Újdonságok a T-sejtes lymphomák kezelésében

Szomor Árpád
Fejér Vármegyei Szent György Egyetemi Oktatókórház
III. Belgyógyászat Hematológia

Hematológiai szintentartó tanfolyam 2025.02.28.

WHO-HAEM5 (2022) klasszifikáció újdonságai (érett T/NK-sejtes lymphomák)

Új entitások: **1.** Primary cutaneous peripheral T-cell lymphoma, NOS
2. Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
3. EBV-positive nodal T- and NK-cell lymphoma
Változások: 1. T-~~(cell)~~ large granular lymphocytic leukaemia
2. NK-large granular lymphocytic leukaemia ~~(Chronic lymphoproliferative disorder of NK)~~
3. Primary cutaneous acral CD8-positive lymphoproliferative disorder ~~(T-cell lymphoma)~~
4. Indolent T-cell lymphoma of the gastrointestinal tract ~~(lymphoproliferative disorder)~~
5. ALK-positive anaplastic large cell lymphoma ~~(ALCL, ALK-positive)~~
6. ALK-negative anaplastic large cell lymphoma ~~(ALCL, ALK-negative)~~
7. Nodal TFH cell lymphoma, angioimmunoblastic-type ~~(Angioimmunoblastic T-cell lymphoma)~~
8. Nodal TFH cell lymphoma, follicular-type ~~(Follicular T-cell lymphoma)~~
9. Nodal TFH cell lymphoma, NOS ~~(Nodal peripheral T-cell lymphoma with TFH phenotype)~~
10. Extranodal NK/T-cell lymphoma ~~(Extranodal NK/T-cell lymphoma, nasal-type)~~
11. Hydroa vacciniforme~~(-like)~~ lymphoproliferative disorder
12. Systemic chronic active EBV disease ~~(Chronic active EBV infection of T- and NK-cell type, systemic form)~~

T-sejtes lymphoma epidemiológia

ITCLP
1314 beteg
1990-2000
Retrospektív
Globális
Vose JCO 2008

SLR
755 beteg
2000-2009
Retrospektív
Svéd
Ellin Blood 2014

TCProject 1.0
1553 beteg
2006-2018
Prospektív
Globális
Chiattone Hematol Oncol 2022

TCProject 2.0
folyamatban
2016-tól

GELL
2110 beteg
1975-2023
Retrospektív
Latin Amerika
Fischer Blood 2023

ICT Study
486 beteg
2016-2018
Prospektív
Ázsia
Yoon Lancet RHWP2021

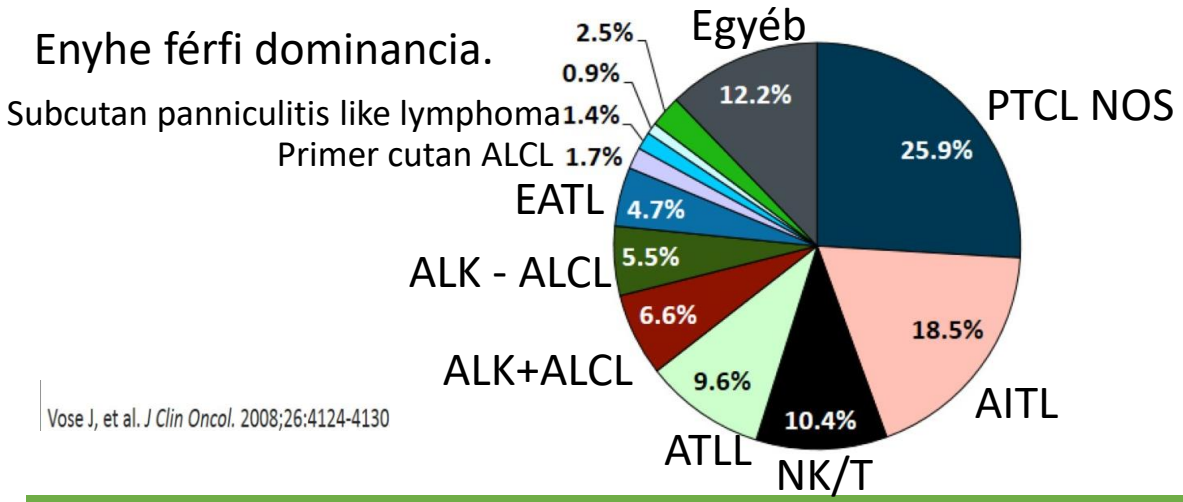
LEO-MER
1132 beteg
2002-2020
Prospektív
USA
Ruan Blood 2023

Chen JJ et al. Current Hematologic Malignancy Reports 2024;19;93-103

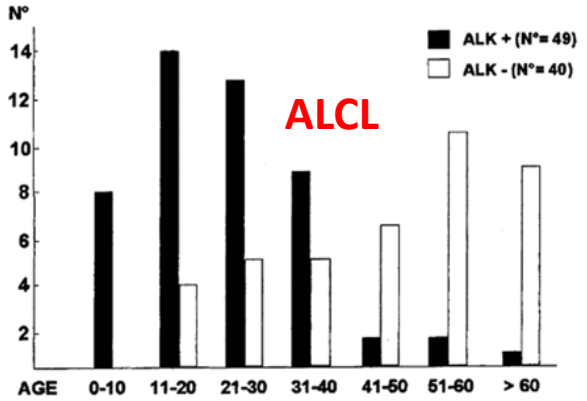
Perifériás T-sejtes lymphoma epidemiológia

22 különálló szubtípus, USA, Európa: összes lymphoma <15 %-a, Ázsia: 25-30 %-a;
USA:9500 új beteg/év Incidencia mindenhol nő (öregedés, diagnosztika javulása)

Enyhe férfi dominancia.



Vose J, et al. *J Clin Oncol.* 2008;26:4124-4130



Szubtípus (%)	Észak Amerika	Európa	Ázsia
PTCL, NOS	**34.4**	**34.3**	**22.4**
Angioimmunoblastos	**16.0**	**28.7**	17.9
ALCL, ALK+	**16.0**	6.4	3.2
ALCL, ALK-	7.8	9.4	2.6
NK/T sejtes	5.1	4.3	**22.4**
ATLL	2.0	1.0	**25.0**

Lunning MA. Current Treatment Options in Oncology 2013;14:212-223. Zinzani PL. Critical Review in Oncology/Hematology 2016;99:214-227. Zhang Y. J Hematology&Oncology 2016;9:37-53. Beaven AW. ASH Education Book 2015. 550-558.

T-sejtes lymphoma altípusok klinikai jellemzői (>1300 beteg)

Table 2. Patient Characteristics by Histologic Type

Diagnosis	Median Age (years)	%					
		Male	Stage III/IV	Marrow Positive	IPI 0/1	IPI 2/3	IPI 4/5
PTCL-NOS	60	66	69	22	28	57	15
Angioimmunoblastic	65	56	89	29	14	59	28
Nasal NKTCL	52	64	27	10	51	47	2
Extranasal NKTCL	44	68	69	18	26	57	17
ATLL	62	55	90	28	19	65	16
ALCL, ALK+	34	63	65	12	49	37	14
ALCL, ALK−	58	61	58	7	41	44	15
Enteropathy-type	61	53	69	3	25	63	13
Primary cutaneous ALCL	55	64	14	0	86	14	0
Hepatosplenic	34	68	95	74	5	47	47
Subcutaneous panniculitis-like	33	75	83	8	42	42	17

Abbreviations: IPI, International Prognostic Index; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; NKTCL, natural killer/T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large-cell lymphoma.

Vose J et al. J Clin Oncol 2008;26:4124-30

Prognosztikus faktorok

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:	INTERNATIONAL INDEX, ALL PATIENTS:	
• Age >60 years	• Low	0 or 1
• Serum LDH > normal	• Low-intermediate	2
• ECOG Performance Status 2–4	• High-intermediate	3
• Stage III or IV	• High	4 or 5
• Extranodal involvement >1 site		

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:	INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:	
• Stage III or IV	• Low	0
• Serum LDH > normal	• Low-intermediate	1
• ECOG Performance Status 2–4	• High-intermediate	2
	• High	3

PROGNOSTIC INDEX FOR PTCL-U (PIT)[b]

RISK FACTORS:	PROGNOSTIC RISK:	
• Age >60 years	• Group 1	0
• Serum LDH > normal	• Group 2	1
• ECOG Performance Status 2–4	• Group 3	2
• Bone marrow involvement	• Group 4	3 or 4

PROGNOSTIC INDEX FOR PTCL-U (modified-PIT)[c]

RISK FACTORS:	PROGNOSTIC RISK:	
• Age >60 years	• Group 1	0 or 1
• Serum LDH > normal	• Group 2	2
• ECOG Performance Status 2–4	• Group 3	3 or 4
• Ki-67 ≥80%		

INTERNATIONAL T-CELL LYMPHOMA PROJECT[d]

RISK FACTORS:		
• Age >60 years	• Group 1	0
• ECOG Performance Status 2–4	• Group 2	1
• Platelet count (<150 x 10^9/L)	• Group 3	2
	• Group 4	3

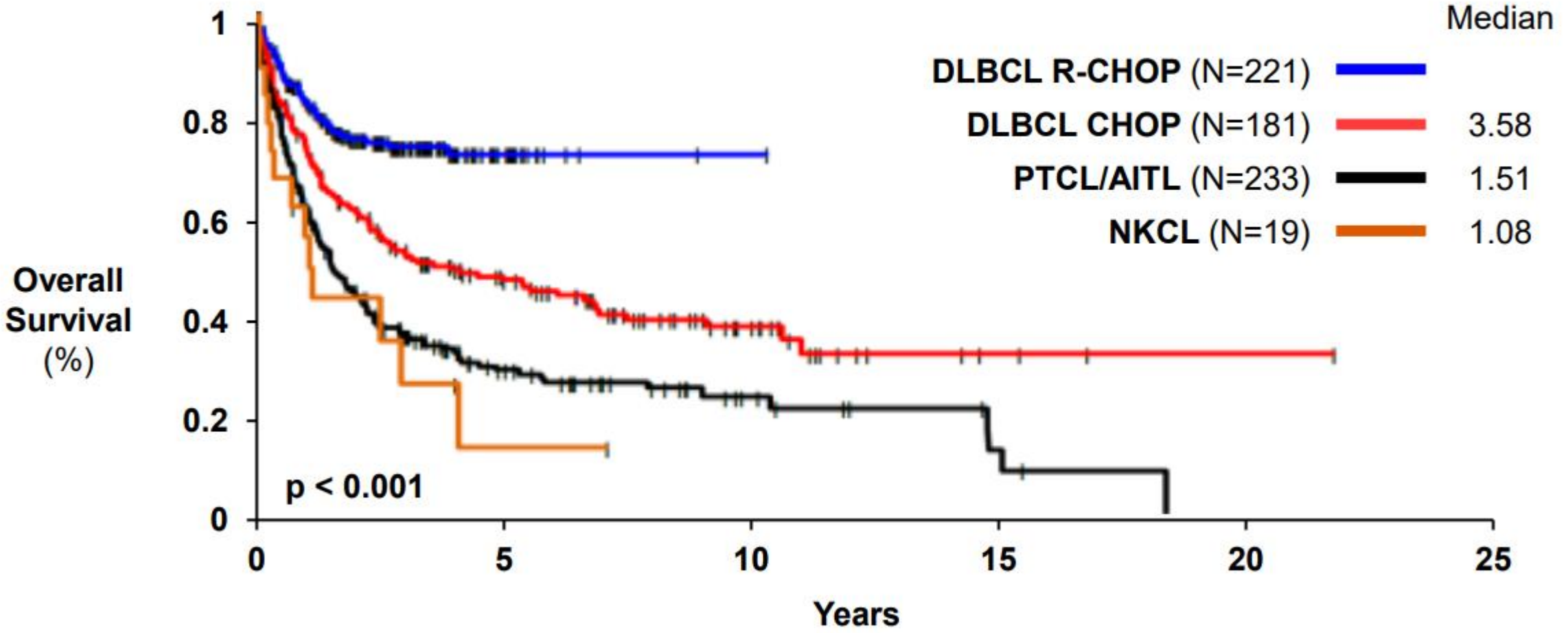
PINK kis rizikó:0; közepes:1, nagy rizikó ≥2)
Kor (> 60 év)
Ann Arbor st. (III/IV)
Távoli nycs érintettség (igen)
Nem nasalis betegség (igen)

AITL score kis rizikó:0; közepes:1, nagy rizikó ≥2
Kor (> 60 év)
ECOG Performance Status (>2)
Emelkedett CRP (igen)
Emelkedett béta 2 microglobin (igen)

[a] International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987-994.
[b] Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479.
[c] Went P, Agostinelli C, Gallamini A, et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol 2006;24:2472-2479.
[d] Vose JM. International peripheral T-cell lymphoma (PTCL) clinical and pathologic review project: poor outcome by prognostic indices and lack of efficacy with anthracyclines [abstract]. Blood 2005;106:Abstract 811a.

SM Horwitz at al. J Natl Compr Canc Netw 2022;20(3):285–308 doi: 10.6004/jnccn.2022.0015

Improved Outcomes in Every Type of B-Cell Malignancy and Hodgkin Lymphoma, but None in PTCL



Lone et al, 2018

Table 1. PFS and OS outcomes for patients with PTCL in registry studies

Registry	N	PTCL-NOS		AITL		ALCL, ALK negative		ALCL, ALK positive	
		PFS (%)	OS (%)	PFS (%)	OS (%)	PFS (%)	OS (%)	PFS (%)	OS (%)
IPTCLP[4]	1153	20	32	18	32	36	49	60	70
Swedish Lymphoma Registry[5]	755	21.3	28.1	20.4	31.6	31.4	38.4	63.2	79.4
T-cell Project[8-10,14,15]	1553	23	32	32	44	43	49	64	77
ICT Study*[6]	486	47	NR	35	NR	50	NR	65	NR
LEO/MER†[7]	718	38.9	47.3	36.2	57.3	79.4	69.4	79.0	90.5

Registry	N	ATLL		EATL		NK/T-cell		HSTCL	
		PFS (%)	OS (%)	PFS (%)	OS (%)	PFS (%)	OS (%)	PFS (%)	OS (%)
IPTCLP[4]	1153	12	14	4	20	29/6‡	42/9‡	0	7
Swedish Lymphoma Registry[5]	755	NR	NR	17.6	20.4	13.8	20.5	20	42.9
T-cell Project[10,87,88]	1553	NR	NR	28++	30	47/26‡	54/34‡	40++	40
ICT Study*[6]	486	NR	NR	NR	NR	NR	NR	NR	NR
LEO/MER†[7]	718	NR	NR	NR	NR	NR	NR	NR	NR

The table presents 5-year outcomes, unless otherwise specified.

EATL, enteropathy-associated T-cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; ICT, International Cooperative Non-Hodgkin T-cell Lymphoma Prospective Registry Study; IPTCLP, International Peripheral T-cell Lymphoma Project; NR, not reported.

*Median follow-up of 31.6 months; 5-year outcomes are NR.

†Data represent 2-year outcomes for PFS, and 3-year outcomes for OS.

‡Nasal/extranasal.

Vose JCO 2008.
Ellin Blood 2014
Advani Blood 2021

Yoon Lancet 2021
Ruan Blood 2022

Shea L és Mehta-Shah N. Blood 2024;144:2604-2612.

bjh guideline

Guidelines for the management of mature T- and natural killer-cell lymphomas (excluding cutaneous T-cell lymphoma): a British Society for Haematology Guideline

Christopher P. Fox,[1] Matthew J. Ahearne,[2] Ruth Pettengell,[3] Claire Dearden,[4] Dima El-Sharkawi,[4] Shireen Kassam,[5] Lucy Cook,[6] Kate Cwynarski,[7] Tim Illidge[8,9] and Graham Collins[10]

[1]*Department of Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, and* [2]*Department of Haematology, University Hospitals of Leicester NHS Trust, Lymphoid Malignancies Group, University of Leicester, Leicester,* [3]*Haematology and Medical Oncology, St. George's Healthcare NHS Trust, London,* [4]*Department of Haemato-Oncology, The Royal Marsden NHS Foundation Trust, Sutton,* [5]*Department of Haematological Medicine, King's College Hospital,* [6]*Department of Haematology and National Centre for Human Retrovirology, Imperial College Healthcare NHS Trust,* [7]*Department of Haematology, University College Hospital, London,* [8]*Division of Cancer Sciences, University of Manchester, Manchester,* [9]*The Christie NHS Foundation Trust, Manchester,* [10]*Department of Clinical Haematology, Oxford Cancer and Haematology Centre, Oxford University Hospitals NHS Trust, Oxford, UK*

British Journal of Haematology, 2022,196,507–522

Recommendations—general

- All PTCL cases, should be discussed at a regional lymphoma MDT to include expert pathology review and clinical management recommendations (GRADE 1B).
- All PTCL cases aged <25 years should be discussed with a TYA specialist (GRADE 1B).
- Re-biopsy at relapse is essential where clinically feasible (GRADE 1B).
- A staging and end-of-treatment PET-CT is recommended for all non-leukaemic PTCL types (GRADE 1C).
- A bone marrow biopsy is recommended in nodal PTCL for accurate staging (GRADE 1C).
- All PTCL cases, both untreated and relapsed/refractory, should be considered for a clinical trial wherever possible (GRADE 1B).

Recommendations—PTCL-NOS/AITL

- Offer CHOP chemotherapy as first-line remission induction therapy (GRADE 1B).
- Consider involved-site radiation therapy (ISRT) as consolidation, for responding patients after full-course CHOP, for patients with early stage PTCL-NOS/AITL (GRADE 2B).
- Consider high-dose chemotherapy conditioned (e.g. BEAM or similar) auto-HSCT to consolidate first complete remission (GRADE 2B).
- Offer non-cross resistant multiagent chemotherapy as second-line therapy for relapsed/refractory disease (GRADE 1C).
- Consider consolidation with an allo-HSCT in second or subsequent response (GRADE 2C).
- Consider CNS prophylaxis according to the same risk assessment applied for DLBCL (GRADE 2C).

Recommendations—ALCL

- Offer six cycles of CHP + brentuximab vedotin (CHP-BV) as first-line therapy for ALK^- and ALK^+ ALCL (GRADE 1A).
- Consider high-dose chemotherapy conditioned auto-HSCT in first complete remission for ALK^- ALCL or ALK^+ ALCL with high-risk features (e.g. IPI ≥ 2 and/or age >40 years) (GRADE 2B).
- Consider involved-site radiation therapy (ISRT) as consolidation, following six cycles of CHP-BV, for patients with early stage ALCL in first response (GRADE 1B).
- Offer brentuximab vedotin as second-line therapy for patients with relapsed/refractory ALCL who have not previously been treated with brentuximab vedotin (GRADE 1B).
- Consider retreatment with brentuximab vedotin monotherapy for patients with relapsed ALCL who previously responded to CHP-BV (GRADE 2B).
- Consider multiagent non-cross-resistant chemotherapy for patients with relapsed/refractory ALCL previously treated with CHP-BV, particularly for those with a short first response (GRADE 2B).
- Consider auto- or allo-HSCT as consolidation for relapsed/refractory ALCL based on response to prior therapy, current remission quality, co-morbid conditions, patient preferences and estimated risks of transplant toxicities (GRADE 2B).

Recommendations—EATL/MEITL

- Offer initial therapy with CHOP, particularly for patients with impaired performance status and/or nutritional deficits (GRADE 1B).
- Consider intensification of first-line chemotherapy with non-cross resistant regimens (such as the NCRI/SNLG protocol) followed by consolidation with high-dose chemotherapy conditioned (e.g. BEAM or similar) auto-HSCT for eligible patients (GRADE 2B).

