Outcomes of Relapsed or Refractory Mature T/NK-Cell Lymphomas in the Era of Novel Agents: A Nationwide Observational Study in Japan

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Introduction

- Mature T/NK-Cell Lymphomas (MTNKL) accounts for approximately 10% of all malignant lymphomas and is considered to have a poorer prognosis compared to B-cell lymphomas.
- Multiple novel agents have been developed for MTNKL, and as of May 2024, nine drugs have been approved for MTNKL in Japan.
- There is no established standard treatment for relapsed or refractory (R/R) MTNKL.
- This study aims to clarify the treatment landscape and prognosis of R/R MTNKL over the past five years across multiple institutions in Japan.

Table 1. Novel agents approved in Japan as of May 2024

Agent	Market launch in Japan
Mogamulizumab[a]	March 2014
Brentuximab vedotin	April 2014[b] / December 2019[c]
Forodesine	May 2017
Pralatrexate	August 2018
Romidepsin	April 2018
Alectinib[c]	February 2020
Denileukin diftitox	May 2021
Tucidinostat (Chidamide)	June 2021
Darinaparsin	June 2021

[a]For patients with CCR4-positive disease only. [b]For patients with CD30-positive ALCL only. [c]Expanded for patients with CD30-positive PTCL. [d]For patients with ALK-positive ALCL only.

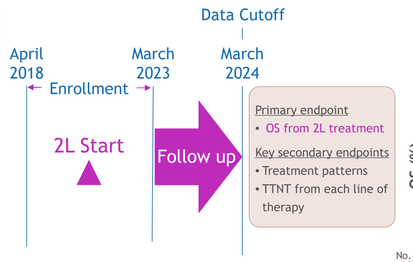
Study design

Figure 1. Study design

- 292 eligible patients were enrolled.
- 23 sites across Japan.

Key eligibility criteria

- Start 2L treatment for **MTNKL** between 2018–2023.
- Diagnosis of PTCL-NOS, TFH lymphoma (AITL and other nodal lymphomas of TFH origin), ALK-positive ALCL, ALK-negative ALCL, BIA-ALCL, ENKTL, MF with LCT (according to WHO-4R).
- Not receive unapproved drugs as of data cutoff.
- Not participate in the registrational studies of tucidinostat and darinaparsin.



Primary endpoint
- OS from 2L treatment

Key secondary endpoints
- Treatment patterns
- TTNT from each line of therapy

Results

Baseline patient and disease characteristics

Table 2. Baseline patient and disease characteristics

n (%)	Overall, N = 292	n (%)	Overall, N = 292
Age		**Laboratory values**	
Median (Q1, Q3), year	68.5 (55.5, 77)	LDH[h] > ULN	170 (60)
> 60 years	193 (66)	sIL-2R[i] > ULN	210 (89)
≥ 65 years	172 (59)	CRP[j] > ULN	208 (73)
Male	195 (67)	**CD30 positive at diagnosis[k], n(%)**	148 (69)
ECOG PS[a]		**1L regimen**	
0-1	209 (78)	CHOP-like	228 (78)
2-4	60 (22)	BV-CHP	32 (11)
Diagnosis		DeVIC[l]	20 (7)
PTCL-NOS	124 (42)	SMILE-like[m]	9 (3)
AITL and other TFH lymphoma	108 (37)	Others	32 (11)
ALK-positive ALCL	8 (3)	**Response to 1L regimen at EOT[n]**	
ALK-negative ALCL	19 (7)	CR or PR	168 (58)
BIA-ALCL	0 (0)	SD or PD	120 (42)
ENKTL	28 (10)	**Best response to 1L regimen[o]**	
MF with LCT	5 (2)	CR or PR	203 (71)
Extranodal involvement[b]	151 (52)	SD or PD	84 (29)
Skin[c]	54 (19)	**Consolidative HSCT in 1L**	
Central nervous system[d]	6 (2)	Autologous-HSCT	9 (3)
Bone marrow[e]	52 (20)	Allogeneic-HSCT	2 (1)
Ann Arbor stage[f]		**Consolidative RT in 1L**	9 (3)
I-II	55 (20)	**Time from 1L initiation to 2L initiation[p]**	
III-IV	216 (80)	Median (Q1, Q3)[q]	7.1 (2.8, 14.1)
IPI score[g]		Less than 6 months[q]	121 (42)
0-2	114 (49)	Less than 12 months[q]	200 (69)
3-5	118 (51)	Less than 24 months[q]	248 (86)

