and/or AraC	16 (12)
Yes, HD-MTX	4 (3)
Yes, combined	1 (1)
No	113 (84)
Missing	1 (1)
<b>HCT in CR<sup>1</sup></b>	

AHCT	12 (24)
AlloHCT	7 (14)
None	30 (61)
<b>HCT at any point prior to CNS relapse<sup>1</sup></b>	
AHCT	14 (10)
AlloHCT	11 (8)
None	110 (81)

<sup>1</sup>All patients who underwent AHCT in CR1 received BEAM (carmustine, etoposide, cytarabine, melphalan) for conditioning; conditioning with total body irradiation was most commonly used for those undergoing frontline consolidative alloHCT (N=5) with 2 patients of these patients receiving a thiotepa-containing regimen.

<sup>2</sup>Assessed per institutional guidelines

<sup>3</sup>CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CHOEP/EPOCH: etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone; BV-CH(E)P: brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone +/- etoposide; HyperCVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; SMILE: dexamethasone, methotrexate, ifosfamide, l-asparaginase, etoposide; mSMILE: SMILE modified with peg-asparaginase; Newcastle regimen: CHOP followed by ifosfamide, vincristine, etoposide/methotrexate; AZT/IF: zidovudine/interferon-based regimens; TSEB: total skin electron beam  
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; HCT, hematopoietic stem cell transplant

**Supplementary Table S4. Treatment of CNS relapse in CNS relapse cohort.**

<b>Treatment characteristics (N=135)</b>	
	<b>N (%)</b>
<b>Initial CNS-directed treatment after CNS relapse</b>	
IT therapy +/- systemic therapy	45 (33)
HD-MTX +/- systemic therapy	34 (25)
Combined IT/HD-MTX therapy +/- systemic therapy	32 (24)
Other systemic chemotherapy	4 (3)
Radiation	15 (11)
Supportive care only	14 (10)
Targeted agent	10 (7)
ICI	1 (1)
Mogamulizumab	3 (2)
BV	3 (2)
<b>Best response after CNS relapse<sup>1</sup></b>	
CR	29 (21)
PR	20 (15)
SD	13 (23)
PD	31 (23)
NE <sup>2</sup>	42 (31)

<sup>1</sup>Assessed per institutional guidelines

<sup>2</sup>Not evaluable due to lack of repeat CNS assessment, death, and/or transition to hospice  
 Abbreviations: ICI, immune checkpoint inhibitor; BV, brentuximab vedotin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

**Supplementary Table S5. Baseline characteristics for patients in training and validation sets with missing data.**

Baseline Characteristics	Training set		P-value	Training set (N=226)	Validation set (N=745)	P-value
	CNS relapse cohort (N=91)	UPenn control cohort (N=135)				
	Median (range)			Median (range)		
<b>Age, years</b>	62 (24-81)	59 (20-85)	0.507	60 (20-85)	67 (18-96)	<0.001
<b>Age</b>	N (%)			N (%)		
>60 years	47 (52)	65 (48)	0.588	112 (50)	510 (68)	<0.001
≤60 years	43 (47)	70 (52)		113 (50)	235 (32)	
Missing	1 (1)	0 (0)		1 (0)	0 (0)	
<b>Sex</b>						
Male	52 (57)	73 (54)	0.684	125 (55)	440 (59)	0.318
Female	39 (43)	62 (46)		101 (45)	305 (41)	
<b>MTNKN histology</b>						
PTCL, NOS	34 (37)	18 (13)	<0.001	52 (23)	252 (34)	0.002
TFH-TCL (incl. AITL)	20 (22)	33 (24)	0.750	53 (23)	104 (14)	0.001
ALCL, ALK+	1 (1)	18 (13)	0.001	19 (8)	68 (9)	0.792
ALCL, ALK-	18 (20)	23 (17)	0.602	41 (18)	115 (15)	0.352
ALCL, ALKu	0 (0)	0 (0)	1.000	0 (0)	36 (5)	<0.001
ENKTL	7 (8)	15 (11)	0.495	22 (10)	31 (4)	0.002
SPTCL (includes SPTCL and PCGD-TCL)	2 (2)	13 (10)	0.030	15 (7)	12 (2)	<0.001
EATL (includes EATL and MEITL)	7 (8)	5 (4)	0.232	12 (5)	68 (9)	0.073
HSTCL	2 (2)	6 (4)	0.480	8 (4)	8 (1)	0.017
TCL UNS	0 (0)	0 (0)	1.000	0 (0)	51 (7)	<0.001
ALCL, BIA	0 (0)	4 (3)	0.150	4 (2)	0 (0)	0.003
<b>ECOG PS</b>			1.000			<0.001
2-4	16 (18)	28 (21)		44 (19)	262 (35)	
0-1	62 (68)	106 (79)		168 (74)	483 (65)	
Missing	13 (14)	1 (1)		14 (6)	0 (0)	
<b>Elevated LDH</b>			0.232			0.740
Yes	49 (54)	67 (50)		116 (51)	434 (58)	
No	26 (29)	52 (39)		78 (35)	275 (37)	
Missing	16 (18)	16 (12)		32 (14)	36 (5)	