Recommendations—HSTL

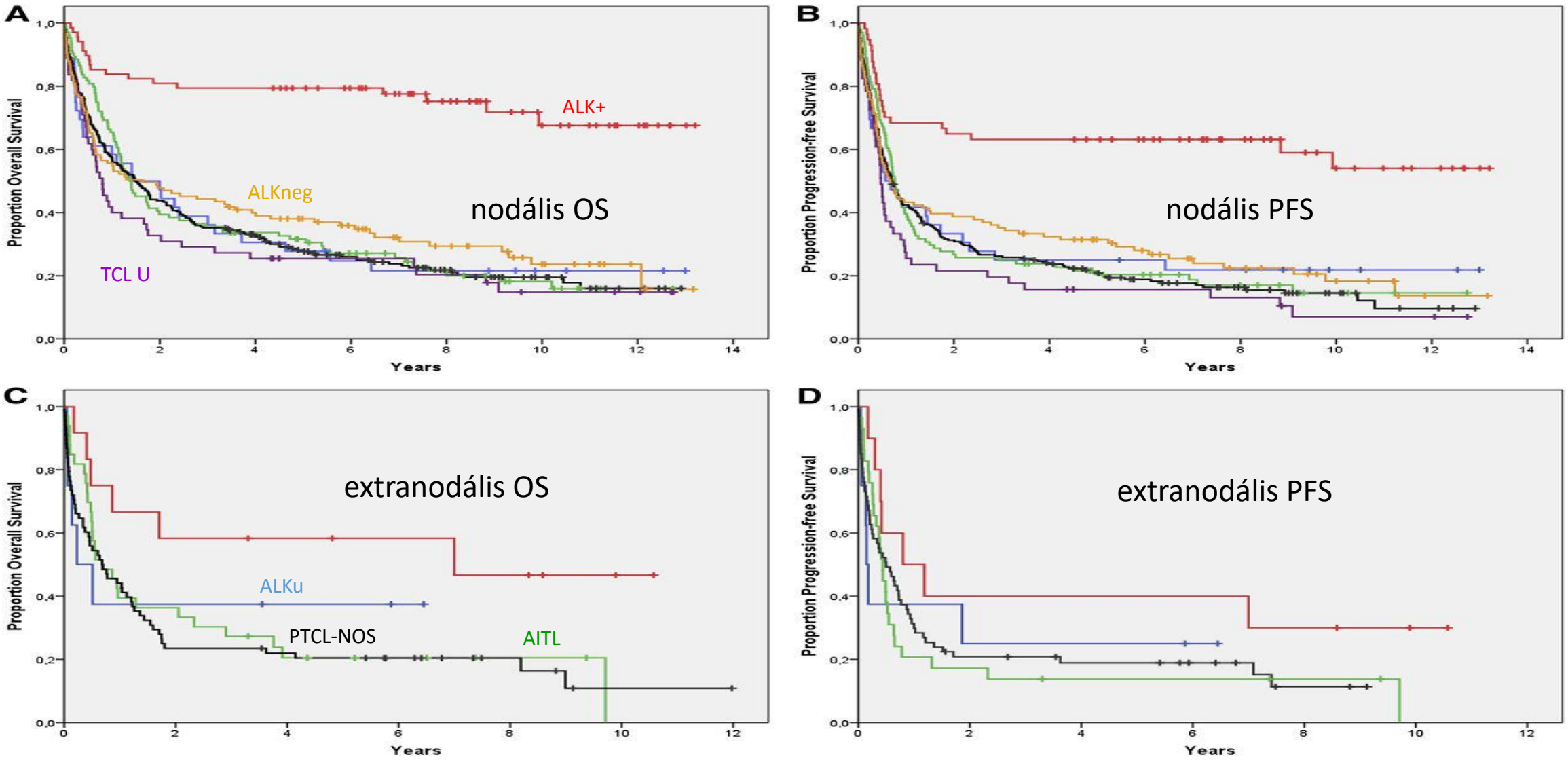
- Offer intensive multiagent non-anthracycline-based chemotherapy regimens (e.g. IVAC or ICE) to all potentially eligible patients (GRADE 2C).
- Refer all potentially eligible patients to an allo-HSCT centre early following diagnosis with a plan to offer consolidation allo-HSCT if a suitable donor can be identified (GRADE 1C).

Recommendations—ENKTL and ANKL

- Offer staging with PET-CT given the different treatment protocols for localised and advanced-stage disease (GRADE 1B).
- Consider MRI for localised disease to assess local extent (GRADE 2C).
- Confirm EBV in the tumour cells using EBER ISH (GRADE 1A).
- Consider monitoring EBV DNA copy number in peripheral blood by qPCR, at baseline and during therapy, as a corroborative biomarker of response (GRADE 2B).
- Offer non-anthracycline, platinum- and/or L-asparaginase-containing chemotherapy with concurrent or sequential radiation (>50 Gy) for Stage I and II disease (GRADE 1B).
- Offer a multiagent, L-asparaginase-containing, non-anthracycline-based regimen, such as DDGP, SMILE or AspMetDex, for Stage III and IV disease (1B).
- Consider auto- or allo-HSCT to consolidate first response in advanced stage disease; the quality of response to first-line therapy, co-morbid conditions, patient preferences and estimated risks of transplant toxicities should be carefully considered (2B).
- For patients with aggressive NK leukaemia, offer an intensive remission induction chemotherapy regimen, akin to that for ENKTL advanced-stage disease, with intent to consolidate first response with allo-HSCT (1B).

Fox CP. Et al. British Journal of Haematology, 2022,196,507–522

Való-világ adatok T-sejtes lymphomában: Swedish Lymphoma Registry (755 beteg)



Ellin F, et al. Blood 2014;124:1570-1577.

ELSŐ VONALBELI KEZELÉS

SUGGESTED TREATMENT REGIMENS[a]

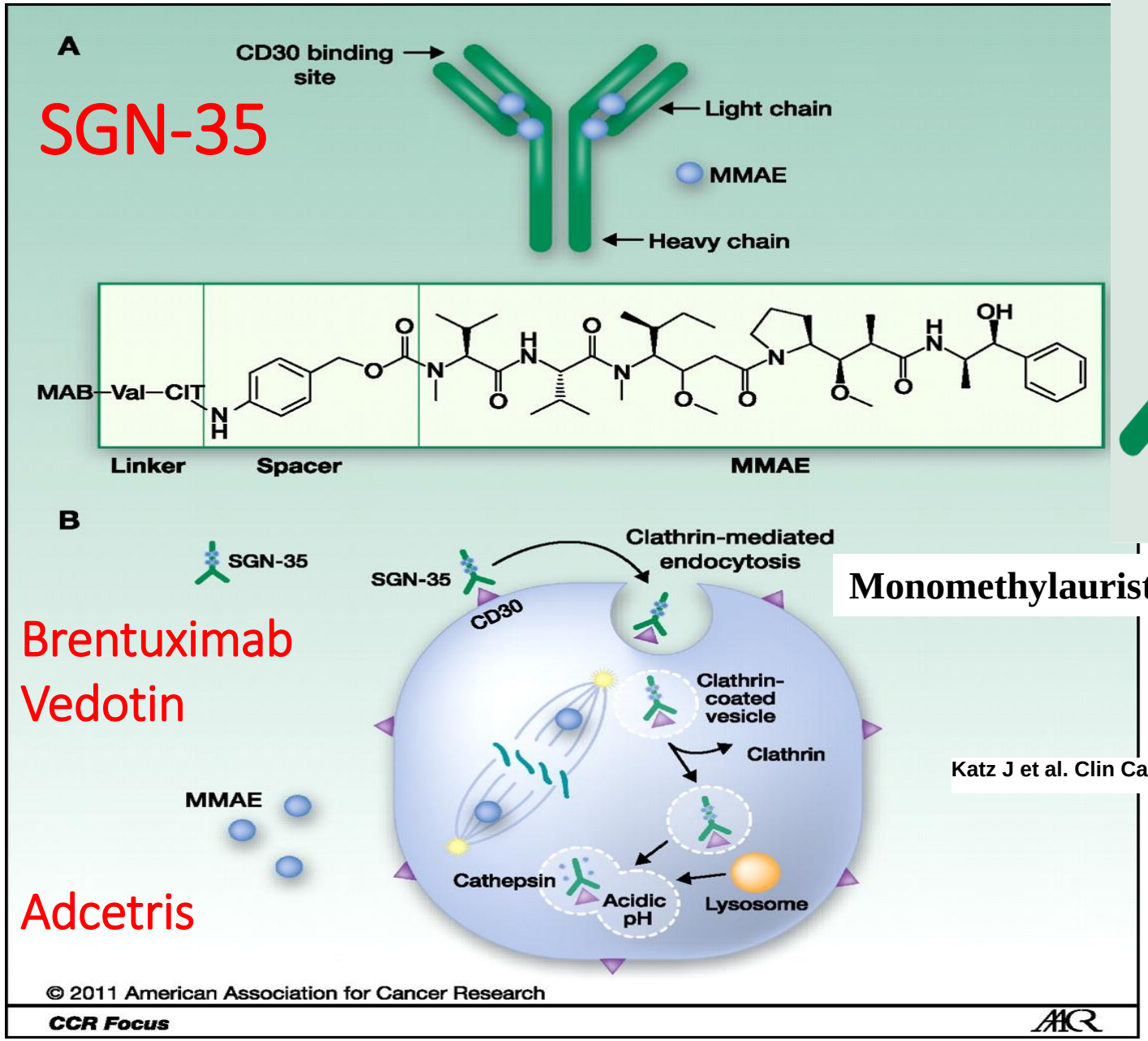
FIRST-LINE THERAPY[b]	
ALCL[c]	Preferred regimen • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] (category 1) Other recommended regimens • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) • CHOEP[e] (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
Other histologies (PTCL-NOS; AITL; EATL; MEITL; nodal PTCL, TFH; and FTCL)[f]	Preferred regimens (alphabetical order) • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] for CD30+ histologies[g] • CHOEP[e] • CHOP • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) Other recommended regimens (alphabetical order) • CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate (Newcastle Regimen; studied only in patients with EATL)[h] • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)

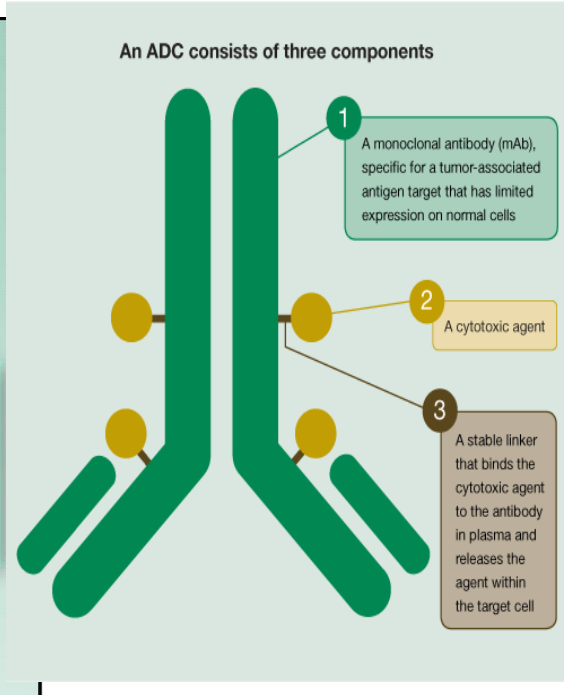
FIRST-LINE CONSOLIDATION
• Consider consolidation with high-dose therapy and autologous stem cell rescue.

See Initial Palliative Intent Therapy (TCEL-B 2 of 7)

See Second-line and Subsequent Therapy:
• PTCL-NOS; EATL; MEITL; FTCL (TCEL-B 3 of 7)
• AITL, including nodal PTCL, TFH (TCEL-B 4 of 7)
• ALCL (TCEL-B 5 of 7)

[a] See references for regimens on TCEL-B 6 of 7* and TCEL-B 7 of 7*.
[b] While anthracycline-based regimens confer a favorable prognosis in ALCL, ALK-positive, these regimens have not provided the same favorable results for other PTCL histologies; clinical trial is therefore preferred for the management of these other histologies.
[c] ALCL, ALK-negative with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK-positive disease and treatment according to the ALCL, ALK-positive algorithm may be considered (Parrilla Castellar ER, et al. Blood 2014;124:1473-1480; Hapgood G, et al. Br J Haematol 2019;186:e28-e31; Pedersen MB, et al. Blood 2017;130:554-557).
[d] See Supportive Care (TCLYM-B).
[e] Oral etoposide dose of 200 mg/m² (PO dosing of etoposide is 2x the IV dose) may be substituted on day 2 and 3 for IV etoposide. Consider splitting the daily doses of oral etoposide over 200 mg.
[f] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[g] Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30-positivity.
[h] CHOP followed by IVE regimen includes HCT.

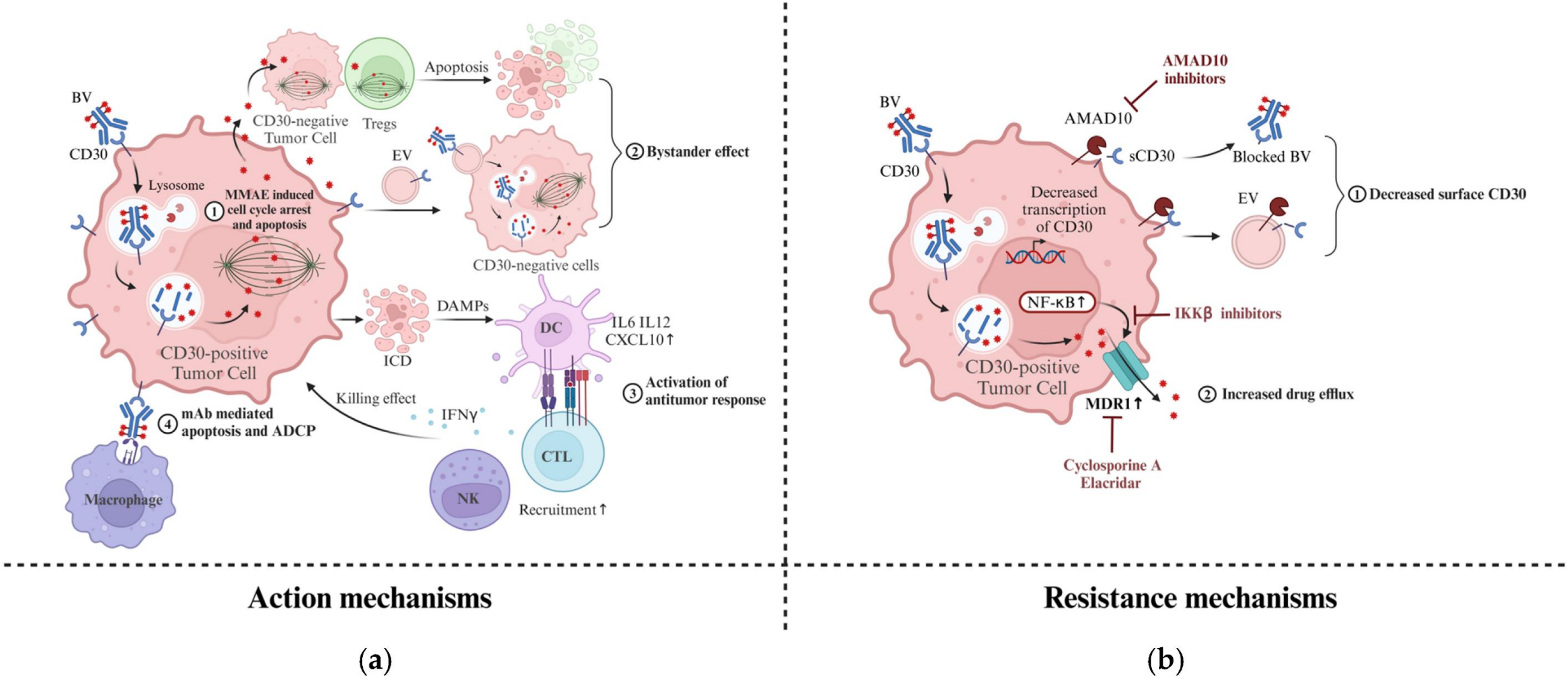




Monomethylauristatin E

Katz J et al. Clin Cancer Res 2011;17:6428-6436

80-87 % ORR
ALCL-ben



Yi Jiang et al. *Cancers* **2025**, *17*(3), 496; https://doi.org/10.3390/cancers17030496

Brentuximab vedotin magyar szabályozás T-sejtes lymphomában

„Tételes” keretből rendelhető:

Relabáló vagy rezisztens *szisztémás anapláziás nagysejtes lymphomás (ALCL) felnőtt beteg

Egyedi méltányossági engedéllyel adható:

1.) Kezeletlen *szisztémás anapláziás nagysejtes lymphomás (ALCL) felnőtt beteg CHP-vel kombinálva

2.) CD30+ cutan T-sejtes lymphomás (CTLC) felnőtt beteg 2. vonalban (*szisztémás kezelés után)

OGYÉI + EMK engedéllyel adható (off label):

Kezeletlen vagy relabáló T-sejtes lymphomás beteg

Adv Ther (2021) 38:3789–3802
https://doi.org/10.1007/s12325-021-01764-0

ORIGINAL RESEARCH

Systemic ALCL Treated in Routine Clinical Practice: Outcomes Following First-Line Chemotherapy from a Multicentre Cohort

Nicolas Martinez-Calle · Amy A. Kirkwood · Maxine Lamb · Alex Smith · Jahanzaib Khwaja · Kate Manos · Caroline Shrubsole · Nicola Gray · Katharine Lewis · Ann Tivey · Mark J. Bishton · Eliza Hawkes · Matthew J. Ahearne · Wendy Osborne · Graham P. Collins · Timothy Illidge · Kim M. Linton · Kate Cwynarski · Cathy Burton · Christopher P. Fox

214 beteg adata 14 angol és ausztrál centrumból 2003-2017. között ALCL kezelés.

52 év (16-93); ECOG >= 3: 18 % 40% ALK pozitív

CHOP : 71 % !!! ORR:65 % CR:47 %

CHOEP: 4 % !!! 4 éves Time to treatment failure: 41,2 %

ASCT: 9 % !!! 4 éves OS: 58,9 %

CD30 pozitivitás különböző T-sejtes lymphomákban

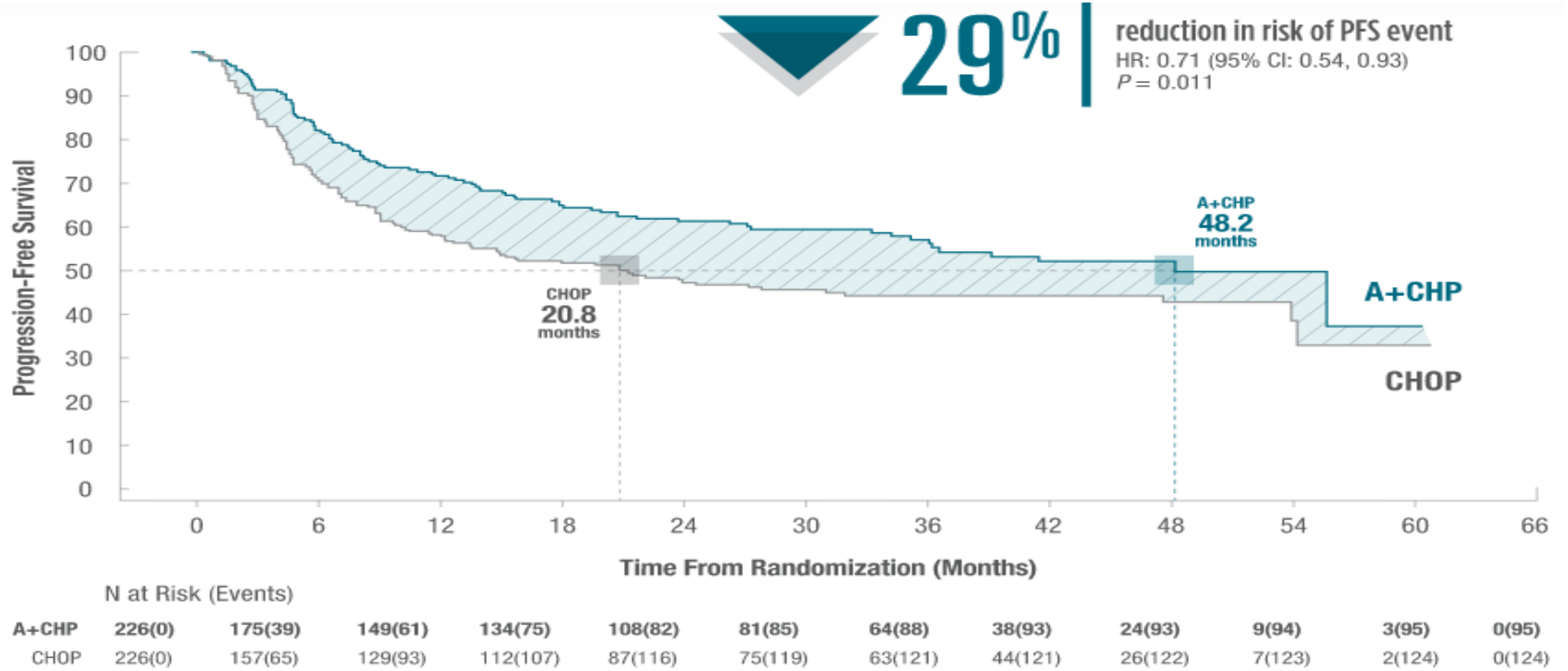
Subtype	Percent CD30-positivity*	References
PTCL		
sALCL	100	[22]
PTCL-NOS	16–58	[16, 23, 24]
AITL	21–63	[16, 23, 24]
EATL	50–100	[16, 23, 25]
ATLL	39–56	[16, 24]
ENKTL	46–72	[16, 23, 24, 26]
HSTL	Rare	[16, 27]
CTCL		
LyP	Near universal with exception of Type B	[28]
cALCL	≥75% by definition	[28]
MF/SS	12–23	[23, 29]
MF with large cell transformation	48–55	[30, 31]

*Definitions vary; please refer to individual studies for details

AITL, angioimmunoblastic T cell lymphoma; *ATLL*, HTLV-1 associated adult T cell leukemia/lymphoma; *cALCL*, cutaneous anaplastic large cell lymphoma; *EATL*, enteropathy-associated T cell lymphoma; *ENKTL*, extra-nodal NK/T cell lymphoma; *HSTL*, hepatosplenic T cell lymphoma; *MF*, mycosis fungoides; *PTCL-NOS*, peripheral T cell lymphoma not otherwise specified; *sALCL*, systemic anaplastic large cell lymphoma; *SS*, Sézary syndrome

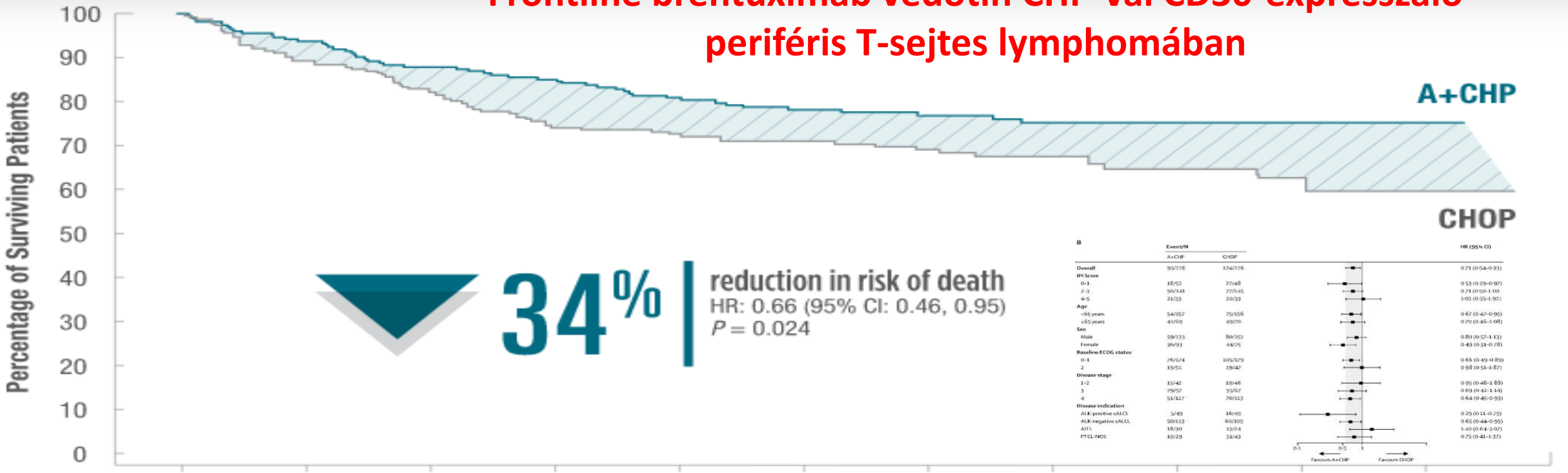
Shea L. Current Hematologic Malignancy Report 2020; https://doi.org/10.1007/s11899-020-00561-w

Frontline brentuximab vedotin CHP-val CD30-expresszáló perifériás T-sejtes lymphomában



Horwitz S. Lancet 2019;393:229-240.