[a]Data were unknown in 23 patients; [b]Data were unknown in 4 patients; [c]Data were unknown in 7 patients; [d]Data were unknown in 11 patients; [e]Data were unknown in 28 patients; [f]Data were unknown in 21 patients; [g]Data were unknown in 60 patients; [h]Data were unknown in 7 patients; [i]Data were unknown in 57 patients; [j]Data were unknown in 9 patients; [k]Data were unknown in 78 patients; [l]DeVIC = Dexamethasone + Etoposide + Ifosfamide + Mesna + Carboplatin; [m]SMILE = Methotrexate + Leucovorin + Ifosfamide + Mesna + Etoposide + Dexamethasone + L-Asparaginase; [n]Data were unknown in 4 patients; [o]Data were unknown in 5 patients; [p]Duration between 1L treatment initiation and 2L treatment initiation was calculated; [q]Data were unknown in 4 patients.

- The median age was 68.5 years, with 59% of patients aged ≥ 65. The most common diagnoses were PTCL-NOS and TFH lymphomas. More than half of patients presented with adverse prognostic factors, including extranodal involvement in 52%, advanced Ann Arbor stage in 80%, and high LDH levels in 60%.
- Overall, 78% of patients received CHOP-like first-line therapy, including BV-CHP therapy. Only 4% of patients received consolidative hematopoietic stem cell transplantation (HSCT) in 1L therapy.

OS

Figure 2A. OS by line of therapy

	N	Median (95% CI), mo
2L	292	17.9 (14.5-23.9)
3L	184	11.0 (7.1-13.5)
4L	110	7.3 (4.8-9.8)
5L	57	4.9 (3.4-8.2)
6L	34	5.7 (3.5-9.2)

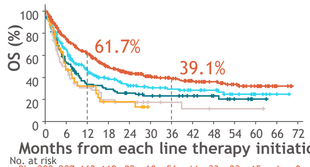


Figure 2B. OS from 2L therapy by histology

	N	Median (95% CI), mo
PTCL-NOS	124	14.5 (11.6-20.3)
TFH lymphoma	108	19.7 (12.9-49.1)
ALK-positive ALCL	8	NR (14.8-NE)
ALK-negative ALCL	19	28.1 (4.6-38.3)
ENKTL	28	15.6 (5.3-28.3)
MF with LCT	5	22.9 (13.7-NE)

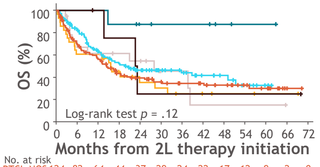


Figure 2C. OS from 2L therapy by HSCT in 2L+

	N	Median (95% CI), mo
HSCT in 2L+	83	NR (27.9-NE)
No HSCT in 2L+	209	12.9 (9.3-15.9)

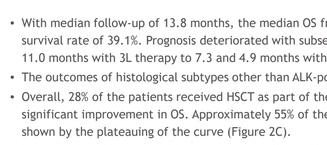
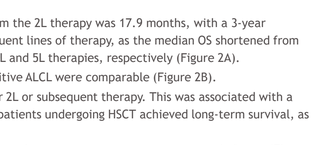


Figure 2D. OS from 2L therapy by time from 1L initiation to 2L initiation

	N	Median (95% CI), mo
≤ 6 months	121	9.0 (5.8-15.5)
6-≤ 12 months	79	16.8 (13.1-25.3)
> 12 months	88	37.7 (20.3-NE)