<b>Ann Arbor Stage</b>			0.006			0.139
III or IV	72 (79)	88 (65)		160 (71)	480 (64)	
I or II	15 (16)	47 (35)		62 (27)	242 (33)	
Missing	4 (4)	0 (0)		4 (2)	23 (3)	
<b>B-symptoms</b>			0.580			<0.001
Yes	42 (46)	58 (43)		100 (44)	441 (59)	
No	45 (49)	75 (56)		120 (53)	282 (38)	
Missing	4 (4)	2 (1)		6 (3)	22 (3)	
<b>Site of EN involvement (excl. BM/PB)</b>						
None	30 (33)	61 (45)	0.097	91 (40)	303 (41)	0.816
Liver	9 (10)	6 (4)	0.108	15 (7)	36 (5)	0.312
GI tract	14 (15)	11 (8)	0.086	25 (11)	110 (15)	0.155
GU tract	3 (3)	2 (1)	0.388	5 (2)	1 (1)	0.003
Breast	2 (2)	4 (3)	1.000	6 (3)	2 (0.5)	0.003
Testicles	1 (1)	2 (1)	1.000	3 (1)	5 (1)	0.402
Skin	16 (18)	20 (15)	0.579	36 (16)	53 (7)	<0.001
Bone	11 (12)	13 (10)	0.517	24 (11)	28 (4)	<0.001
Other	5 (5)	1 (1)	0.038	6 (3)	36 (5)	0.192
Lung	16 (18)	17 (13)	0.336	33 (15)	42 (6)	<0.001
Soft tissue	11 (12)	8 (6)	0.140	19 (8)	20 (3)	0.001
Sinus	5 (5)	7 (5)	1.000	12 (5)	11 (2)	0.002
Pleura	2 (2)	2 (1)	0.651	4 (2)	37 (5)	0.037
Peritoneum	3 (3)	0 (0)	0.061	3 (1)	11 (2)	1.000
Missing	2 (2)	0 (0)		2 (1)	20 (3)	
<b>BM/PB involvement</b>			<0.001			0.005
Yes	40 (44)	24 (18)		64 (28)	153 (20)	
No	43 (47)	108 (80)		151 (67)	592 (80)	
Missing	8 (9)	3 (2)		11 (5)	0 (0)	
<b>≥2 sites of EN involvement (incl. BM/PB)</b>			<0.001			<0.001
Yes	40 (44)	23 (17)		63 (28)	103 (14)	
No	50 (55)	112 (83)		162 (72)	620 (83)	
Missing	1 (1)	0 (0)		1 (0)	22 (3)	