Frontline brentuximab vedotin CHP-val CD30-expresszáló perifériás T-sejtes lymphomában



N at Risk (Events)

A+CHP	226(0)	208(14)	193(27)	184(33)	159(42)	128(47)	108(49)	83(51)	45(51)	20(51)	4(51)	0(51)
CHOP	226(0)	196(24)	181(39)	158(57)	140(60)	121(63)	103(66)	79(68)	46(71)	22(72)	4(73)	0(73)

NCCN RECOMMENDATION

Brentuximab vedotin (ADCETRIS®) + CHP recommended by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for first-line PTCL

Category 1 for ALCL and Category 2A for CD30+ histologies other than ALCL[3]

ALCL = anaplastic large cell lymphoma.

Horwitz S. Lancet 2019;393:229-240.

ECHELON-2 tanulmány 5 éves eredmények

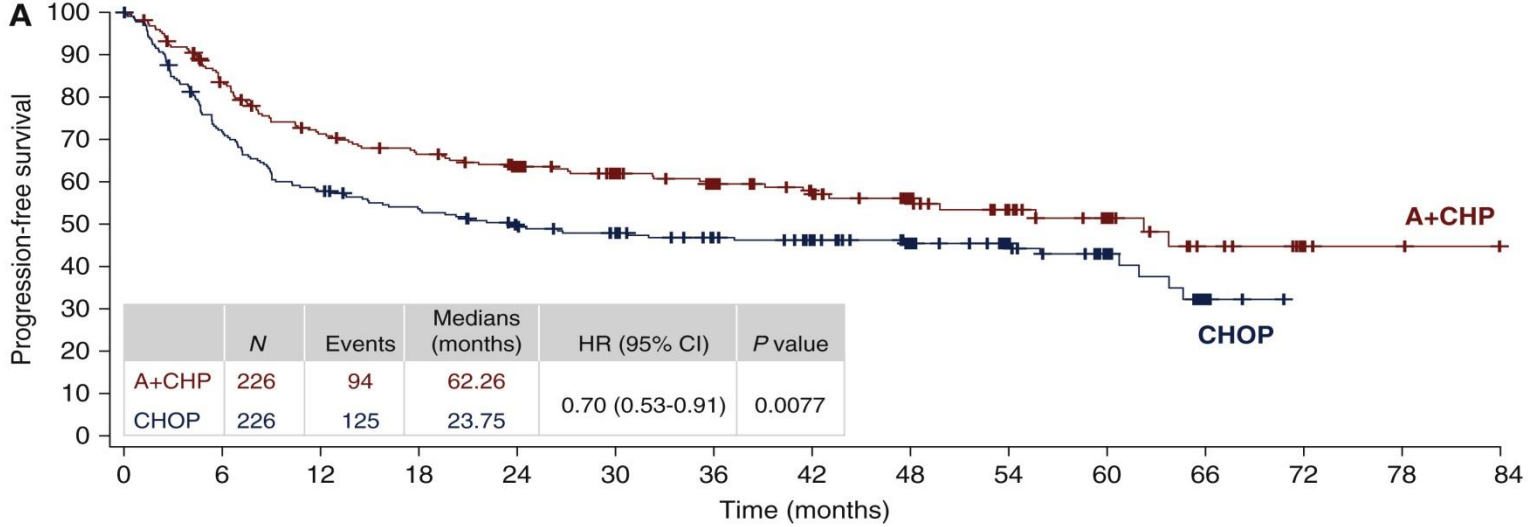
5 éves PFS: **51,4 % A-CHP** **vs** **43 % CHOP**

5 éves OS: **70,1 % A-CHP vs** **61 % CHOP**

Perifériás neuropathia megszűnt 72% A-CHP vs 78 % CHOP

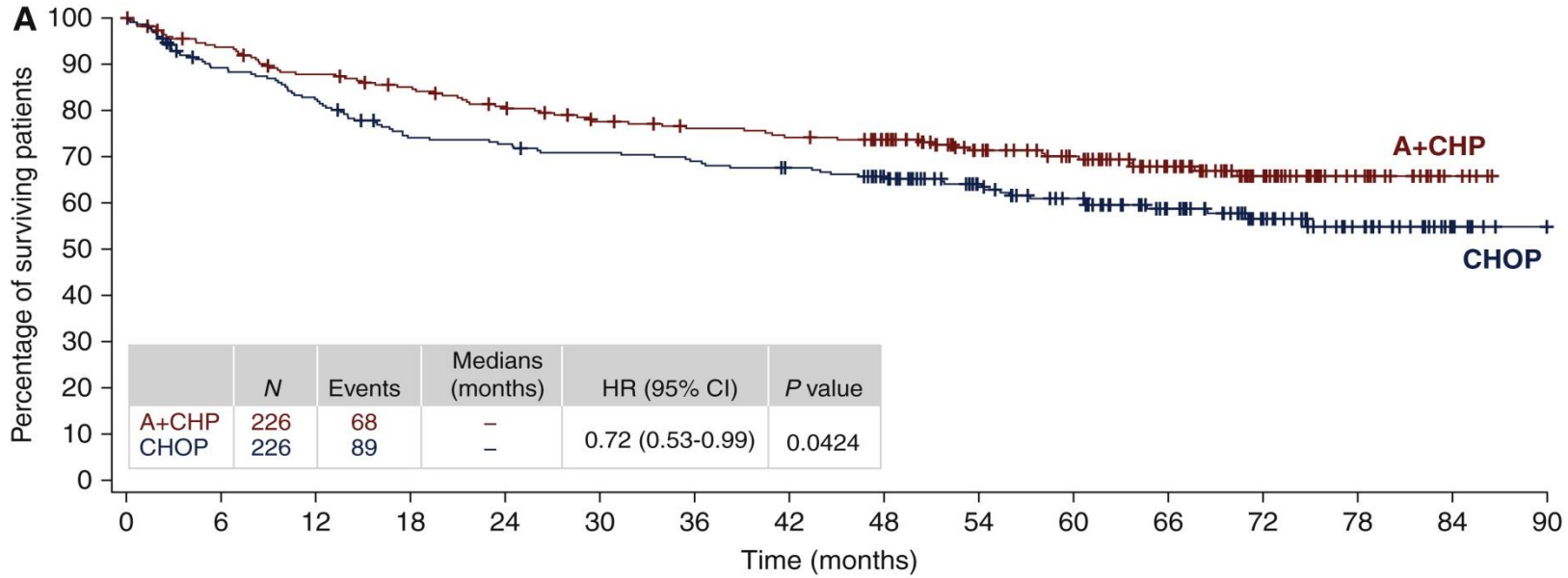
ORR: **59 % brentuximab retreatment A+CHP után vs brentuximab CHOP után**

Horwitz S et al. Annals of Oncology 2022;33:288-298. (2022. március 1.)



N at risk (events)

A+CHP	226 (0)	179 (36)	150 (62)	138 (72)	123 (78)	104 (81)	85 (85)	67 (88)	44 (89)	31 (91)	21 (92)	10 (94)	4 (94)	2 (94)	0 (94)
CHOP	226 (0)	159 (63)	128 (94)	116 (103)	101 (112)	94 (115)	79 (117)	70 (118)	55 (119)	39 (119)	24 (121)	6 (125)	0 (125)	0 (125)	0 (125)



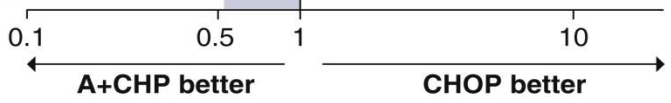
N at risk (events)

A+CHP	226 (0)	208 (14)	193 (27)	184 (33)	173 (42)	162 (49)	156 (52)	152 (56)	143 (57)	117 (61)	103 (63)	80 (66)	48 (68)	23 (68)	5 (68)	0 (68)
CHOP	226 (0)	196 (24)	181 (39)	160 (57)	157 (60)	152 (64)	148 (68)	143 (71)	132 (75)	105 (78)	90 (83)	68 (86)	43 (88)	25 (89)	8 (89)	0 (89)

Horwitz S et al. Annals of Oncology 2022;33:288-298. (2022. március 1.)

ECHELON-2

ITT subgroups	Event/*N* A+CHP	Event/*N* CHOP	Hazard ratio (95% CI)
Overall survival	68/226	89/226	0.72 (0.53-0.99)
IPI score			
0-1	8/52	13/48	0.58 (0.24-1.39)
2-3	40/141	59/145	0.61 (0.41-0.91)
4-5	20/33	17/33	1.23 (0.64-2.34)
Age, years			
<65	37/157	44/156	0.79 (0.51-1.23)
≥65	31/69	45/70	0.62 (0.39-0.98)
Sex			
Male	41/133	59/151	0.73 (0.49-1.08)
Female	27/93	30/75	0.68 (0.40-1.16)
Baseline ECOG status			
0	25/84	38/93	0.59 (0.35-0.99)
1	25/90	38/86	0.54 (0.33-0.90)
2	18/51	13/47	1.42 (0.69-2.93)
Disease stage			
I	2/12	2/9	1.34 (0.12-14.81)
II	7/30	14/37	0.66 (0.26-1.68)
III	18/57	22/67	0.70 (0.37-1.33)
IV	41/127	51/113	0.73 (0.48-1.10)
Disease indication			
ALK-positive sALCL	5/49	10/49	0.48 (0.16-1.40)
ALK-negative sALCL	34/113	39/105	0.71 (0.44-1.12)
ATLL	2/4	3/3	0.70 (0.11-4.27)
AITL	12/30	8/24	1.01 (0.40-2.55)
EATL	1/1	2/2	Not estimable
PTCL-NOS	14/29	27/43	0.75 (0.37-1.48)
sALCL	39/162	49/154	0.66 (0.43-1.01)
Non-sALCL	29/64	40/72	0.76 (0.46-1.23)



Horwitz S et al. Annals of Oncology 2022;33:288-298. (2022. március 1.)

CD30 expresszió és a therápiás válasz ECHELON-2-ben

Supplementary Table S1: CR and PR rates by CD30 expression in patients with AITL or PTCL-NOS in the A+CHP arm

	CD30	Patients *N*	Complete remission *n* (%)	Partial remission *n* (%)	*P* value, CR rates for CD30 above vs below median [a]
AITL	CD30 > median	14	8 (57)	1 (7)	0.84
	CD30 ≤ median[b]	15	8 (53)	3 (20)	
	CD30 = 10%	8	5 (63)	0	
PTCL-NOS	CD30 > median	14	8 (57)	2 (14)	0.44
	CD30 ≤ median[b]	14	10 (71)	2 (14)	
	CD30 = 10%	6	4 (67)	2 (33)	

AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified

a Cochran-Mantel-Haenzel test comparing CR rates in patients with CD30 above vs below median

b Patients with CD30 = 10% were included in the category CD30 ≤ median

Reprinted from Advani RH, Horwitz SM, Iyer SP, et al. Response to A+CHP by CD30 expression in the ECHELON-2 trial. Poster presented at: Annual Meeting of the American Society of Clinical Oncology; Chicago, IL, May 31-Jun 4, 2019 with permission from the Author.

Horwitz S et al. Annals of Oncology 2022;33:288-298. (2022. március 1.)

Transzplantáció az ECHELON-2 tanulmányban

Supplementary Table S2: Summary of use of SCT by treatment group

Regimen category n (%)	A+CHP *N*=226	CHOP *N*=226	Total *N*=452
Overall use of SCT	68 (30)	64 (28)	132 (29)
Autologous	63 (28)	52 (23)	115 (25)
Allogeneic, related donor	3 (1)	6 (3)	9 (2)
Allogeneic, unrelated donor	9 (4)	13 (6)	22 (5)
Use of SCT as consolidation	50 (22)	39 (17)	89 (20)
Autologous	49 (22)	39 (17)	88 (19)
Allogeneic, unrelated donor	1(0)	0	1 (0)
Use of SCT as subsequent therapy	23 (10)	31 (14)	54 (12)
Autologous	14 (6)	13 (6)	27 (6)
Allogeneic, related donor	3 (1)	6 (3)	9 (2)
Allogeneic, unrelated donor	8 (4)	13 (6)	21 (5)

A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; SCT, stem-cell transplantation

Horwitz S et al. Annals of Oncology 2022;33:288-298. (2022. március 1.)

Az ECHELON-2 tanulmányban > 10 %-os CD30 pozitvitású PTCL-es beteg került be

Frontline brentuximab vedotin and CHP (A+CHP) in patients (pts) with peripheral T-cell lymphoma with less than 10% CD30 expression: Results from the phase 2 SGN35-032 study.

Eredmények: 70 beteg kapott ≥1 dózist. Átlag életkor: 63.5 év, 57% férfi, 90% ECOG ≤1. IV sádium: 63% CD30 1%-10%: 55%. Átlag kezelés hossz: 18 hét (0-24 hét).
ORR 77% - CR: 65% Grade ≥3 treatment-emergent adverse events (TEAEs) 61%, leggyakoribb: neutropenia (20%), lázas neutropenia (17%), anemia (10%).
Hat beteg (9%) hagyta abba a kezelést TEAE miatt. Tizenkilenc vetegnél (27%) volt BV-related súlyos TEAE. Kettő (3%) treatment-related halál: 1 beteg „csökkent étvágy” miatt, egy beteg „általános fizikai állapot romlás”
Konklúzió: A nem-sALCL-es PTCL-es betegeknél <10% CD30 expresszióval A+CHP frontline kezelésként hatásosnak és biztonságosnak bizonyult . Klinikai trial információk: NCT04569032.

Iyer SP etal. MDACC ASCO Meeting 2024.06.03.

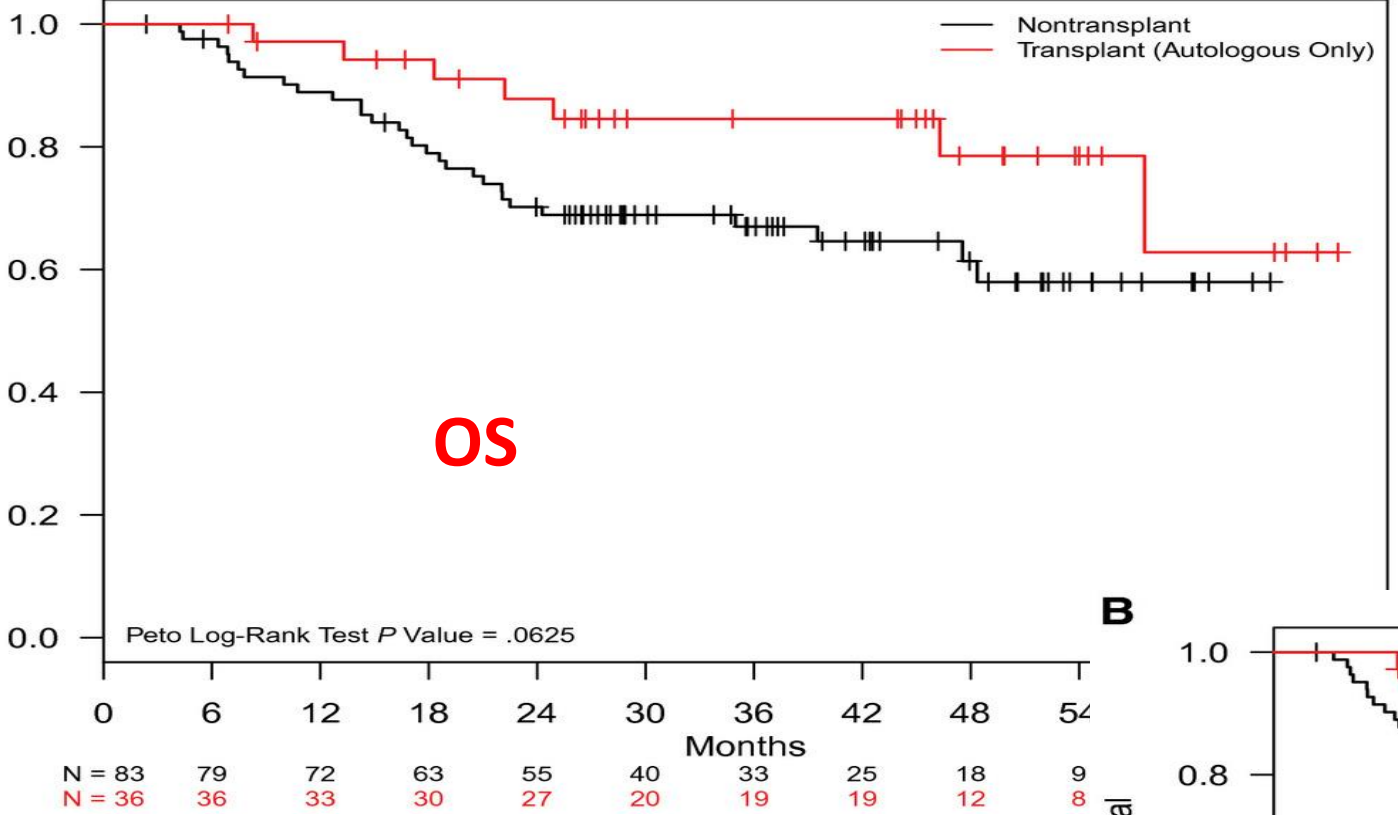
Első vonalbeli kezelés

TABLE 2. Selected Large-Scale Retrospective Outcome Studies including Nodal PTCLs Treated With Primarily Anthracycline-Based Chemotherapy[3-5]