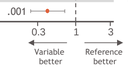


- With median follow-up of 13.8 months, the median OS from the 2L therapy was 17.9 months, with a 3-year survival rate of 39.1%. Prognosis deteriorated with subsequent lines of therapy, as the median OS shortened from 11.0 months with 3L therapy to 7.3 and 4.9 months with 4L and 5L therapies, respectively (Figure 2A).
- The outcomes of histological subtypes other than ALK-positive ALCL were comparable (Figure 2B).
- Overall, 28% of the patients received HSCT as part of their 2L or subsequent therapy. This was associated with a significant improvement in OS. Approximately 55% of the patients undergoing HSCT achieved long-term survival, as shown by the plateauing of the curve (Figure 2C).
- Less than 6 or 12 months of interval between 1L and 2L therapies can be seen as a strong prognostic factor (Figure 2D).

Factors associated with OS from 2L therapy

Figure 3. Factors associated with OS from 2L therapy

			Univariable		Multivariable		
Characteristics	**Variable**	**Reference**	**Crude HR (95% CI)**	***P***	**Adjusted HR (95% CI)**	***P***	
Age (years)	≥ 65	< 65	1.53 (1.11-2.10)	.009	1.50 (1.03-2.18)	.035	
ECOG PS	≥ 2	0-1	2.06 (1.44-2.95)	< .001	1.78 (1.21-2.61)	.003	
Histopathology	Others	TFH lymphoma	1.19 (0.86-1.64)	.29	1.46 (1.01-2.10)	.043	
Extranodal involvement	Present	Absent	1.77 (1.29-2.42)	< .001	1.78 (1.26-2.52)	.001	
Ann Arbor stage	III-IV	I-II	1.84 (1.20-2.83)	.006			
IPI score	3-5	0-2	2.22 (1.58-3.12)	< .001			
LDH	> ULN	≤ ULN	1.40 (1.02-1.93)	.037	1.18 (0.83-1.68)	.37	
IgG	> LLN	≤ LLN	0.95 (0.61-1.50)	.84			
B2M	> ULN	≤ ULN	0.69 (0.29-1.66)	.41			
CRP	> ULN	≤ ULN	1.75 (1.19-2.57)	.004	1.40 (0.91-2.15)	.12	
CD30 at diagnosis	Positive	Negative	0.86 (0.58-1.26)	.44			
Response to 1L regimen at EOT[a]	SD or PD	CR or PR	1.68 (1.23-2.28)	.001	1.41 (0.99-2.01)	.054	
HSCT in 1L	Yes	No	0.76 (0.34-1.73)	.52			
Time from 1L initiation to 2L initiation[b]	≤ 12 months	> 12 months	1.71 (1.21-2.42)	.003			
2L regimen	SAs	CCs	1.10 (0.80-1.51)	.56			
HSCT in 2L	Yes	No	0.39 (0.24-0.64)	< .001	0.41 (0.24-0.71)	.001	



To select the explanatory variables for inclusion in the multivariable model, we then considered their statistical significance in the univariable analysis ($p < .05$), their clinical relevance, and their correlation with other variables. To mitigate multicollinearity, variables with a correlation coefficient ≥ 0.6 were excluded.
[a]Therapeutic response was determined based on the Lugano classification using FDG-PET/CT (including diagnostic CT) or clinical assessment. [b]Duration between 1L treatment initiation and 2L treatment initiation was calculated.

- The multivariable analysis identified five factors as independent predictors. Age of ≥ 65 years, PS of ≥ 2, and extranodal involvement were independently associated with a worse prognosis.
- Conversely, receiving consolidative HSCT in 2L therapy was the strongest factor associated with a better outcome.