<b>IPI score</b>						
0-1	17 (19)	49 (36)	0.005	66 (29)	172 (23)	0.221
2-3	60 (66)	67 (50)	0.020	127 (56)	382 (51)	0.818
4-5	14 (15)	19 (14)	0.848	33 (15)	137 (18)	0.093
Missing	0 (0)	0 (0)		0 (0)	54 (7)	

Abbreviations: ALCL, anaplastic large cell lymphoma; ALKu, ALK status unknown; BIA, breast implant associated; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; PCGD-TCL, primary cutaneous gamma-delta T-cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; TCL, T-cell lymphoma; UNS, unspecified; ENKTL, extranodal NK/T-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; TFH-TCL, T-follicular helper T-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; PS, performance status; LDH, lactate dehydrogenase; EN, extranodal; GI, gastrointestinal; GU, genitourinary; BM/PB, bone marrow/peripheral blood; IPI, International Prognostication Index

**Supplementary Table S6. Frontline treatment in training and validation sets.**

Treatment modifications	Training set			Training set (N=226)	Validation set (N=745)	
	CNS relapse cohort (N=91)	UPenn control cohort (N=135)				
<b>Initial treatment<sup>1</sup></b>	<b>N (%)</b>		<b>P-value</b>	<b>N (%)</b>		<b>P-value</b>
CHOP	39 (43)	58 (43)	1.000	97 (43)	342 (46)	0.446
CHOEP/EPOCH	26 (29)	24 (18)	0.072	50 (22)	157 (21)	0.781
Intensive treatment other than CHO(E)P /EPOCH	17 (19)	21 (16)	0.588	38 (17)	42 (6)	<0.001
Palliative therapy	9 (10)	21 (16)	0.238	30 (13)	48 (6)	0.002
Radiation only	0 (0)	9 (7)	0.012	9 (4)	15 (2)	0.138
No therapy	0 (0)	2 (1)	0.517	2 (1)	61 (8)	<0.001
<b>Use of etoposide with initial therapy</b>			0.003			0.008
Yes	43 (47)	37 (27)		80 (35)	182 (24)	
No	48 (53)	98 (73)		146 (65)	518 (74)	
Missing	0 (0)	0 (0)		0 (0)	45 (6)	
<b>CNS prophylaxis</b>			0.107			0.012
Yes	12 (13)	9 (7)		21 (9)	113 (15)	
No	79 (87)	126 (93)		205 (91)	587 (84)	
<b>HCT type in CR1</b>			0.313			0.140
AHCT	11 (12)	26 (19)		37 (16)	105 (14)	
AlloHCT	3 (3)	2 (1)		5 (2)	5 (1)	

<sup>1</sup>CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CHOEP/EPOCH: etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone

**Supplementary Table S7. Multivariate analysis of treatment modifications for training set patients (N=182).**

Variable	Hazard Ratio (95% CI)	P-Value
MTNKN Histology:		
PTCL, NOS	2.75 (1.47-5.17)	0.002
ALCL, ALK+	0.11 (0.01-0.83)	0.032
EATL (includes EATL and MEITL)	2.90 (0.89 -9.41)	0.077
SPTCL (includes SPTCL and PCGD-TCL)	0.97 (0.20-4.67)	0.974
Elevated LDH	1.10 (0.57-2.11)	0.775
Stage ≥III	1.27 (0.60-2.73)	0.532
B-symptoms	1.37 (0.75-2.49)	0.301
≥2 sites of EN involvement (incl. BM/PB)	3.00 (1.63-5.54)	<0.001
Treatment modifications:		
Frontline etoposide	1.26 (0.70-2.28)	0.446
Frontline anthracycline	4.71 (1.71-12.96)	0.003
HCT in CR1	0.38 (0.17-0.85)	0.018
CNS Prophylaxis	1.10 (0.50-2.42)	0.813

Abbreviations: ALCL, anaplastic large cell lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; PCGD-TCL, primary cutaneous gamma-delta T-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; LDH, lactate dehydrogenase; EN, extranodal; BM/PB, bone marrow/peripheral blood