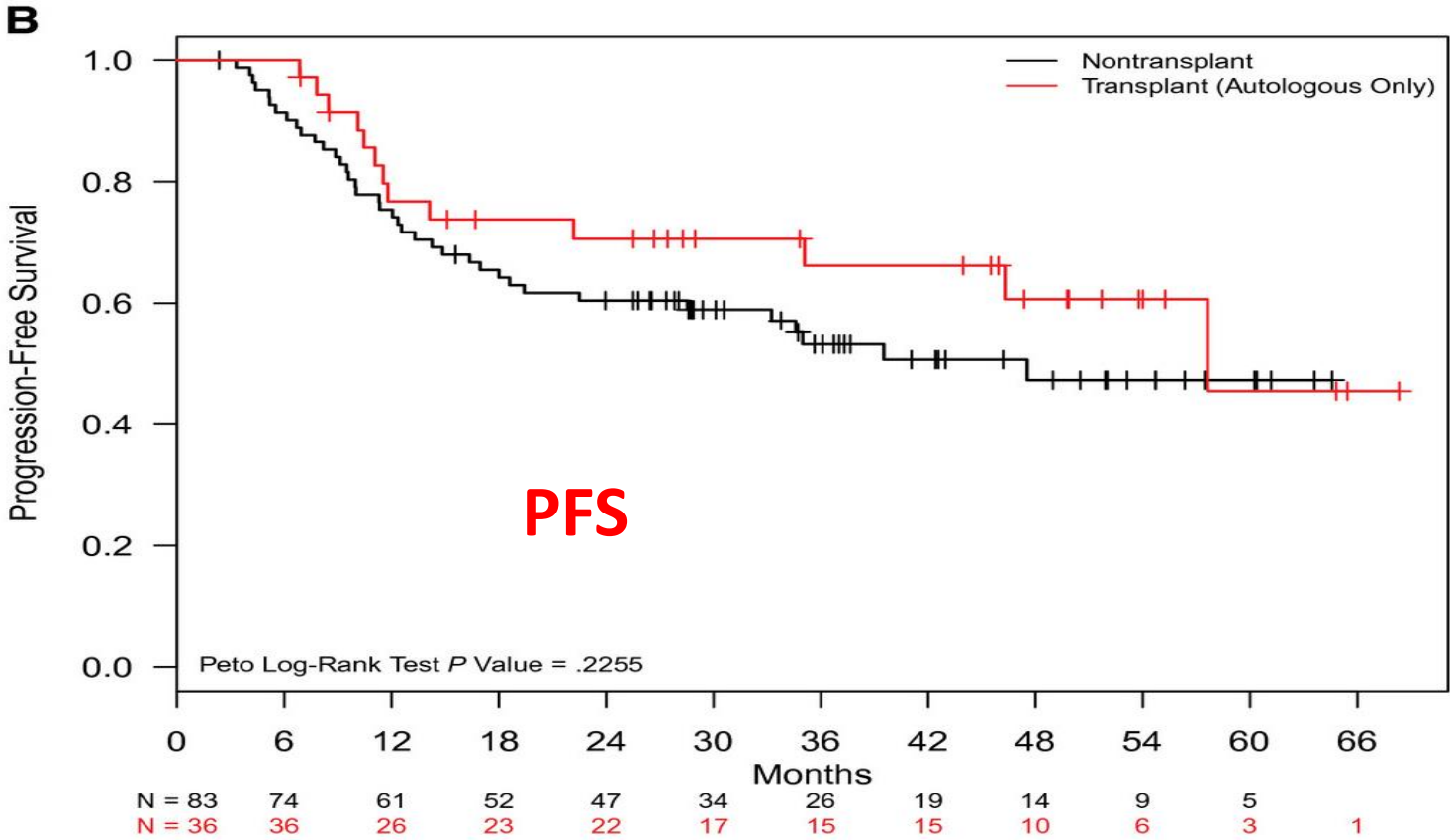
Retrospective Study	International Peripheral T-Cell Lymphoma Project All Ages		Swedish Registry All Ages		Netherland Cancer Registry <65 Years	
Patients, No. Years of PTCL diagnosis	1,153 (overall) 1990-2002		755 (overall) 2000-2009		1,427 (nodal only) 1989-2018	
Central pathology review	Yes		No		No	
Patients, No.		%		%		%
ALK-positive ALCL	87	7,5	68	9	145	10,2
ALK-negative ALCL	72	6,5	115	15,2	90	6,3
PTCL-NOS	340	29,5	256	33,9	629	44
AITL	243	21,1	104	13,8	294	20,6
5-year PFS, %						
ALK-positive ALCL	60		63		NR	
ALK-negative ALCL	36		31		NR	
PTCL-NOS	20		21		NR	
AITL	18		20		NR	
5-year OS, %						
ALK-positive ALCL	70		79		72	
ALK-negative ALCL	49		38		52	
PTCL-NOS	32		28		32	
AITL	33		32		44	

Ngu HS, Savage KJ.
ASCO Handbook 2023.

Autológ SCT szerepe nodális PTCL-ben frontline: prospective vizsgálat (COMPLETE study)

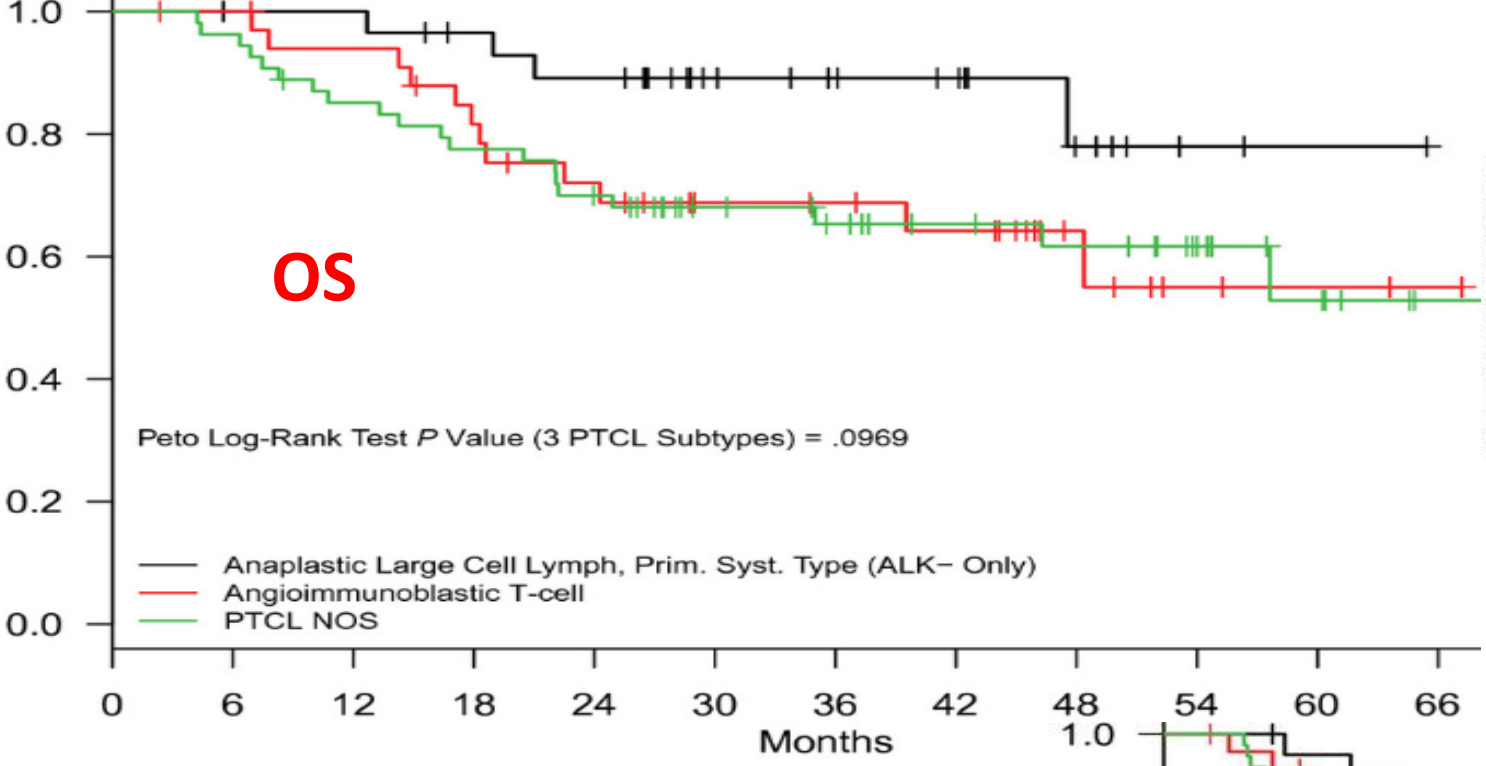


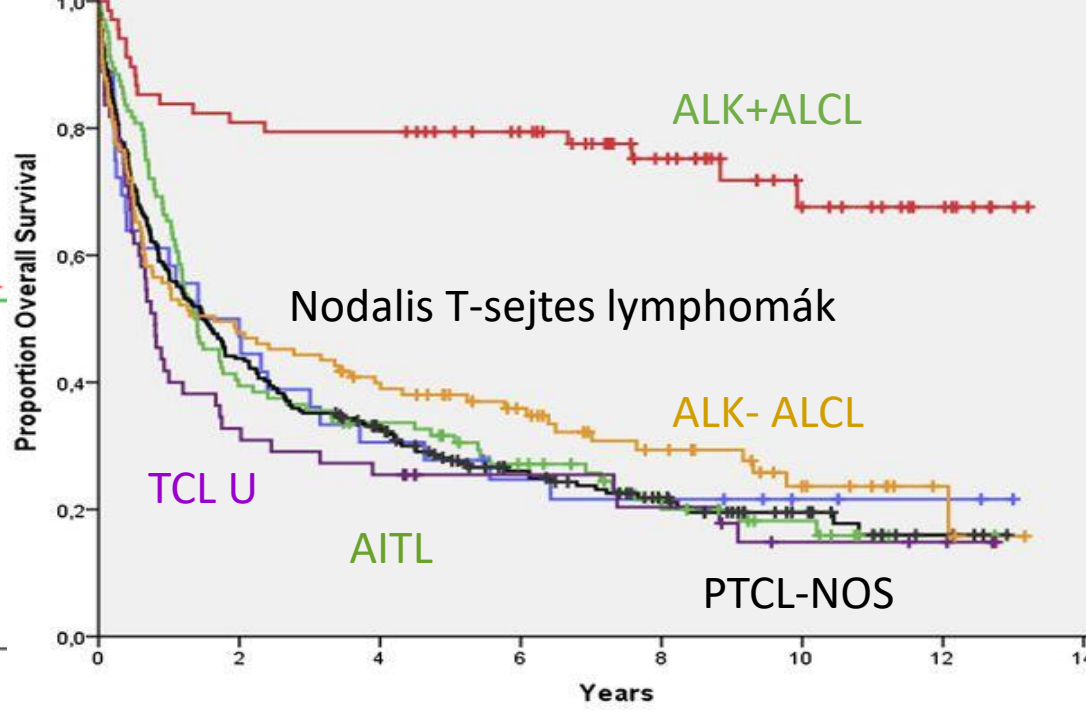
OS



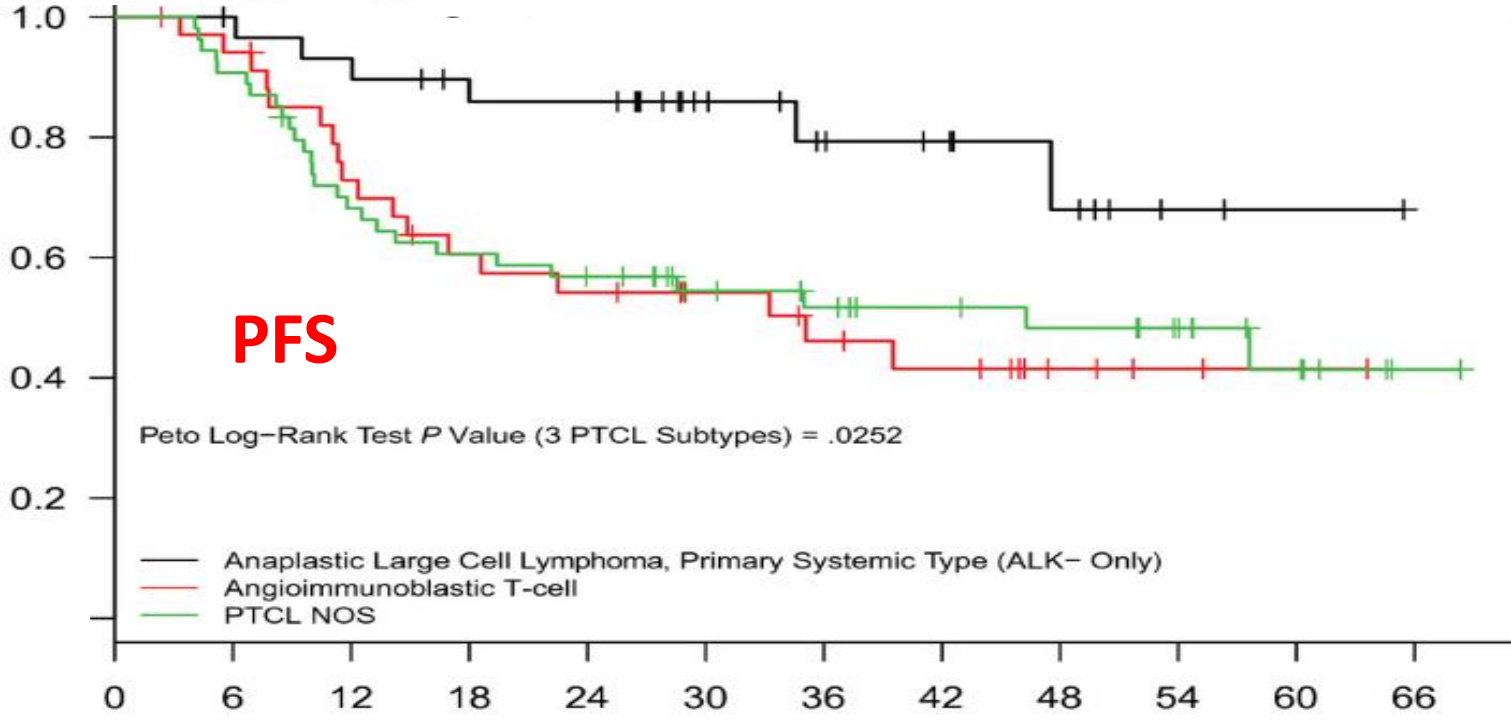
PFS

Park SI, et al. Cancer 2019;125:1507-1517





Autológ SCT szerepe nodális PTCL-ben frontline: prospective vizsgálat (COMPLETE study)



Park SI, et al. Cancer 2019;125:1507-1517

Table 1. Large prospective trials on autoHCT consolidation as part of PTCL frontline therapy

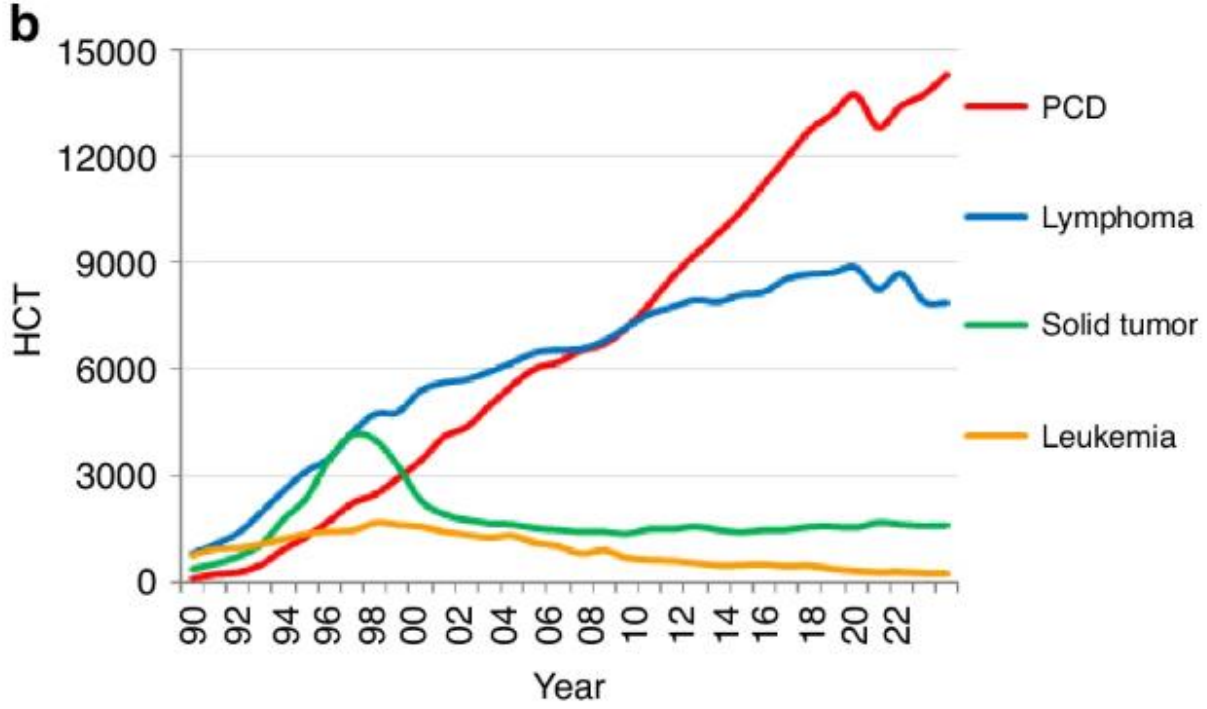
	GLA/LYSA AATT[10,11] (autoHCT arm only)	Nordic[8]	German[9]
Study type	RCT (auto vs allo)	Phase 2, prospective	Phase 2, prospective
Eligibility	NOS, AITL, ALCL ALK−, EATL, HSTL, SPPTCL	NOS, AITL, ALCL ALK−, EATL, HSTL, ENKTCL	NOS, AITL, ALCL ALK−, EATL, HSTL, ENKTCL
	18–60 y	18–67 y	18–65 y
N (% AITL+ALCL+NOS)	54 (78%)	160 (77%)	111 (85%)
AITL	31%	19%	33%
ALCL ALK−	17%	19%	14%
PTCL-NOS	30%	39%	38%
Period	2011–2014	2001–2007	2001–2010
Age (years; median [range])	50 (28–60)	57 (22–67)	49 (23–66)
PS > 1 (ECOG)	20%	29%	NA
aaIPI high/high-intermediate	56%	NA	58%
LDH>N	61%	62%	58%
Proceeded to HCT	63%	72%	68%
High-dose regimen	BEAM	BEAM	TBI/CY
Progression-free survival			
3 y	39%	48%	49%[b]
Long-term	35% (7 y)	44% (5 y)	30% (7 y)[b]
Overall survival			
3 y	70%	56%	56%[b]
Long-term	61% (7 y)	51% (5 y)	39% (7 y)[b]
Adverse factors	PFS: LDH > N[a]	OS, PFS: non-ALCL, age, PS >1	OS: aaIPI high/high-intermediate
Follow-up (mo)	84 (0–109)	61 (26–96)	59 (1–107)

Dreger P és Schmitz N Hematology Am Soc Hematol Educ Program (2024) 2024 (1): 69–77. https://doi.org/10.1182/hematology.2024000670

kondicionálás

Túlélés

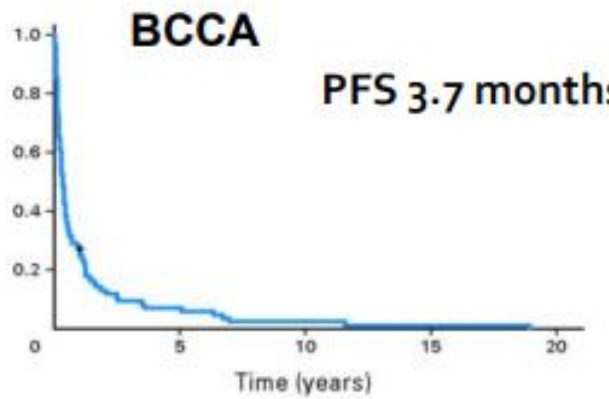
Európában 2023-ban
NHL-ban 5609 auto SCT, az előző évhez képest 10,5 %-os csökkenés.
50,6 % DLBCL
35,4 % egyéb B-sejtes lymphoma
14,0 % (783 fő) T-sejtes lymphoma
593 allo SCT T-sejtes lymphomában
57 % auto – 43 % allo TCL-ban

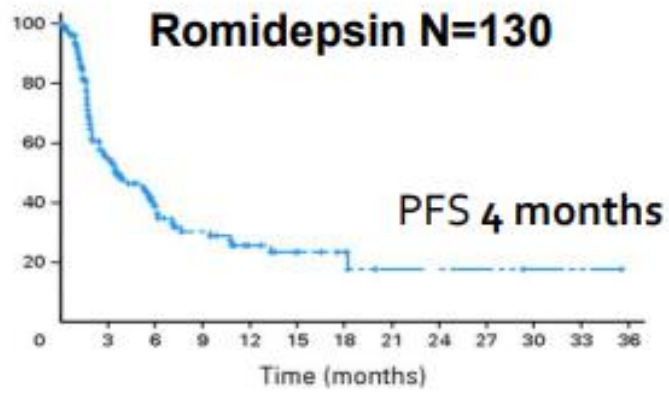


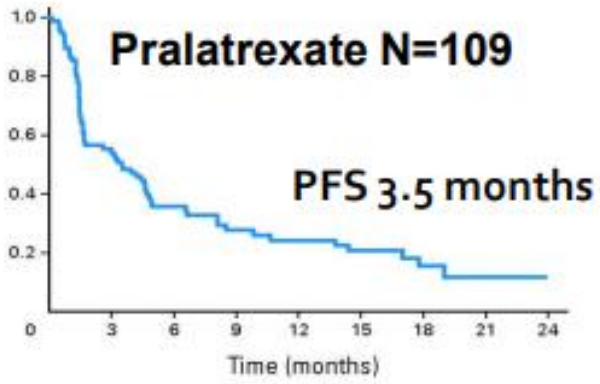
Passweg JR et al. Bone Marrow Transplant (2025). https://doi.org/10.1038/s41409-025-02524-2