Treatment patterns

Figure 4A. Aged < 65 years (N = 120)

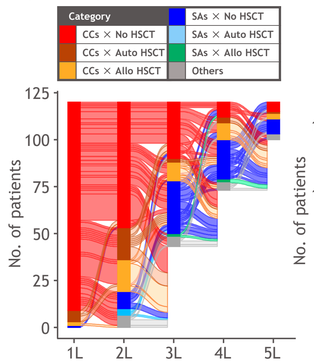


Figure 4B. Aged ≥ 65 years (N = 172)

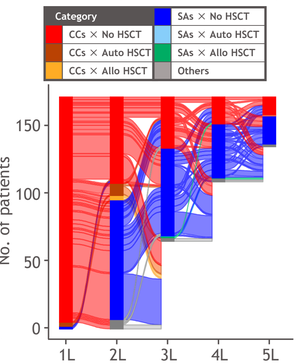


Figure 4C. PTCL-NOS (N = 124)

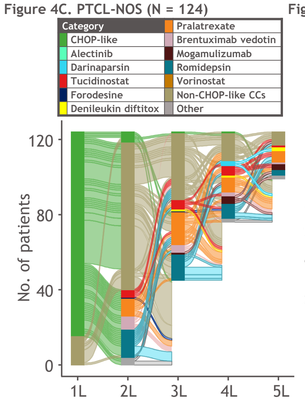
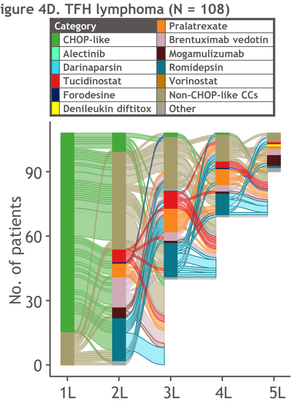


Figure 4D. TFH lymphoma (N = 108)



- For patients aged < 65 years, the treatment strategy was centered on conventional multiagent-chemotherapies (CCs). CCs were preferred over single agents (SAs) in the 2L and 3L therapies. CCs are frequently used to bridge patients to HSCT (Figure 4A).
- For patients aged ≥ 65 years, treatment frequently involved SAs. While the utilization of SAs was comparable to that of CCs in 2L therapy, administered to over half of the patients, their role became more prominent in subsequent lines (Figure 4B).
- At the start of 2L, the median age of patients with PTCL-NOS and TFH lymphoma were 66 and 72 years old, respectively. CD30 positivity was similar between the groups.
- In patients with PTCL-NOS, 30% of patients received SAs in 2L, among whom romidepsin and pralatrexate were most commonly used (Figure 4C).
- In patients with TFH lymphoma, on the other hand, 47% of patients received SAs in 2L, among of which romidepsin and brentuximab vedotin were most commonly used (Figure 4D).

Conventional multiagent-chemotherapies (CCs) vs. single agents (SAs) in 2L therapy

Figure 5A. OS from 2L therapy by CCs vs. SAs

	N	Median (95% CI), mo
CCs	180	18.5 (13.9-28.1)
SAs	103	15.9 (11.0-27.9)

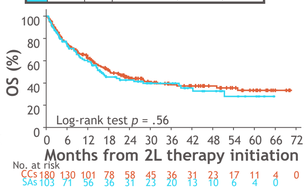
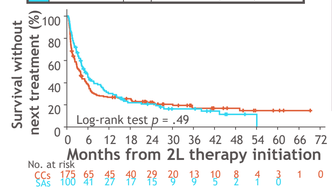


Figure 5B. TTNT from 2L therapy by CCs vs. SAs

	N	Median (95% CI), mo
CCs	175	3.9 (2.7-5.1)
SAs	100	5.1 (3.9-7.7)



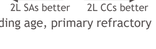
- SAs were preferentially used in patients aged ≥ 65 years ($p < .001$) and those with TFH lymphoma ($p < .001$), whereas CCs were administered to patients with primary refractory disease ($p = .002$), high LDH levels ($p = .017$), and advanced-stage disease ($p = .040$).
- Despite this distinctive background, overall survival from 2L and time to next treatment were not significantly different between patients with CCs and those with SAs in 2L (Figures 5A and 5B). This similarity was evident in PTCL-NOS as well as TFH lymphoma.