**Supplementary Table S8. Multivariate analysis of treatment modifications for high-risk training set patients (N=55).**

<b>Variable</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-Value</b>
MTNKN Histology:		
PTCL, NOS	4.27 (1.29-14.09)	0.017
ALCL, ALK+	No patients	
EATL (includes EATL and MEITL)	2.50 (0.37-17.10)	0.350
SPTCL (includes SPTCL and PCGD-TCL)	No patients	
Elevated LDH	0.62 (0.21-1.80)	0.380
Stage ≥III	0.58 (0.12-2.84)	0.501
B-symptoms	3.17 (1.04-9.64)	0.042
≥2 sites of EN involvement (incl. BM/PB)	4.05 (1.13-14.50)	0.032
Treatment modifications:		
Frontline etoposide	0.46 (0.19-1.11)	0.085
Frontline anthracycline	3.56 (0.97-13.08)	0.056
HCT in CR1	0.36 (0.10-1.28)	0.113
CNS Prophylaxis	0.52 (0.18-1.55)	0.243

Abbreviations: ALCL, anaplastic large cell lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; PCGD-TCL, primary cutaneous gamma-delta T-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; LDH, lactate dehydrogenase; EN, extranodal; BM/PB, bone marrow/peripheral blood

**Supplementary Table S9. Multivariate analysis of treatment modifications for training set patients who had CR1 after completion of frontline therapy (N=110).**

Variable	Hazard Ratio (95% CI)	P-Value
MTNKN Histology:		
PTCL, NOS	3.95 (1.48 - 10.53)	0.006
ALCL, ALK+	No estimate due to model separation	
EATL (includes EATL and MEITL)	13.11 (1.22 - 141.30)	0.034
SPTCL (includes SPTCL and PCGD-TCL)	No estimate due to model separation	
Elevated LDH	0.90 (0.37 - 2.18)	0.815
Stage ≥III	4.47 (0.93 - 21.59)	0.062
B-symptoms	1.95 (0.86 - 4.45)	0.112
≥2 sites of EN involvement (incl. BM/PB)	2.13 (0.80 - 5.67)	0.128
Treatment modifications:		
Frontline etoposide	1.87 (0.79 - 4.41)	0.155
Frontline anthracycline	2.64 (0.58 - 12.02)	0.208
HCT in CR1	0.37 (0.14 - 1.01)	0.051
CNS Prophylaxis	2.30 (0.66 - 8.06)	0.191

Abbreviations: ALCL, anaplastic large cell lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; PCGD-TCL, primary cutaneous gamma-delta T-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; LDH, lactate dehydrogenase; EN, extranodal; BM/PB, bone marrow/peripheral blood

**Supplementary Table S10. Multivariate analysis of treatment modifications for high-risk training set patients who had CR1 after completion of frontline therapy (N=23).**

<b>Variable</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-Value</b>
MTNKN Histology:		
PTCL, NOS	3.88 (0.49 - 30.58)	0.199
ALCL, ALK+	No patients	
EATL (includes EATL and MEITL)	No estimate due to model collinearity	
SPTCL (includes SPTCL and PCGD-TCL)	No patients	
Elevated LDH	0.54 (0.07 - 4.27)	0.560
Stage ≥III	0.45 (0.01 - 26.53)	0.699
B-symptoms	1.95 (0.21 - 18.39)	0.559
≥2 sites of EN involvement (incl. BM/PB)	2.33 (0.17 - 31.80)	0.526
Treatment modifications:		
Frontline etoposide	0.77 (0.14 - 4.08)	0.756
Frontline anthracycline	1.49 (0.07 - 33.21)	0.800
HCT in CR1	0.25 (0.02 - 2.82)	0.262
CNS Prophylaxis	1.40 (0.20 - 9.93)	0.736

Abbreviations: ALCL, anaplastic large cell lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; PCGD-TCL, primary cutaneous gamma-delta T-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; LDH, lactate dehydrogenase; EN, extranodal; BM/PB, bone marrow/peripheral blood