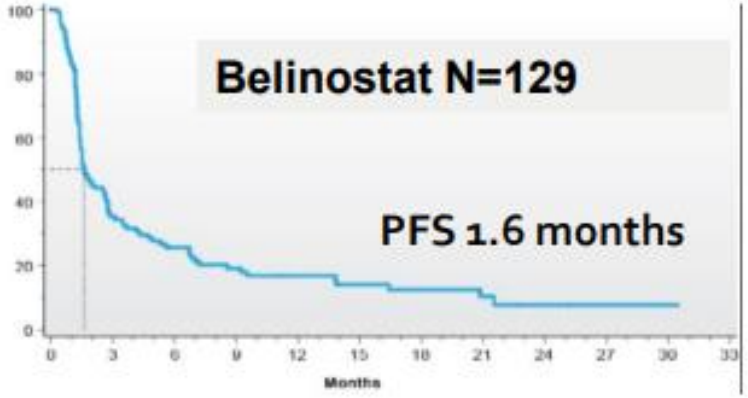
Túlélési adatok refrakter/relapszusos T-sejtes lymphomában

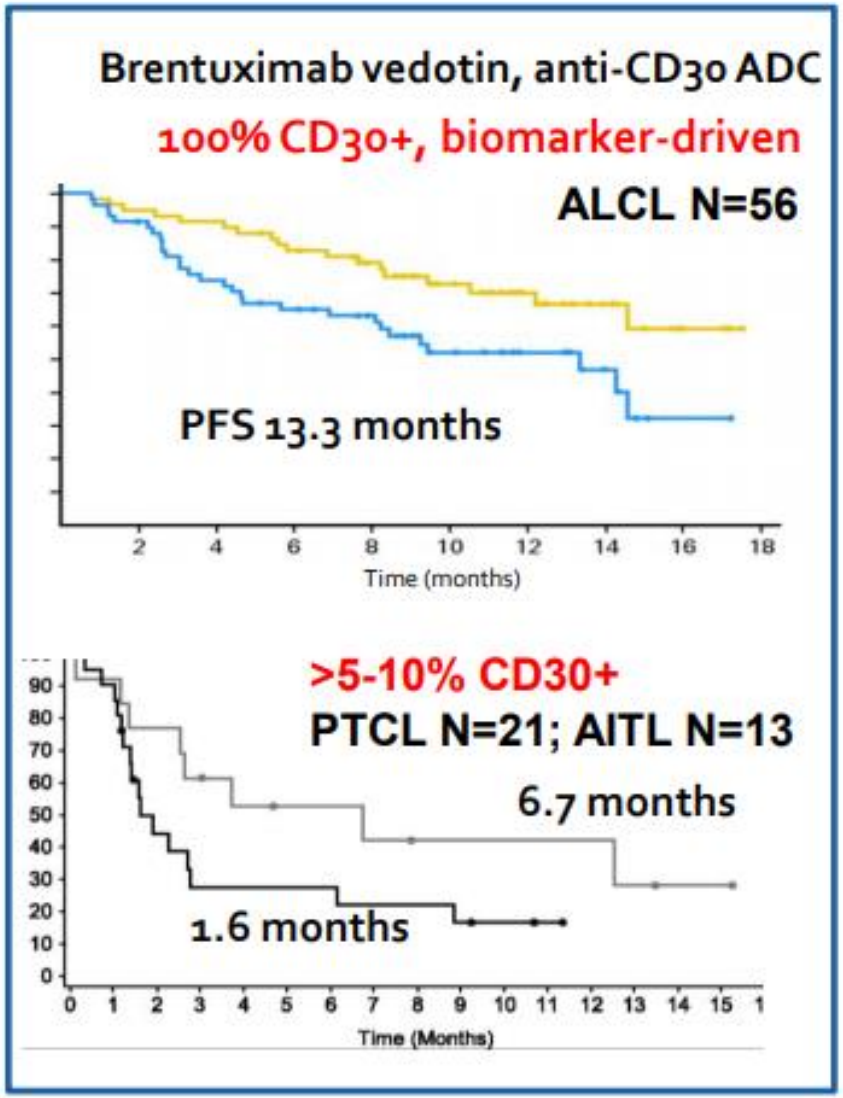
Approval data in relapsed/refractory setting











Mak V et al. JCO 2013;31:1970-1976, O'Connor OA, et al. *J Clin Oncol*. 2011;29:1182-1189, Coiffier B, et al. *J Clin Oncol*. 2012;30 :631-636, O'Connor OA et al ASCO 2013, Pro B, et al. J Clin Oncol. 2012;30:2190-2196, Horwitz SM et al. Blood 2014;123:3095-3100

MÁSODVONALBELI KEZELÉSEK

NCCN GUIDELINES®

T-Cell Lymphomas, Version 2.2022

SUGGESTED TREATMENT REGIMENS[a]
PTCL-NOS; EATL; MEITL[f]

SECOND-LINE THERAPY AND SUBSEQUENT THERAPY (WITH INTENTION TO PROCEED TO TRANSPLANT)

- Clinical trial preferred

Preferred regimens

- Single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ PTCL[d,g]
  - Pralatrexate
  - Romidepsin
- Combination regimens (alphabetical order)
  - DHAP (dexamethasone, cytarabine, cisplatin)
  - DHAX (dexamethasone, cytarabine, oxaliplatin)
  - ESHAP (etoposide, methylprednisolone, cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

Other recommended regimens

- Single agents (alphabetical order)
  - Bendamustine[d]
  - Duvelisib[k]
  - Gemcitabine
  - Lenalidomide[d]
- Combination regimen
  - GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[p]

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO TRANSPLANT)

- Clinical trial preferred

Preferred regimens (alphabetical order)

- Belinostat
- Brentuximab vedotin for CD30+ PTCL[d,g]
- Pralatrexate
- Romidepsin

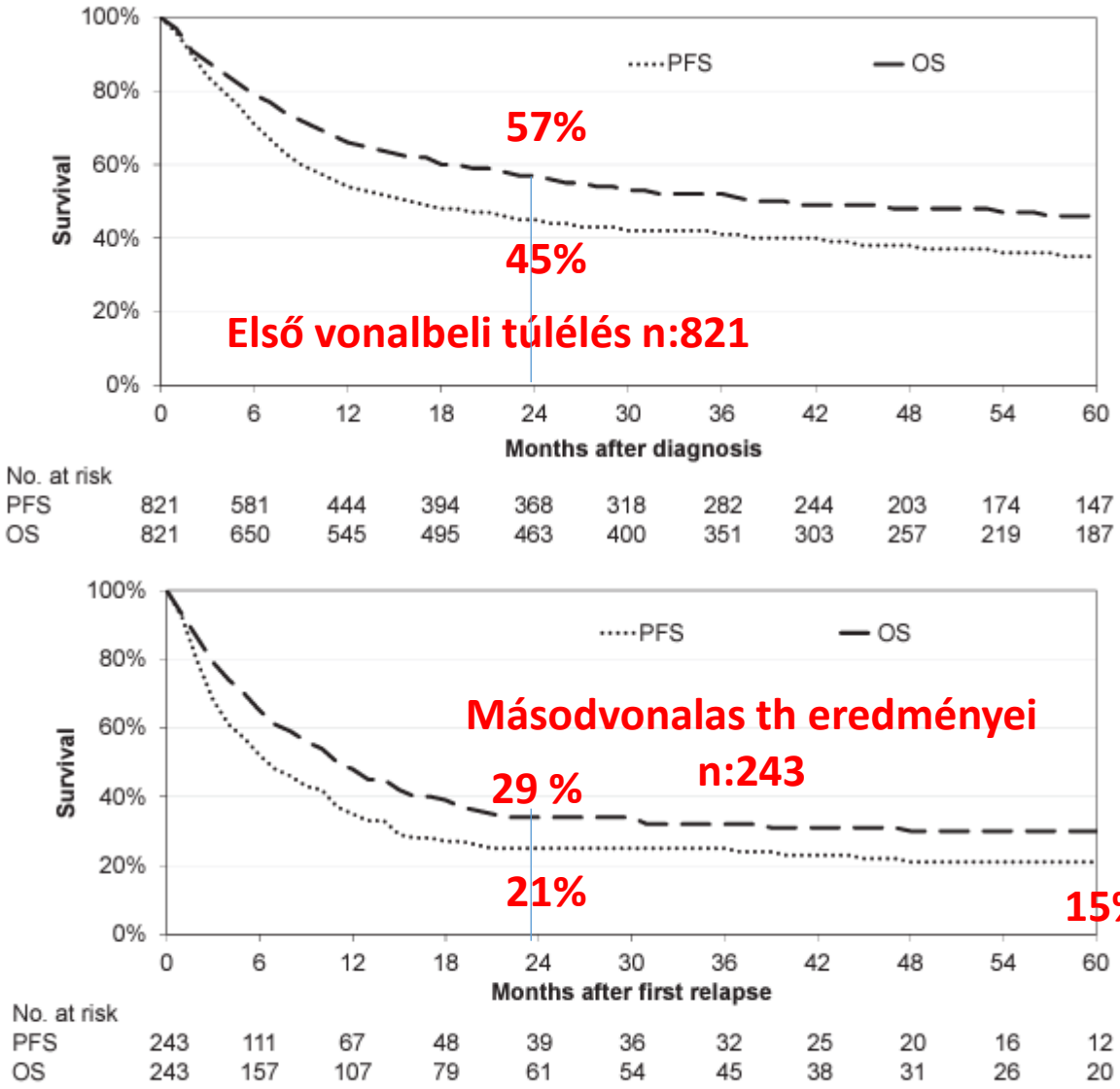
Other recommended regimens (alphabetical order)

- Alemtuzumab[i]
- Bendamustine[d]
- Bortezomib[j] (category 2B)
- Cyclophosphamide and/or etoposide (IV or PO)
- Duvelisib[k]
- Gemcitabine
- Lenalidomide[d]
- RT[l]

See First-line Therapy on TCEL-B 1 of 7.
See Second-line and Subsequent Therapy:
AITL, including nodal PTCL, TFH and FTCL (TCEL-B 4 of 7)
ALCL (TCEL-B 5 of 7)

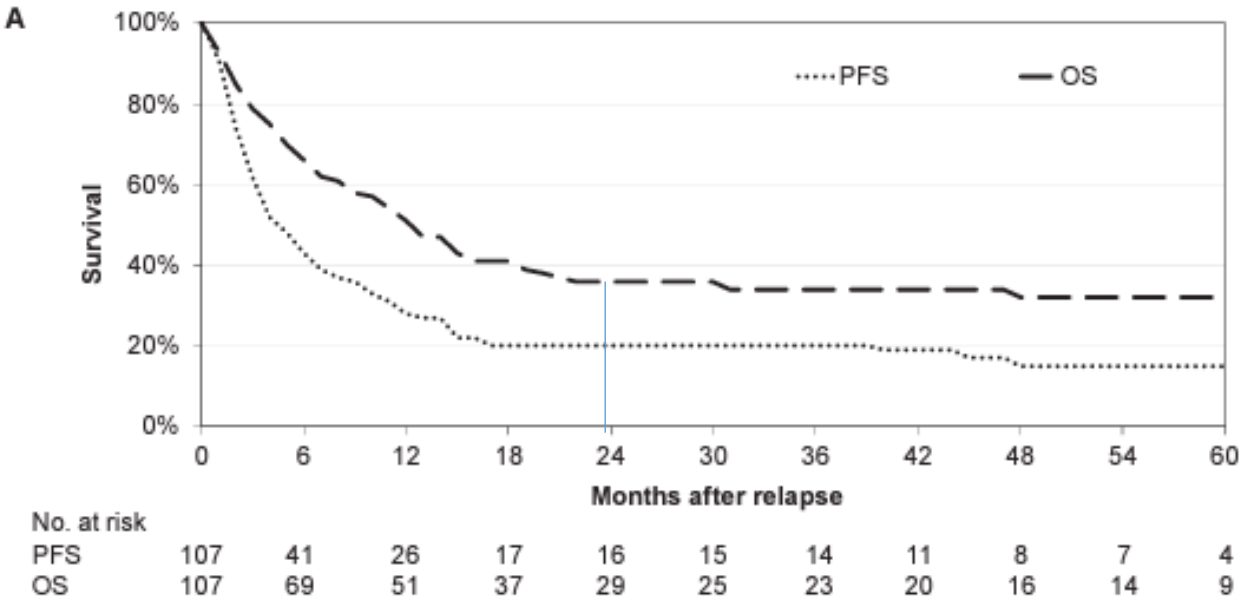
[a] See references for regimens on TCEL-B 6 of 7* and TCEL-B 7 of 7*.
[d] See Supportive Care (TCLYM-B).
[f] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[g] Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30-positivity.
[i] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. CMV monitoring or prophylaxis is recommended. (See TCLYM-B).
[j] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[k] In the phase II study, the preferred dosing regimen of duvelisib was 75 mg for 2 cycles followed by 25 mg BID for long-term disease control.
[l] See Principles of Radiation Therapy (TCLYM-D).
[p] Data suggest there may be excessive pulmonary toxicity with GVD (gemcitabine, vinorelbine, liposomal doxorubicin) regimen when used in combination with unconjugated anti-CD30 monoclonal antibodies for the treatment of Hodgkin lymphoma (Blum KA, et al. Ann Oncol 2010;21:2246-2254). A similar regimen, gemcitabine and liposomal doxorubicin, may be used for mature T-cell lymphoma; however, it is recommended to wait 3 to 4 weeks following treatment with brentuximab vedotin before initiation.

Holland rákregiszter PTCL NOS, AITL, ALCL-es betegei 2014.01.01.-2019.12.31.



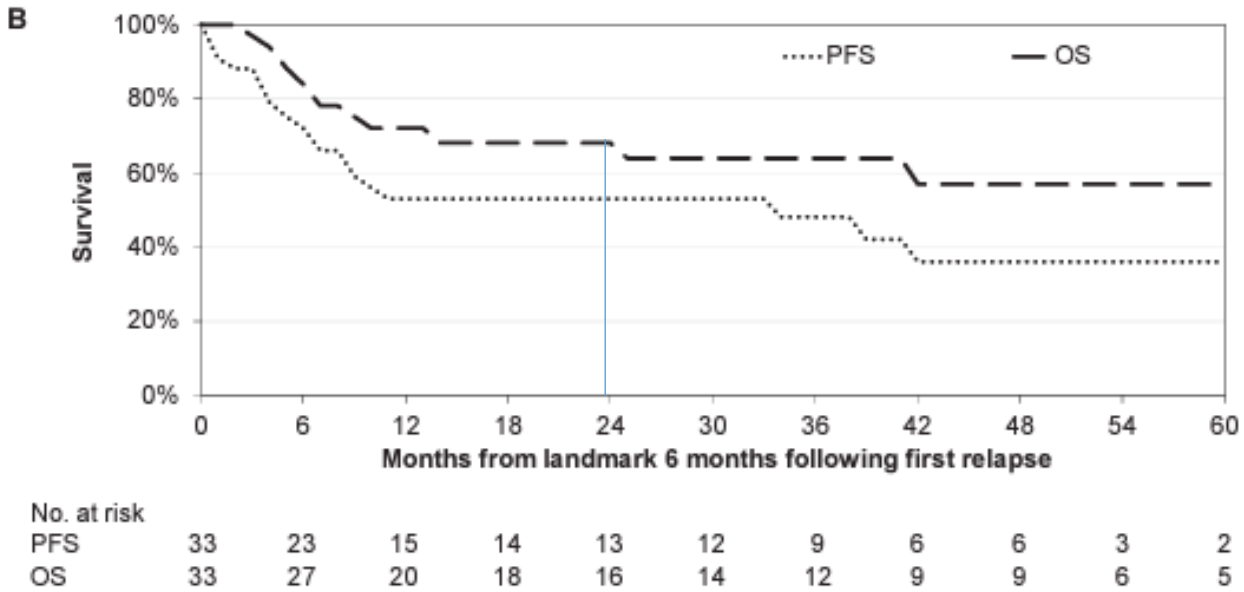
PTCL NOS:32 %; AITL:37 %,
ALCL:30 % (61% ALK neg, 39% +)
CR: CHOP+ASCT: 88%
CHOP noASCT:45 %
egyéb: 31 %
Relapsus: PTCL NOS: 42 %
AITL: 41 %
ALK neg ALCL: 33 %
ALK+ ALCL: 22%
2. Th: DHAP/GDP +/- BV, egyéb
ORR:47 %, CR:35 %,12 % PR
3. Th ORR:43 %, CR:25 %
Allo Tx 42 (17 %) 2év OS, PFS:60%

Brink M et al Blood Advances 2024. 05.13. https://doi.org/10.1182/bloodadvances.2023012531



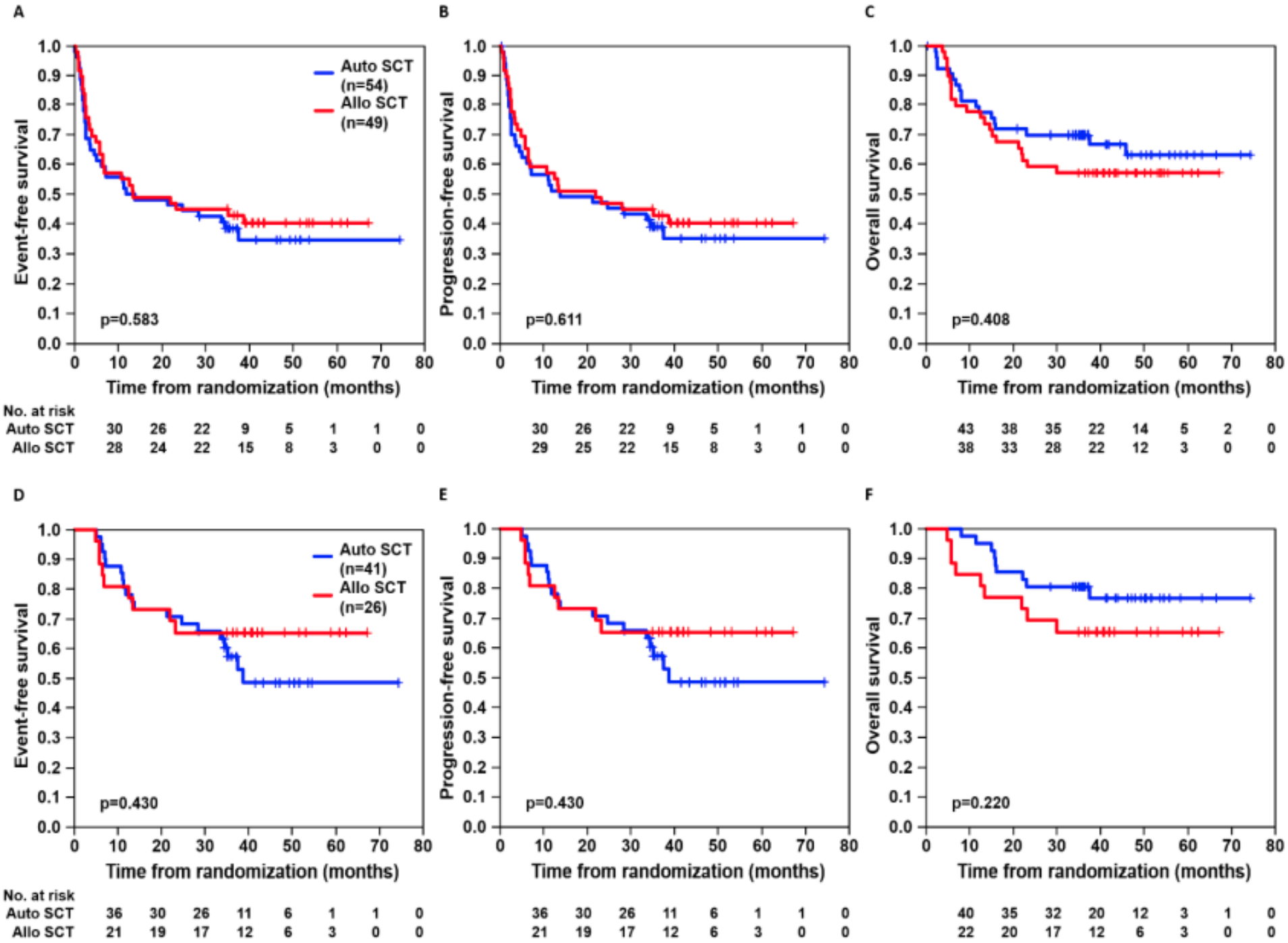
107 beteg túlélése, aki DHAP/GDP-t kapott 2nd line (panel A).

Holland Rákregiszter PTCL NOS, AITL, ALCL-es betegei



33 beteg túlélése, aki a DHAP/GDP után autológ vagy allogén átültetést kapott.s.