TTNT of CCs vs. SAs in 2L therapy by subgroups

Figure 6. TTNT of CCs vs. SAs in 2L by subgroups

Category	Subgroup	2L SAs N	2L SAs Events (%)	2L CCs N	2L CCs Events (%)	HR (95% CI)	*p*
Sex	Male	59	50 (85)	121	96 (79)	1.04 (0.74-1.46)	.84
	Female	41	31 (76)	54	43 (80)	0.77 (0.48-1.22)	.27
Age (years)	< 65	12	10 (83)	101	75 (74)	0.87 (0.50-1.87)	.92
	≥ 65	88	71 (81)	74	64 (86)	0.92 (0.58-1.45)	.25
ECOG PS	0-1	72	64 (89)	125	97 (78)	1.03 (0.75-1.42)	.84
	≥2	21	12 (57)	34	29 (85)	0.53 (0.27-1.04)	.06
Histopathology	TFH lymphoma	50	40 (80)	52	41 (79)	0.88 (0.57-1.36)	.57
	Others	50	41 (82)	123	98 (80)	0.94 (0.65-1.36)	.75
Extranodal involvement	Absent	53	39 (74)	76	55 (72)	0.89 (0.59-1.35)	.59
	Present	47	42 (89)	95	80 (84)	1.04 (0.72-1.51)	.84
Ann Arbor stage	I or II	24	17 (71)	26	17 (65)	1.02 (0.51-2.03)	.95
	III or IV	70	59 (84)	135	111 (82)	0.98 (0.71-1.34)	.88
IPI score	0-2	37	29 (78)	70	48 (69)	0.99 (0.62-1.56)	.95
	3-5	46	38 (83)	65	59 (91)	0.83 (0.55-1.25)	.37
LDH	≤ULN	48	38 (79)	58	42 (72)	1.03 (0.66-1.60)	.89
	>ULN	51	42 (82)	112	92 (82)	0.90 (0.62-1.29)	.55
CRP	≤ ULN	28	22 (79)	37	25 (68)	0.86 (0.48-1.52)	.60
	> ULN	69	56 (81)	133	109 (82)	0.96 (0.69-1.33)	.80
CD30 at 1L	Negative	13	12 (92)	46	35 (76)	0.92 (0.48-1.77)	.80
	Positive	55	50 (91)	85	68 (80)	1.07 (0.74-1.54)	.72
1L treatment response at EOT[a]	CR or PR	69	55 (80)	87	62 (71)	1.18 (0.82-1.70)	.36
	SD or PD	29	25 (86)	20	16 (80)	0.74 (0.47-1.16)	.19
HSCT in 1L	No	100	81 (81)	166	134 (81)	0.87 (0.66-1.14)	.31
	Yes	0	0 (0)	9	5 (56)	NE	NA
Time from 1L initiation to 2L initiation[b]	≤ 12 months	62	51 (82)	127	107 (84)	0.82 (0.59-1.15)	.25
	> 12 months	38	30 (79)	44	30 (68)	1.16 (0.70-1.93)	.56

[a]Therapeutic response was determined based on the Lugano classification using FDG-PET/CT (including diagnostic CT) or clinical assessment. [b]Duration between 1L treatment initiation and 2L treatment initiation was calculated.



- TTNT from 2L was similar between SAs and CCs across a variety of subgroups, including age, primary refractory disease, high LDH, and TFH lymphoma (Figure 6).
- This trend was consistent for OS from 2L as well (Data not shown).