Brink M et al Blood Advances 2024. 05.13. https://doi.org/10.1182/bloodadvances.2023012531



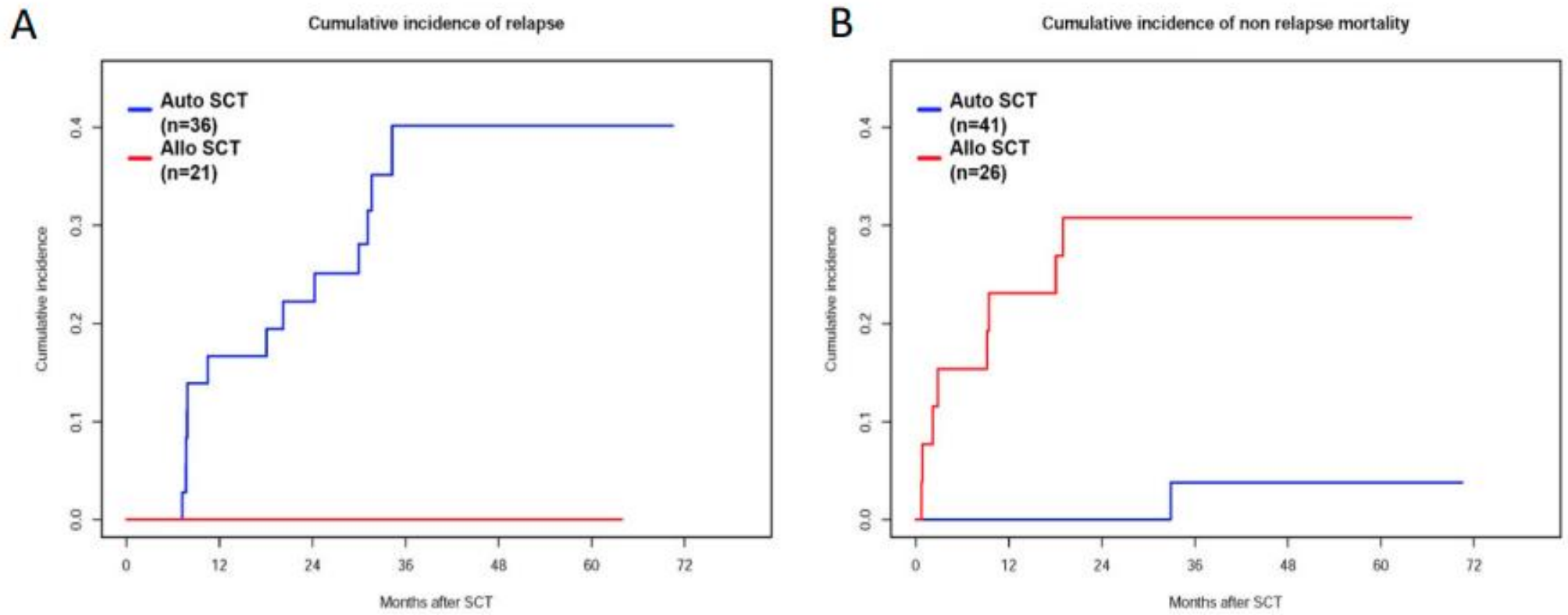
A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL

A,B,C: randomizált

D,E,F: transzplantált

Schmitz N et al. Blood 2021;137:2646-2656.

A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL

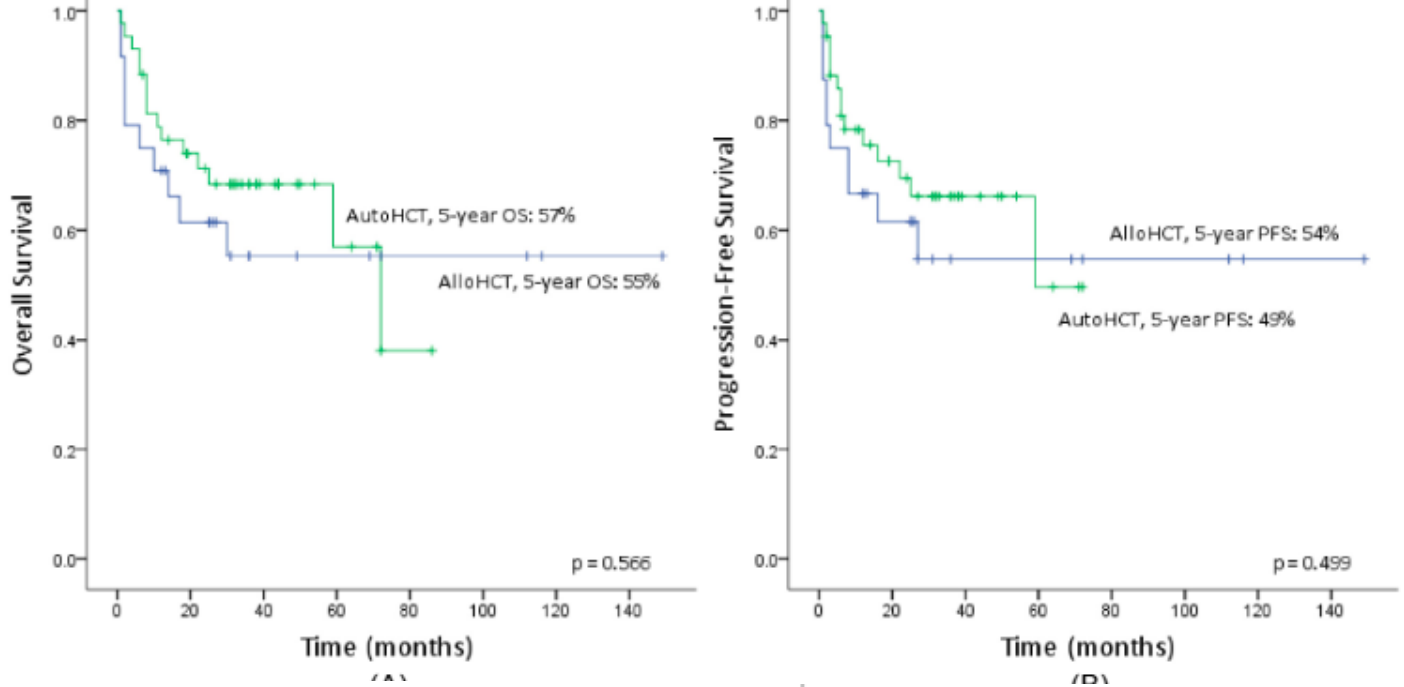


Schmitz N et al. Blood 2021;137:2646-2656.

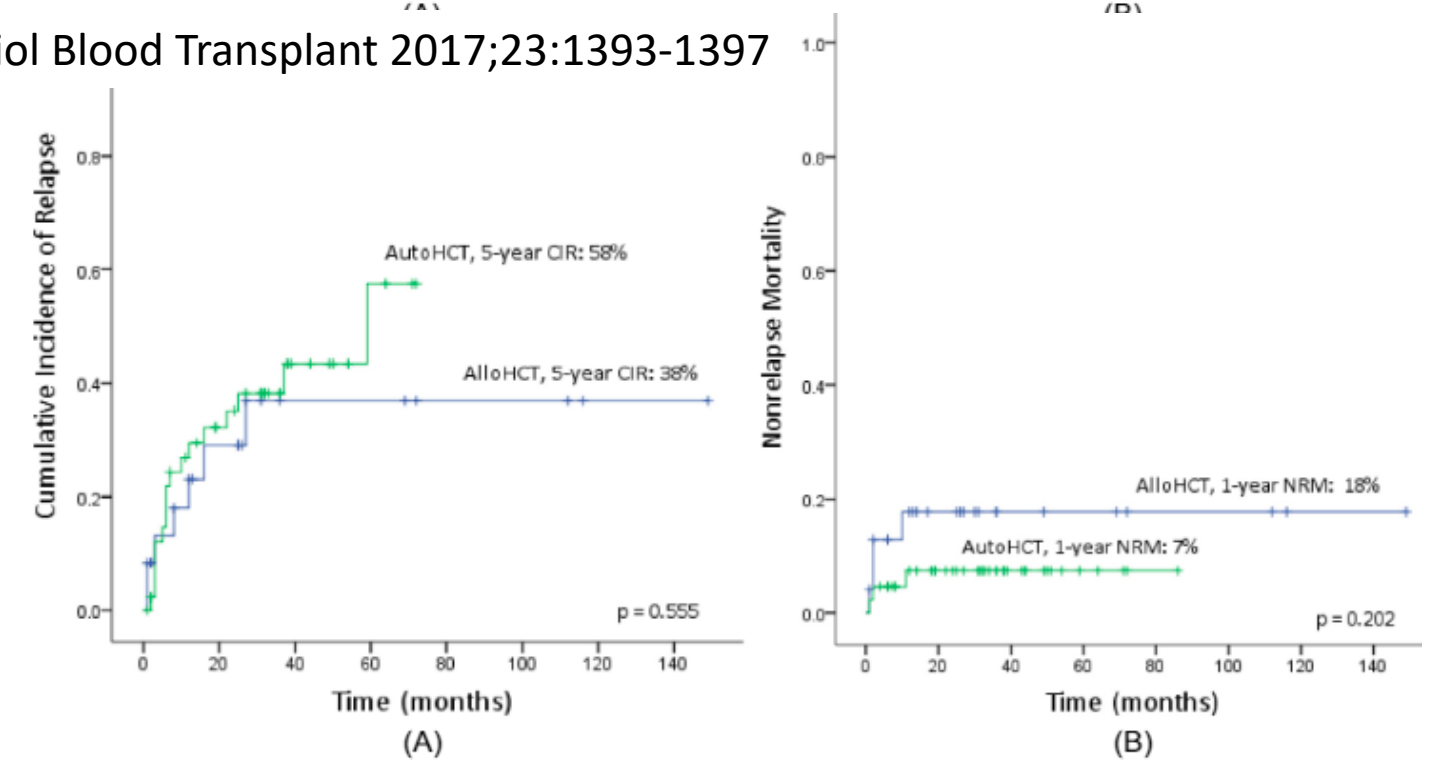
Transplantation-Related Characteristics

Characteristic	AutoHCT		AlloHCT		P
	No.	%	No.	%	
Disease status at transplantation					<.01
CR1	20	46.5	0	0	
CR2	6	13.9	2	8.3	
PR	7	16.3	6	25.0	
NR	10	23.3	16	66.7	
Conditioning regimen (auto)			NA		
BEAM	38	88.4			
Other*	5	11.6			
Conditioning regimen (allo)	NA				
TBI/Cy			6	25.0	
Bu/Cy			18	75.0	
Type of donor	NA				
HLA-identical sibling			3	12.5	
Matched unrelated			5	20.8	
Mismatched related			16	66.7	
Donor-recipient sex match	NA				
Male to male			9	37.5	
Male to female			5	20.8	
Female to male			7	29.2	
Female to female			3	12.5	
Tissue for graft	NA				
BM			1	4.2	
PB			11	45.8	
BM+PB			4	16.7	
BM+PB+CB			8	33.3	
GVHD prophylaxis	NA				
CSA+MTX			5	20.8	
ATG+CSA+MMF+MTX			19	79.2	
GVHD	NA				
aGVHD			9	37.5	
cGVHD			4	16.7	
Responses to transplantation					.695
CR	28	65.1	14	58.3	
PR	9	20.9	7	29.2	
NR	4	9.3	1	4.2	
Death	2	4.7	2	8.3	
Status at last contact					.563
Dead	15	34.9	10	41.7	
AWD	5	11.6	1	4.2	
NED	23	53.5	13	54.1	
Time from transplantation to relapse, months					.568
Median	6		8		
Range	2-59		1-27		

PR indicates partial remission; NR, no remission; NA, not available; BEAM, semustine/carmustine, etoposide, cytarabine, melphalan; TBI/Cy, total body irradiation, cyclophosphamide; Bu/Cy, busulfan, cyclophosphamide; BM, bone



Huang H et al. Biol Blood Transplant 2017;23:1393-1397



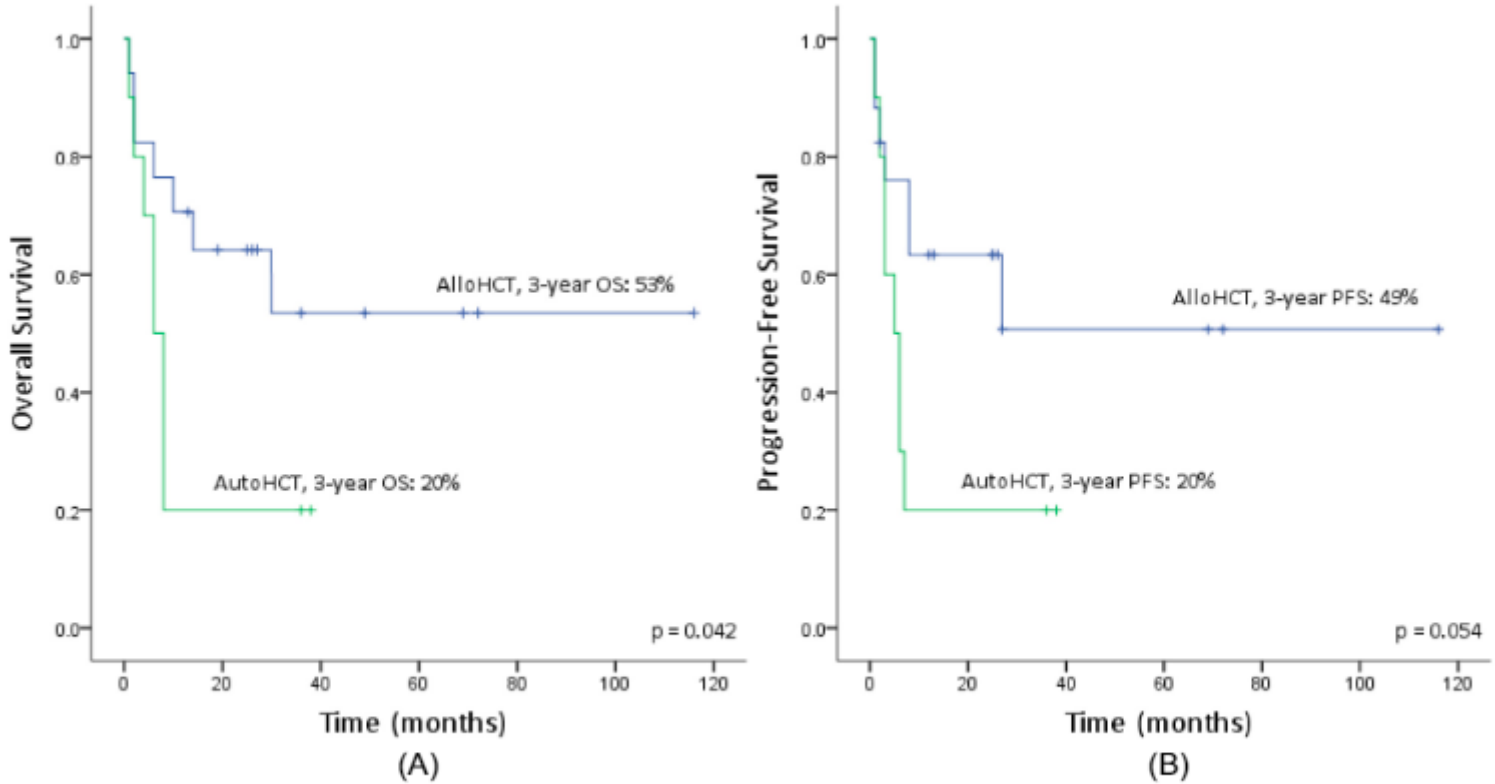


Figure 3. Kaplan-Meier curves for overall survival (OS) (A) and progression-free survival (PFS) (B) for patients in primary refractory disease who underwent autoHCT versus alloHCT.

Huang H et al. Biol Blood Transplant 2017;23:1393-1397

Table 2. Select studies addressing prognosis and the effect of HCT in patients with R/R PTCL using the time point of relapse as baseline

	GLA/LYSA AATT[10,11]	Heidelberg[15]	MDACC[41]	Milan INT[23]	Int. T-cell project[4]
Study type	RCT, post-hoc retrospective	Single-center retrospective	Registry retrospective	Single-center retrospective	Registry retrospective
Eligibility	NOS, AITL, ALCL ALK, EATL, HSTL, R/R on trial	Any R/R PTCL, consecutive	R/R AITL/NOS, consecutive	Any R/R PTCL, **alloHCT eligible**, consecutive	Any R/R PTCL
N	50	91	240	73	633
Relapsed	20 (40%)	44 (48%)	162 (67%)	38 (52%)	197 (31%)
Primary refractory	30 (60%)	47 (52%)	78 (33%)	35 (48%)	436 (69%)
Period	2011–2021	2001–2014	1999–2014	2001–2017	2006–2016
HCT for R/R disease	**26 (52%)**	**38 (42%)**	**67 (28%)**	**45 (62%)**	99 (16%)
AlloHCT	25 (50%)	31 (34%)	31 (13%)	45 (62%)	23 (4%)
AutoHCT	1 (2%)	7 (8%)	36 (15%)	-	76 (12%)
Strategy	Physician's discretion	ITT alloHCT	Physician's discretion	ITT alloHCT	Physician's discretion
Age (years; median [range])	50 (24–58)[a]	51/63 (21–72)[b]	60 (23–83)	55 (18–68)	59 (18–89)
PS >1 (ECOG) or <70% (Karnofsky)	20%[a]	NA	19%	NA	23%
Prior autoHCT (at study entry)	40%	48%/–[b]	18%	23%	8%
Overall survival from R/R (ITT)	**33% (crude)**	**20% (5 y)**	**20–24% (5 y)**	**34% (4y)**	**23% (3 y)**
OS from R/R with alloHCT					
3 y	68%[c]	60%	52%[c]	57%[c]	
5 y	**65%**	**52%**	**52%**	**51% (4 y)**	
OS from R/R with autoHCT					
3 y		14%	55%[c]		48%[d]
5 y		**0%**	**32%**		**42%**[c,d]
OS from R/R without HCT					
3 y	11%[c]	3%	19%[c]	NA	18%
5 y	11%[c]	**3%**	**10%**	**19% (4 y)**	NA
Untransplanted patients among those surviving ≥3 y[e]	**2/18 (11%)**	**2/18 (11%)**	NA	**2/22 (9%)**	-
Follow-up from R/R (mo)	NA	70 (17–148)	NA	40 (9–192)	38 (1–96)

Dreger P és Schmitz N
Hematology Am Soc Hematol Educ Program (2024) 2024 (1): 69–77.
https://doi.org/10.1182/hematology.2024000670

Transzplantáció

Típusa

Életkor

Túlélés a relapszustól

Túlélés allo SCT-vel

Túlélés auto SCT-vel

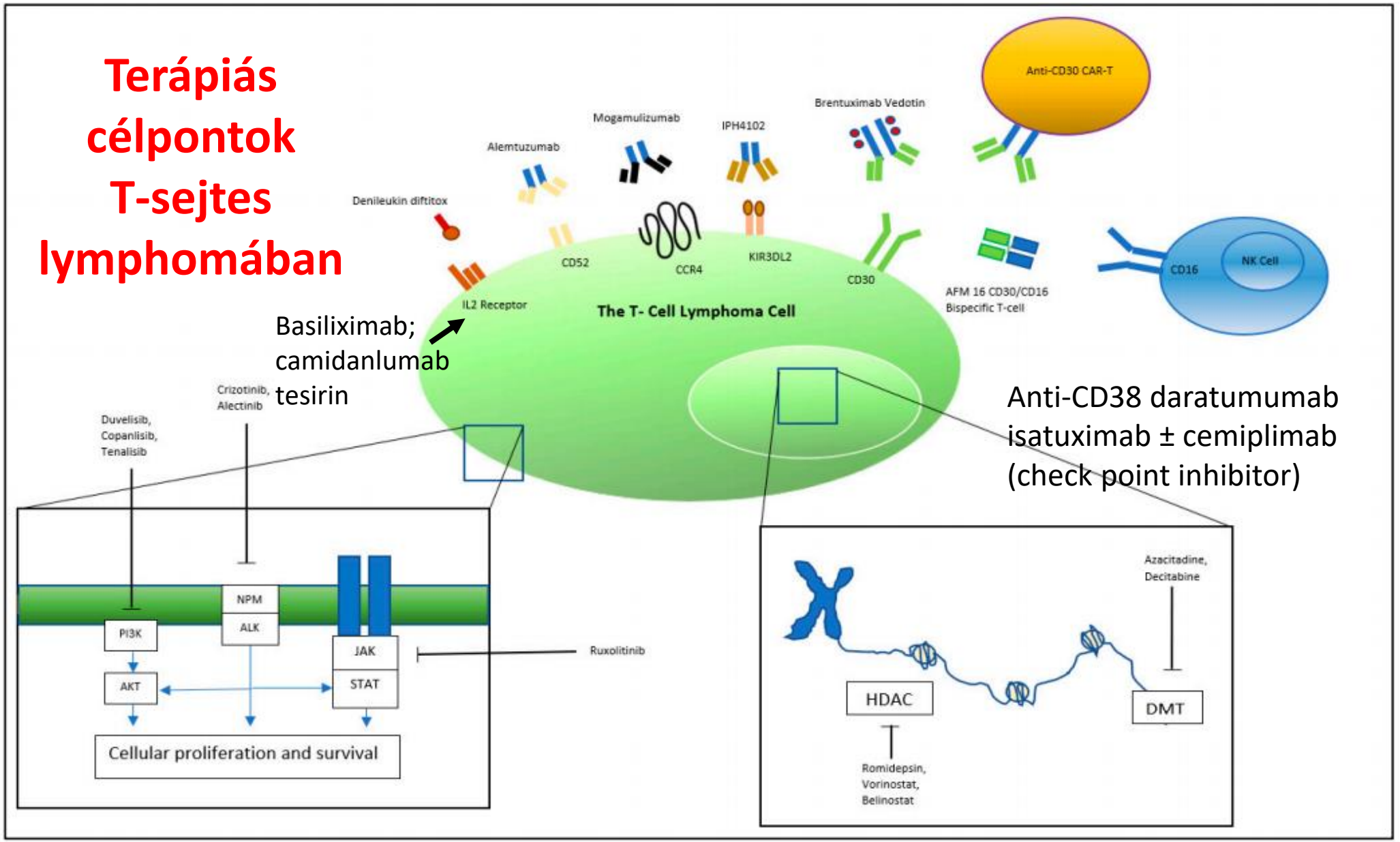
Túlélés SCT nélkül

Table 2. Targeted T-cell therapy by T-cell lymphoma subtype. +++ Data available suggesting particular benefit; + data support routine use; +/− data indeterminate or further data required; − no data to support routine use.

	PTCL-NOS	AITL	sALCL ALK+	sALCL ALK-	MF	SS
Brentuximab Vedotin	+	+	+++	+++	+	+
Alemtuzumab	+/−	+/−	+/−	+/−	+/−	+
Mogamulizumab	+/−	+/−	+/−	+/−	+/−	+
Denileukin diftitox	+/−	+/−	+/−	+/−	+	+
ALK inhibitors	−	−	+++	−	−	−
PI3K inhibitors	+/−	+/−	+/−	+/−	+/−	+/−
JAK/STAT inhibitors	+/−	+/−	+/−	+/−	+/−	+/−
HDAC inhibitors ???	+	+++	+	+	+	+
Hypomethylating agents	+	+	+	+	+/−	+/−

Harrop S et al. J. Pers. Med. 2021, 11, 481. https://doi.org/10.3390/ jpm11060481

Terápiás célpontok T-sejtes lymphomában



Cell adhesion molecule 1 (CADM1) overexpresszálódik konzisztensen az ATLL sejteken Anti-CADM1 Mo Ab

Anti-ICOS (CD278) ab—MEDI-570 (inducible T-cell costimulator (check point inhibitor)

Figure 1. Targets of novel T-cell lymphoma therapy. PI3K, Phosphoinositide 3-kinase; NPM, Nucleophosmin; ALK, Anaplastic lymphoma kinase; JAK, Janus kinases; STAT, signal transducer and activator of transcription proteins; HDAC, Histone deacetylase; DMT, DNA methyltransferase.

Harrop S et al. J. Pers. Med. 2021; 11: 481. https://doi.org/10.3390/ jpm11060481

CLINICAL TRIALS AND OBSERVATIONS | MARCH 28, 2024

T-cell lymphoma: the CAR-T revolution is coming

Clinical Trials & Observations

Natalie S. Grover, Anne W. Beaven

Blood (2024) 143 (13): 1201–1202.
https://doi.org/10.1182/blood.2023023443

Connected Content

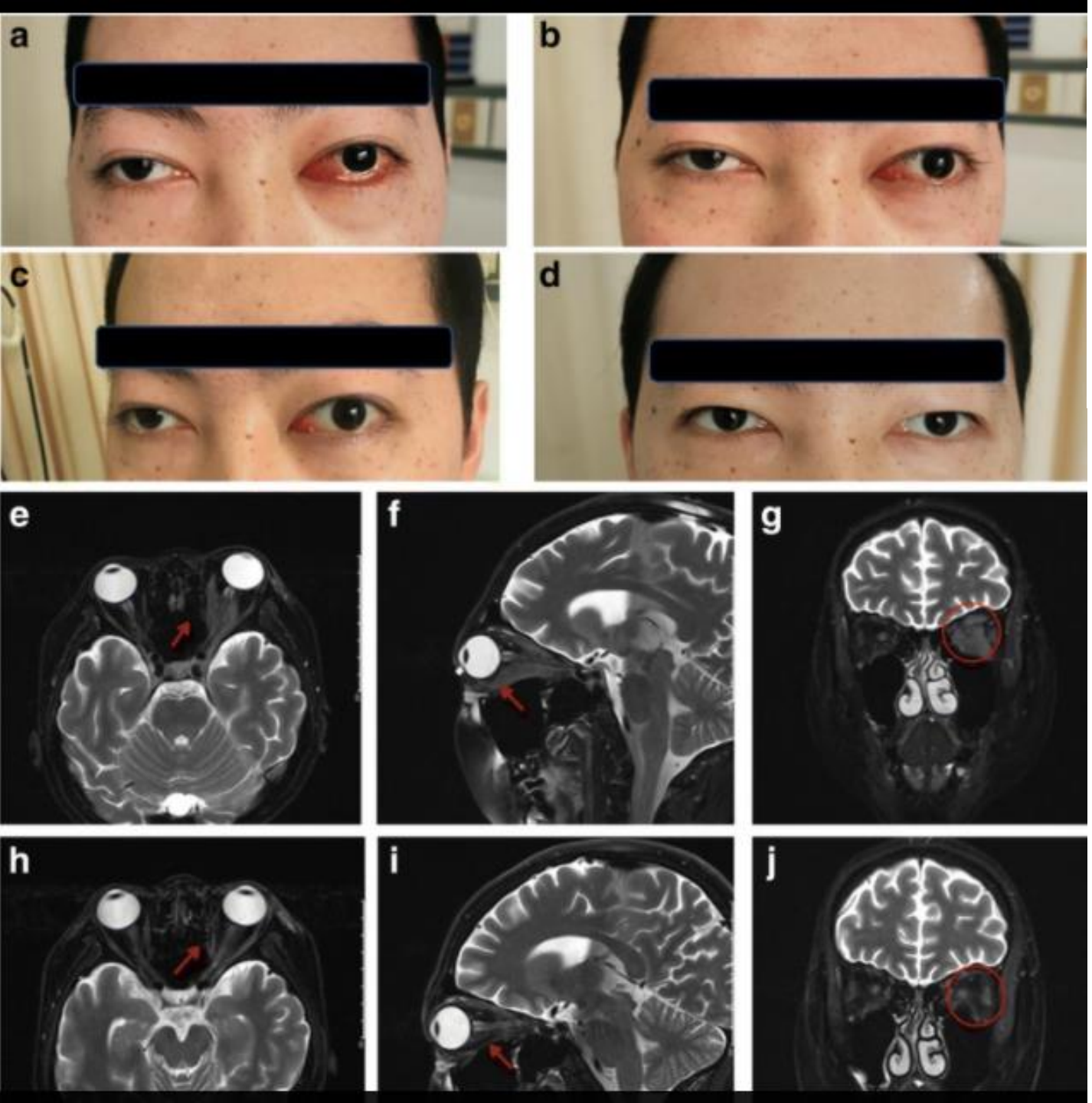
This is a commentary to: Antitumor efficacy and safety of unedited autologous CD5.CAR T cells in relapsed/refractory mature T-cell lymphomas

Subjects: Free Research Articles

In this issue of *Blood*, Hill et al demonstrate the safety and feasibility of chimeric antigen receptor T (CAR T) cells targeting CD5 in treating patients with relapsed and refractory mature T-cell lymphoma.[1]

The prognosis for patients with relapsed or refractory T-cell lymphoma is poor, with few effective therapies, so novel treatment approaches for this patient population are desperately needed.[2] Unfortunately, although CAR T cells have transformed the care for patients with B-cell lymphomas, the CAR-T revolution has not yet had similar success in the treatment of T-cell lymphomas.[3]

The effective design and use of CAR T cells for T-cell lymphoma face several unique challenges. First, most potential target antigens are expressed on normal T cells in addition to malignant T cells. Thus, using pan–T-cell markers could lead to T-cell fratricide with CAR T cells killing other CAR T cells, thereby preventing successful manufacturing of the CAR T product.[4] Similarly, T-cell aplasia and resultant infectious complications could occur as CAR T cells target the normal immune system.[5]



› Stem Cell Rev Rep. 2021 Apr;17(2):652-661. doi: 10.1007/s12015-020-10092-9. Epub 2021 Jan 6.

Treatment of Aggressive T Cell Lymphoblastic Lymphoma/leukemia Using Anti-CD5 CAR T Cells

Jia Feng [1], Haichan Xu [1], Andrew Cinquina [2], Zehua Wu [1], Qi Chen [1], Ping Zhang [1], Xingen Wang [3], Huiming Shan [4], Lei Xu [1], Qian Zhang [1], Lihua Sun [1], Wenli Zhang [1], Kevin G Pinz [2], Masayuki Wada [2], Xun Jiang [2], William M Hanes [2], Yupo Ma [5], Hongyu Zhang [6]

Fig. 2 CD5-IL15/IL15sushi CAR T cells rapidly reduce patient's orbital edema. **a** Prior to CD5-IL15/IL15sushi CAR treatment, the patient's left eye had significant exophthalmos. Repeat imaging **b** 1 week after CD5-IL15/IL15sushi CAR infusion, **c** 2 weeks after infusion, **d** and 3 weeks following therapy demonstrate rapid resolution of the patient's swelling. Prior to CD5-IL15/IL15sushi CAR treatment, MRI showed significant edema in the **e** axial, **f** sagittal, **g** and coronal planes. Red arrows and red circle mark the dense soft tissue infiltrate. 8 weeks following CD5-IL15/IL15sushi CAR treatment, repeat MRI imaging shows reduction in the soft tissue mass shadow in the **h** axial, **i** sagittal, **j** and coronal planes

haematologica
Open access journal of the Ferrata-Storti Foundation, a non-profit organization

ARTICLES

CD28.OX40 co-stimulatory combination is associated with long in vivo persistence and high activity of CAR.CD30 T-cells

Marika Guercio, Domenico Orlando, Stefano Di Cecca, Matilde Sinibaldi, Iolanda Boffa, Simona Caruso, Zeinab Abbaszadeh, Antonio Camera, Biancamaria Cembrola, Katia Bovetti, Simona Manni, Ignazio Caruana, Roselia Ciccone, Francesca Del Bufalo, Pietro Merli, Luciana Vinti, Katia Girardi, Annalisa Ruggeri, Cristiano De Stefanis, Marco Pezzullo, Ezio Giorda, Marco Scarsella, Rita De Vito, Sabina Barresi, Andrea Ciolfi, Marco Tartaglia, Lorenzo Moretta, Franco Locatelli, Concetta Quintarelli, Biagio De Angelis

Vol. 106 No. 4 (2021): April, 2021 https://doi.org/10.3324/haematol.2019.231183

Abstract

The prognosis of many patients with chemotherapy-refractory or multiply relapsed CD30+ non-Hodgkin Lymphoma (NHL) or Hodgkin lymphoma (HL) still remains poor, and novel therapeutic approaches are warranted to address this unmet clinical need. In light of this consideration, we designed and pre-clinically validated a Chimeric Antigen Receptor (CAR) construct characterized by a novel anti-CD30 single-chain variable-fragment cassette, linked to CD3ζ by the signaling domains of two costimulatory molecules, namely either CD28.4-1BB or CD28.OX40. We found that CAR.CD30 T-cells exhibit remarkable cytolytic activity in vitro against HL and NHL cell lines, with sustained proliferation and pro-inflammatory cytokine production, even after multiple and sequential lymphoma cell challenges. CAR.CD30 T-cells also demonstrated anti-lymphoma activity in two in vivo xenograft immune-deficient mouse models of metastatic HL and NHL. We observed that administration of CAR.CD30 T-cells, incorporating the CD28.OX40 costimulatory domains and manufactured in the presence of IL7 and IL15, were associated with the best overall survival in the treated mice, along with the establishment of a long-term immunological memory, able to protect mice from further tumor re-challenge. Our data indicate that, in the context of in vivo systemic metastatic xenograft mouse models, the costimulatory machinery of CD28.OX40 is crucial for improving persistence, in vivo expansion and proliferation of CAR.CD30 T-cells upon tumor encounter. CD28.OX40 costimulatory combination is ultimately responsible for the antitumor efficacy of the approach, paving the way to translate this therapeutic strategy in patients with CD30+ HL and NHL.

Overall, the significant *in vivo* reactivity, the high potency, the negligible toxicity in animals and the long persistence of CAR.CD30.CD28.OX40 T cells contribute to the value of this CAR design, which will be tested in a clinical trial for patients with relapsed/refractory HL and anaplastic large-cell lymphoma.

Leukemia www.nature.com/leu

LETTER OPEN

Check for updates

IMMUNOTHERAPY

Chimeric antigen receptor T cells for gamma–delta T cell malignancies

P. A. Wawrzyniecka[1], L. Ibrahim[1], G. Gritti[2], M. A. Pule[1] and P. M. Maciocia[1]✉

Leukemia; https://doi.org/10.1038/s41375-021-01385-0

TO THE EDITOR:

Cancers derived from the malignant transformation of gamma–delta (γδ) T cells carry very poor prognosis. The major pathologies recognised are γδ T acute lymphoblastic leukaemia (γδ T-ALL), and two lymphoma subtypes: hepatosplenic T cell lymphoma (HSTL) and primary cutaneous γδ T cell lymphoma (PCγδ-TCL) [1]. γδ T-ALL represents approximately 10% of cases of T-ALL and is associated with high rates of induction failure, relapse and excess mortality [2]. HSTL is a rare (approximately 3% of cases of T cell lymphoma [1]) but highly aggressive disorder, which typically presents in males in the 2nd or 3rd decade of life, often in association with immunosuppressive therapy [3]. It carries the worst prognosis of all lymphoma subtypes, with a median survival of only 6–8 months [4] and only isolated cases of long-term survival [5]. PCγδ-TCL is also rare (approximately 1% of skin lymphomas [1]) and presents with cutaneous involvement, typically associated with visceral and/or

transduction with anti-CD19 CAR, a small proportion of γδ T cells persisted in the culture, including some which expressed anti-CD19 CAR. By contrast, for anti-γδ TCR CAR, no γδ T cells were detected in the culture, suggesting 'purging' of these cells by the transduced population (Fig. 1b). CAR-T cells were then co-cultured with T cell lines which natively express (Loucy – Vγ9Vδ2, BE13 – Vγ8Vδ1, MOLT13 – Vγ3Vδ1 [8]) or are negative for surface γδ TCR (SupT1-CD19). While control anti-CD19 CAR lysed only SupT1-CD19 cells, anti-γδ TCR CAR-T lysed only γδ TCR-positive cell lines (Fig. 1c). In addition, anti-γδ TCR CAR-T cells demonstrated specific secretion of cytokines including interferon-γ, IL-2, IL-13 and TNF-α (Fig. 1d). Next, we co-cultured anti-CD19 or anti-γδ CAR-T cells with normal autologous γδ T cells. At a high E:T ratio (1:1), target normal γδ T cells were partially lysed (Fig. 1e), with concomitant expansion of anti-γδ CAR-T cells (Fig. 1f). A marked down-regulation of γδ TCR expression was noted on surviving γδ T cells

További vizsgált CAR T-sejtek T-sejtes lymphomában:

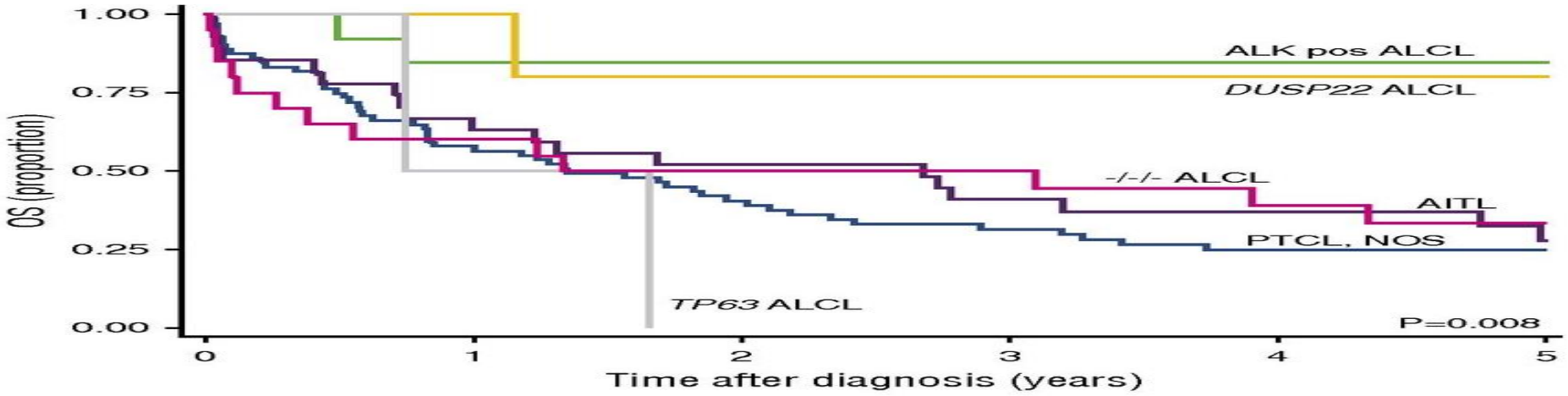
Anti-CD7 CARTs
Anti-CD4 CARTs

Table 1 Genetic findings and biomarkers with potential relevance in the work-up of ALCL

Biomarker	Test	Purpose	Disease	Comment
ALK expression	IHC	Diagnosis	ALCL, ALK+	Surrogate for *ALK* rearrangement
ALK rearrangements	FISH or NGS	Diagnosis	ALCL, ALK+	Useful when ALK IHC is non-contributory
ALK mutations	NGS	Predictor of response	ALCL, ALK+	Resistance to ALK inhibitors
NOTCH1 mutation[a,16]	NGS	Predictor of response	ALCL, AL +	Potential sensitivity to targeted therapy
DUSP22 rearrangement[19,20]	FISH	Prognosis and treatment	ALCL, ALK−	Favorable prognosis in systemic ALCL; consideration of modified treatment algorithm
TP63 rearrangement[24]	FISH	Prognosis	ALCL, ALK−	Aggressive behavior in systemic ALCL
JAK1 and *STAT3*[27]	NGS	Prognosis and treatment	ALCL, ALK−	Could help in the diagnosis of ALK-ALCL and potentially targetable
Loss chr 20[a,41]	FISH	Diagnosis	BIA-ALCL	Relatively specific

ALK anaplastic lymphoma kinase, *ALCL* anaplastic large cell lymphoma, *DUSP22* dual specificity phosphatase 22, *IHC* immunohistochemistry, *BIA-ALCL* breast implant-associated anaplastic large cell lymphoma.

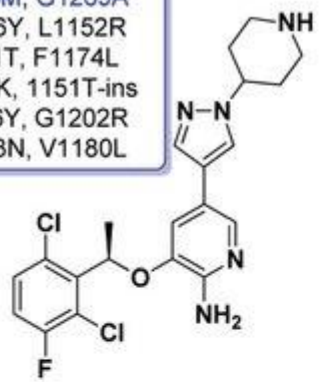
Vega, F. et al. Mod Pathol 2021. https://doi.org/10.1038/s41379-021-00937-0



Pedersen MB at al. Blood 2017;130:554-557.