TTNT and discontinuation of each SA in 2L+

Figure 7. TTNT of each SA in 2L+

	N	Median (95% CI), mo
Brentuximab vedotin	55	7.7 (3.7-16.2)
Tucidinostat	37	5.0 (2.7-6.2)
Romidepsin	99	3.9 (2.3-4.6)
Darinaparsin	7	2.1 (0.4-5.2)
Pralatrexate	70	1.9 (1.3-2.3)
Forodesine	9	1.4 (0.6-NE)
Mogamulizumab	24	1.3 (0.5-2.3)
Denileukin diftitox	7	0.7 (0.4-3.5)
Alectinib	1	NR (NE-NE)

TTNT Analysis: Based on the TTNT Analysis Set, which includes individual 2L+ treatment lines but excludes those that were part of a PTCL clinical trial. Discontinuation Analysis: Based on the Full Analysis Set, which includes all patients who received 2L+ treatment, regardless of clinical trial participation. Patients with ongoing treatment were excluded from this analysis.

Table 3. Reasons of treatment discontinuation

	All	Treatment completion	Efficacy concern	Adverse events	Death	Hospital transfer	Others
CCs	349	131 (38)	174 (50)	29 (8)	3 (1)	9 (3)	10 (3)
SAs	307	40 (13)	195 (64)	53 (17)	5 (2)	7 (2)	20 (7)
Brentuximab vedotin	57	17 (30)	28 (49)	7 (12)	2 (4)	0 (0)	4 (7)
Tucidinostat	33	2 (6)	22 (67)	8 (24)	0 (0)	0 (0)	2 (6)
Romidepsin	94	9 (10)	68 (72)	10 (11)	2 (2)	2 (2)	6 (6)
Darinaparsin	6	0 (0)	2 (33)	3 (50)	0 (0)	0 (0)	2 (33)
Pralatrexate	74	4 (5)	50 (68)	17 (23)	0 (0)	3 (4)	4 (5)
Forodesine	9	0 (0)	8 (89)	1 (11)	0 (0)	1 (11)	1 (11)
Mogamulizumab	25	5 (20)	16 (64)	4 (16)	0 (0)	1 (4)	0 (0)
Denileukin diftitox	7	2 (29)	1 (14)	2 (29)	1 (14)	0 (0)	1 (14)
Alectinib	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- The most frequently used agents were romidepsin, pralatrexate, and brentuximab vedotin. Brentuximab vedotin demonstrated a durable response, with a median TTNT of 7.7 months (Figure 7).
- The primary reason for discontinuation of SAs was efficacy concern such as disease progression at 64%. Likewise, efficacy concerns were the primary reason for discontinuation of CCs at 50% (Table 3).

Summary

- Our study reported the most updated outcome of R/R MTNKL, where nine novel SAs were available.
- Median OS from 2L was 17.9 months, and 40% of patients achieved ≥ 3-year survival.
- 28% of patients could receive HSCT in 2L+, which was associated with better prognosis.
- Diverse treatment patterns were observed, which differed by age and histological subtypes.
- OS and TTNT from 2L therapy were similar between CCs and SAs, despite different patient background and subsequent HSCT rate.
- It remains unclear whether SAs or CCs should be selected in 2L.

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Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BIA-ALCL, breast implant-associated anaplastic large cell lymphoma; BV, Brentuximab vedotin; CCs, conventional multiagent-chemotherapies; CI, confidence interval; CR, complete response; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; ENKTL, extranodal natural-killer/T-cell lymphoma; EOT, end of treatment; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; IgG, immunoglobulin G; IPI, International Prognostic Index; L, line; LCT, large cell transformation; LDH, lactate dehydrogenase; LLN, lower limit of normal; MF, mycosis fungoides; mo, month; MTNKL, Mature T/NK-Cell Lymphomas; NA, not applicable; NE, not estimated; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; PTCL, peripheral T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; Q, quantile; R/R, relapsed/refractory; RT, radiation therapy; SAs, single agents; SD, stable disease; sIL-2R, soluble interleukin-2 receptor; TCL, T-cell lymphomas; TFH, T follicular helper; TTNT, time to next treatment; ULN, upper limit of normal; WHO, World Health Organization.