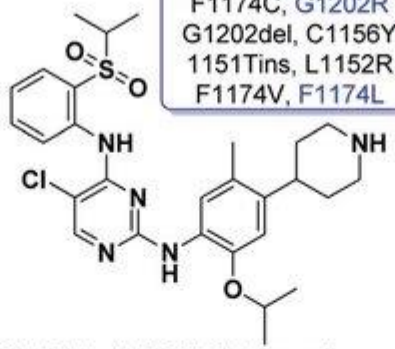
ALK gátlók

Crizotinib Resistance Mutations
L1196M, G1269A
C1156Y, L1152R
I1171T, F1174L
E1210K, 1151T-ins
S1206Y, G1202R
D1203N, V1180L



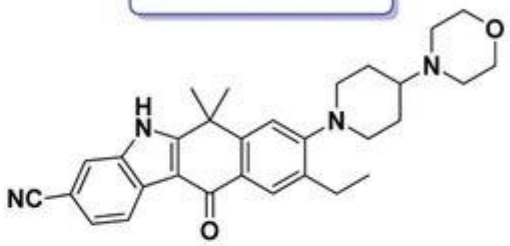
Crizotinib (PF-2341066), Pfizer
1st-generation ALK inhibitor
FDA approved in Aug, 2011 as ALK/c-Met inhibitor
FDA approved in Mar, 2016 as ROS1 inhibitor

Ceritinib Resistance Mutations
F1174C, G1202R
G1202del, C1156Y
1151Tins, L1152R
F1174V, F1174L

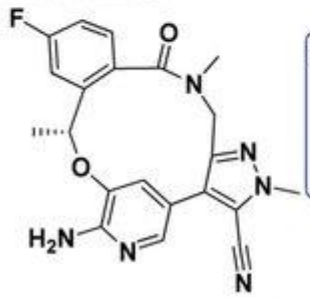


Ceritinib (LDK-378), Novartis
2nd-generation ALK inhibitor
Breakthrough therapy designation in March 2013
FDA approved in April, 2014 as ALK inhibitor
FDA approved in May, 2017 as first line therapy

Alectinib Resistance Mutations
I1171T/N/S, G1202R
V1180L

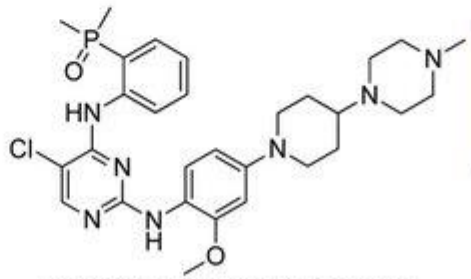


Alectinib (CH5424802), Chugai, Roche
2nd-generation ALK inhibitor
FDA approved in Dec, 2015 (Genentech Inc.)
ALK, GAK and LTK inhibitor



Lorlatinib Resistance Mutations
L1198F,
C1156Y/L1198F
C1156Y

Lorlatinib (PF-06463922), Pfizer
3rd-generation ALK inhibitor
ALK/ROS1 inhibitor in Phase I/II trials
Breakthrough therapy designation in April 2017



Brigatinib Resistance Mutations
G1202R
E1210K + S1206C
E1210K + D1203N

Brigatinib (AP26113), Alunbrig
3rd-generation ALK inhibitor, Phase II
FDA approved in April, 2017 as ALK inhibitor

Clinical Trial > Cancer Sci. 2020 Dec;111(12):4540-4547. doi: 10.1111/cas.14671.
Epub 2020 Oct 28.

Alectinib for relapsed or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: An open-label phase II trial

Reiji Fukano [1], Tetsuya Mori [2], Masahiro Sekimizu [3], Ilseung Choi [4], Akiko Kada [5], Akiko Moriya Saito [5], Ryuta Asada [6], Kengo Takeuchi [7 8 9], Takashi Terauchi [10], Ukihide Tateishi [11], Keizo Horibe [3 5], Hirokazu Nagai [5 12]

Affiliations + expand

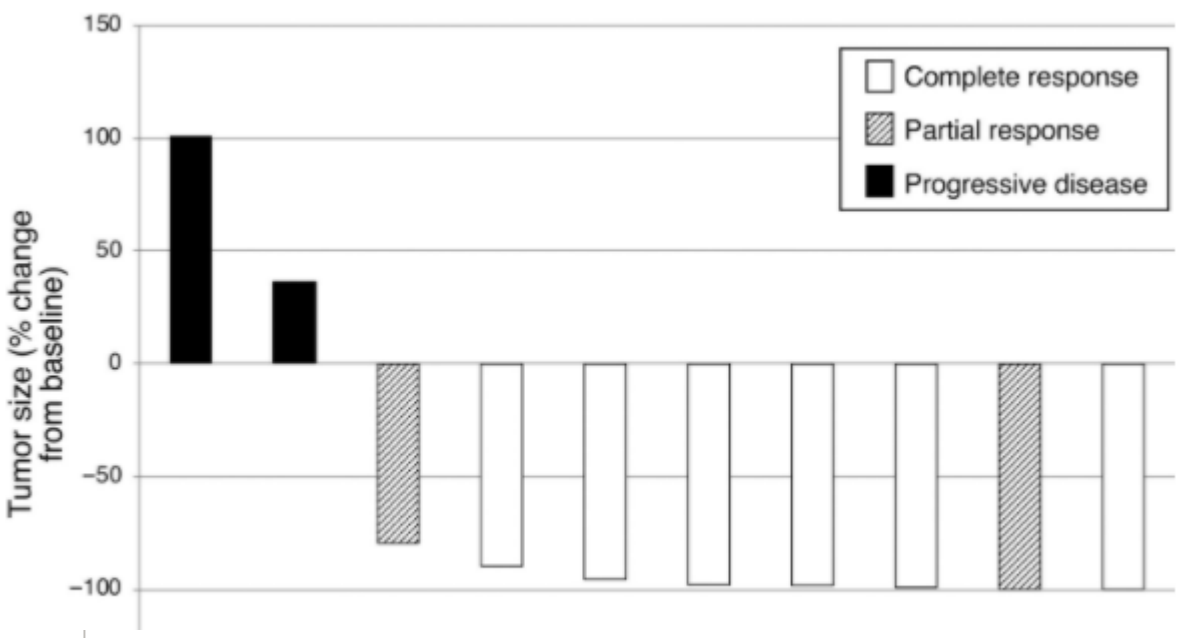
PMID: 33010107 PMCID: PMC7734006 DOI: 10.1111/cas.14671

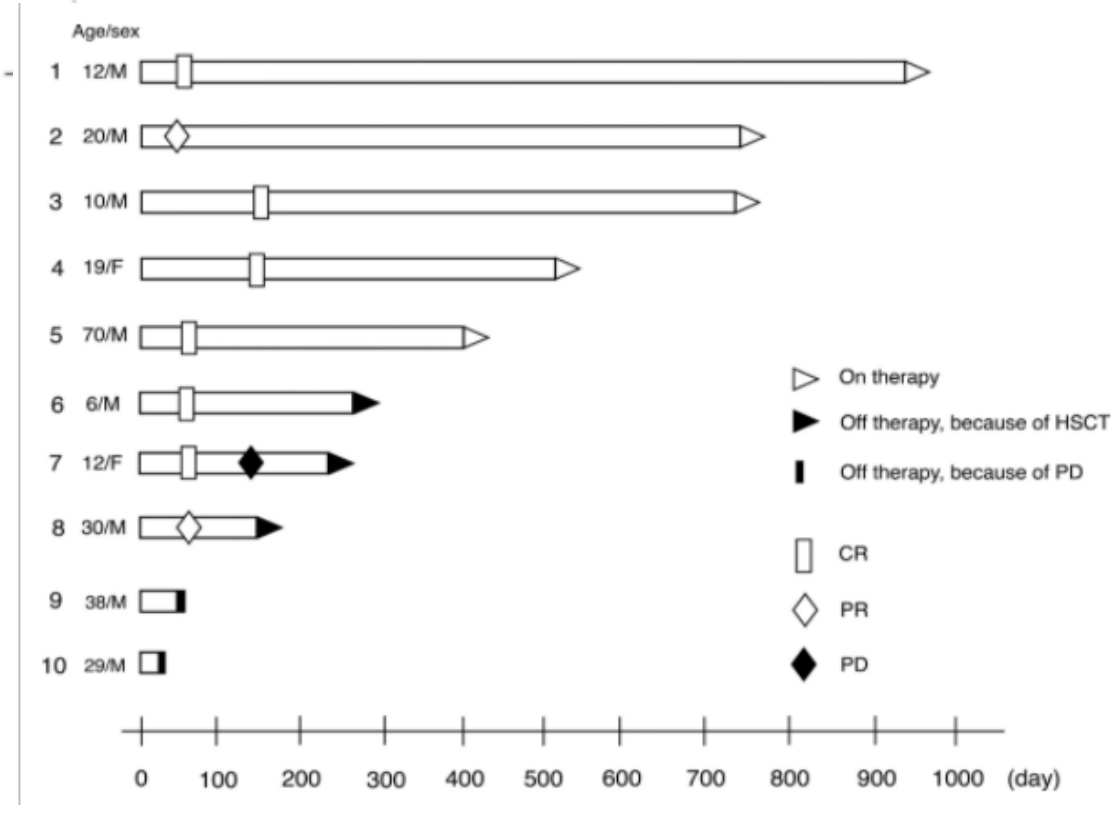
Free PMC article

Magyar valóság: crizotinib EMK

Abstract

Anaplastic lymphoma kinase (ALK) inhibition is expected to be a promising therapeutic strategy for ALK-positive malignancies. We aimed to examine the efficacy and safety of alectinib, a second-generation ALK inhibitor, in patients with relapsed or refractory ALK-positive anaplastic large cell lymphoma (ALCL). This open-label, phase II trial included patients (aged 6 years or older) with relapsed or refractory ALK-positive ALCL. Alectinib 300 mg was given orally twice a day (600 mg/d) for 16 cycles, and the duration of each cycle was 21 days. Patients who weighed less than 35 kg were given a reduced dose of alectinib of 150 mg twice a day (300 mg/d). Ten patients were enrolled, and the median age was 19.5 years (range, 6-70 years). Objective responses were documented in eight of 10 patients (80%; 90% confidence interval, 56.2-95.9), with six complete responses. The 1-year progression-free survival, event-free survival, and overall survival rates were 58.3%, 70.0%, and 70.0%, respectively. The median duration of therapy was 340 days. No unexpected adverse events occurred. The most common grade 3 and higher adverse event was a decrease in neutrophil count in two patients. Alectinib showed favorable clinical activity and was well tolerated in patients with ALK-positive ALCL who had progressed on standard chemotherapy. Based on the results of the current study, the Ministry of Health, Labour and Welfare of Japan approved alectinib for the treatment of recurrent or refractory ALK-positive ALCL in February 2020.





case reports

Lymphomatous Meningitis From Anaplastic Lymphoma Kinase+ Anaplastic Large T-Cell Lymphoma Treated With Lorlatinib: A Case Report

Smitha Mellacheruvu, MD[1,2]; Mark N. Sayegh, MD[1]; R. Alejandro Sica, MD[3]; Haiying Cheng, MD, PhD[2]; Maria Laureana Santos-Zabala, MD[4]; Jacob H. Gebrael, MD[5]; Ulrich Hermanto, MD, PhD[6]; and Norman L. Rosen, MD[1]

JCO Precis Oncol 6:e2100250.

Background

Anaplastic large cell lymphoma (ALCL) accounts for approximately 2% of adult non-Hodgkin lymphoma, and is the second or third most common lymphoma with T-cell histology in adults.[1,2] According to the revised 2016 WHO classification, four distinct entities of ALCL are currently recognized: (1) ALCL, anaplastic lymphoma kinase (ALK)+ (2) ALCL, ALK–, (3) primary cutaneous ALCL, and (4) breast implant–associated ALCL.[3] All cases of ALK+ ALCL have a rearrangement in the ALK gene located on chromosome 2p23. The t (2;5) translocation yields an abundantly expressed chimeric protein containing the oligomerization motif of nucleophosmin 1 and the kinase domain of ALK.[4-6] The nucleophosmin-ALK homodimer cross-phosphorylates itself, leading to persistent kinase activation.[7,8] On the basis of this additional genetic evidence, the WHO recognized ALK+ ALCL in 2008.[9] Typical features of most ALCL tumors include the presence of hallmark cells, which are large cells with kidney-shaped nuclei and a perinuclear eosinophilic region, along with the universal expression of the CD30 antigen.[10]

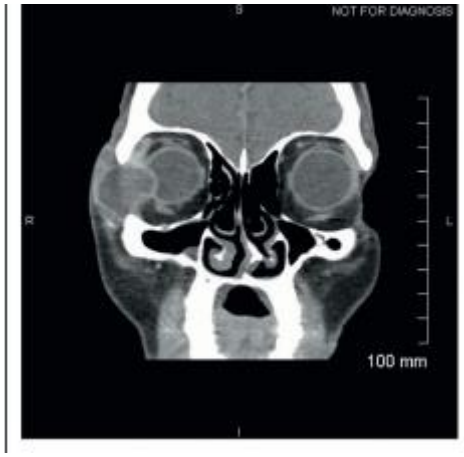
ALK+ ALCL is associated with a better prognosis than

Case Report

A 61-year-old Indian man presented in July 2017 with persistent upper abdominal pain for several weeks. He had a history of diabetes mellitus, ichthyosis, chronic kidney disease, and stage III ALCL (CD30-positive, ALK+); ALCL was diagnosed in 2004 and treated with six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone. Computed tomography (CT) of the abdomen and pelvis done in July 2017 revealed extensive intra-abdominal lymphadenopathy, and biopsy revealed ALK+ ALCL (Fig 2A).

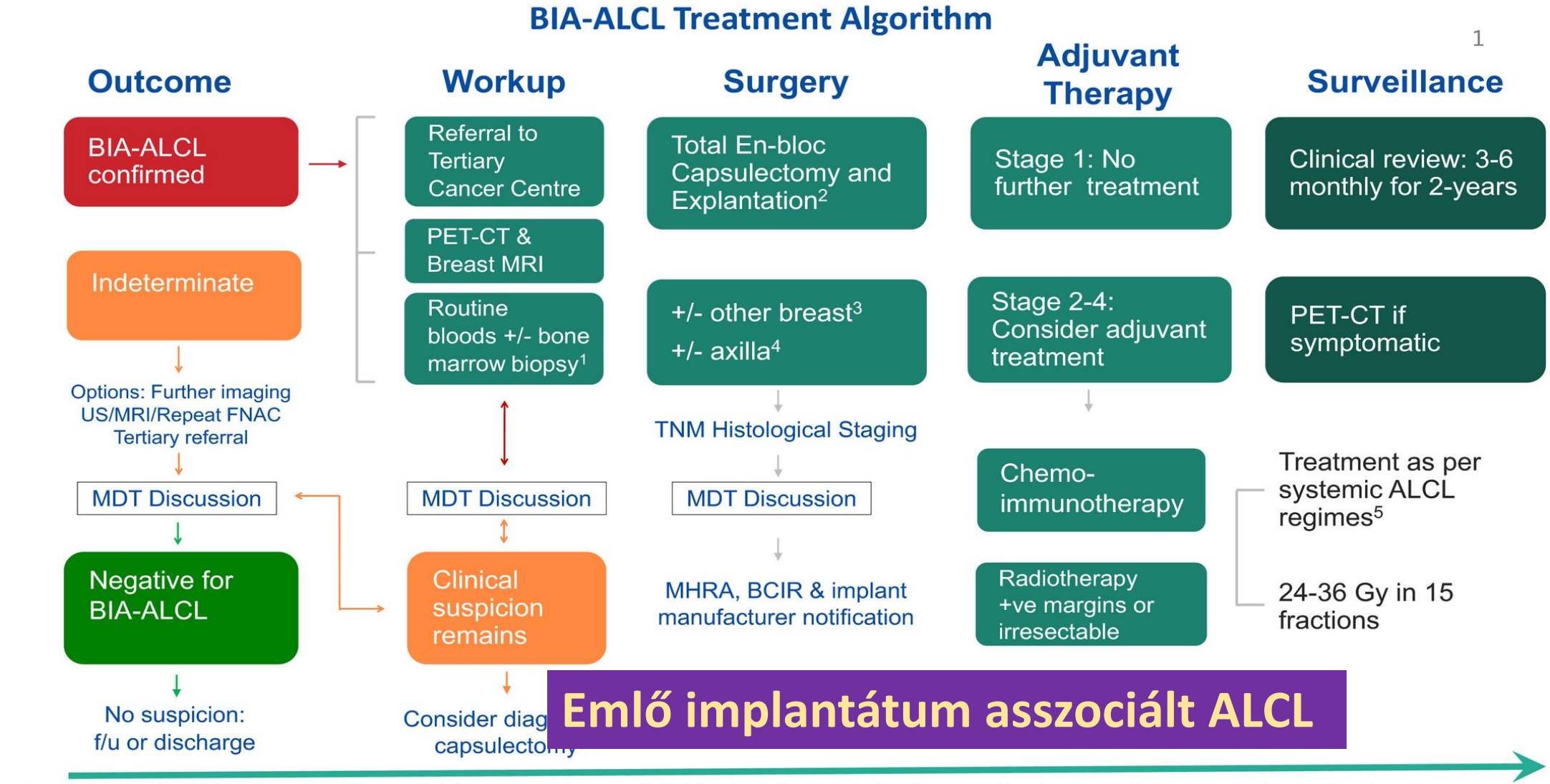
He was started on brentuximab vedotin (BV) and a positron emission tomography (PET)-CT scan after six cycles revealed a complete response. After nine cycles of BV, the patient refused to continue further treatment and declined consolidative autologous stem-cell transplantation (ASCT). Two months after the last dose of BV, he presented with scalp nodules, which were biopsy-confirmed to be ALK+ ALCL. Two cycles of salvage chemotherapy with gemcitabine, dexamethasone, and cisplatin were given followed by ASCT with carmustine, etoposide, cytarabine, and melphalan conditioning. After ASCT, complete response was documented by PET-CT. Patient refused BV maintenance.

2004. ALK+ ALCL 6 ciklus CHOP – CR
2017. Relapszus – 6 brentuximab – CR
9. BV után visszautasít további th-t (ASCT-t is)
2 hónap múlva relapszus – salvage 2 GDC
ASCT BEAM után
BV-t visszautasít, 9 hónap múlva orbita tumor – radioterápia + crizotinib
11 hónap múlva meningeális relapszus – visszautasít MTX-cytosar, intrathecalis th-t RT-t
Lorlatinib indult, csökkenteni kellett a dózist, de 11 hónapja CR-ban, liquor flow is negatív



Publ: 2022.02.07.

UK Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma on behalf of the Medicines and Healthcare products Regulatory Agency Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group



Emlő implantátum asszociált ALCL

1. Bone marrow aspiration & biopsy in aggressive disease 2. Data on reconstruction is very limited. Consider in the delayed setting if desired and low risk of oncological recurrence has been confirmed
3. BIA-ALCL may be contra-lateral in 2-4.6% cases. Consider contra-lateral explantation and capsulectomy 4. sentinel lymph node biopsy (SLNB) not recommended. Only remove clinically abnormal nodes
5. See text for further details

Turton P et al. BrJHaem 2021;192:444-458

M.W. Clemens

Genetic Predisposition BIA-ALCL

- JAK1/STAT3 Mutations implicated
  - Blombery 2016[1]
  - Di Napoli 2016[2]

bjh correspondence

Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in *JAK/STAT* signalling pathway genes, *TP53* and *DNMT3A*

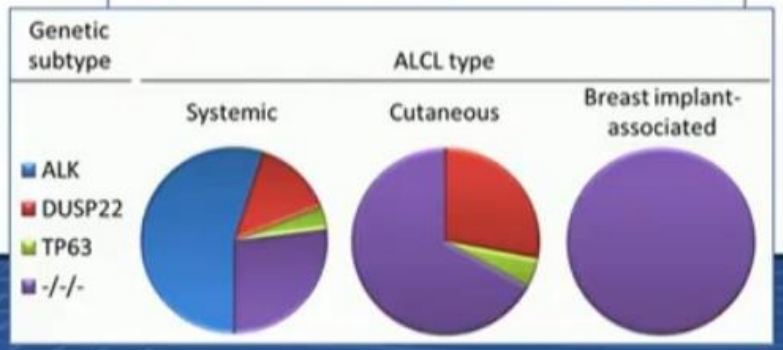
Whole Exome Sequencing Reveals Activating *JAK1* And *STAT3* Mutations In Breast Implant-Associated Anaplastic Large Cell Lymphoma Anaplastic Large Cell Lymphoma

- Feldman 2018
- 36 cases BIA-ALCL
- All cases triple negative
  - Significant homogeneity
- 100% STAT3 Expression
- STAT3 is mediated by JAK1/STAT3 mutations

MAYO CLINIC

Genetic subtyping of breast implant-associated anaplastic large cell lymphomas

Naoki Oishi[a,b], Garry Brody[c], Rhett P. Ketterling[a], Christopher A. Sattler[a], Rebecca L. Boddicker[a], Ellen D. McPhail[a], N. Nora Bennani[d], Cristin A. Harless[e], Kuldeep Singh[e], Mark W. Clemens[f], L. Jeffrey Medeiros[g], Roberto N. Miranda[g]* and Andrew L. Feldman[a]*



Blombery P, et al. Haematologica 2016;10:e387–90;
2. Di Napoli A, et al. Br J Haematol 2016.

Table 2 Genetic findings and biomarkers with potential relevance in the work-up of PTCL-NOS.

From: Genetic profiling and biomarkers in peripheral T-cell lymphomas: current role in the diagnostic work-up

Biomarker	Test	Purpose	Disease	Comment
TBX21/CXCR3 expression[51]	IHC	Prognosis	PTCL-TBX21	Biological subgroup of PTCL-NOS
GATA3/CCR4 expression[51]	IHC	Prognosis	PTCL-GATA3	Biological subgroup of PTCL-NOS
CDKN2A deletion[50]	FISH	Prognosis	PTCL, NOS	Deletion of *CDKN2A* and *PTEN* highly specific for PTCL-NOS
PTEN deletion[55]	FISH	Prognosis	PTCL, NOS	Deletion of *CDKN2A* and *PTEN* highly specific for PTCL-NOS
PT53 deletions and mutations[50]	FISH and NGS	Prognosis	PTCL-NOS	Enriched in PTCL-GATA3 cases[a]. Adverse prognosis.
FAT1 mutations[a,53]	NGS	Prognosis	PTCL, NOS	Adverse prognosis
JAK2 rearrangement[60]	FISH	Diagnosis	PTCL, NOS	Features resembling

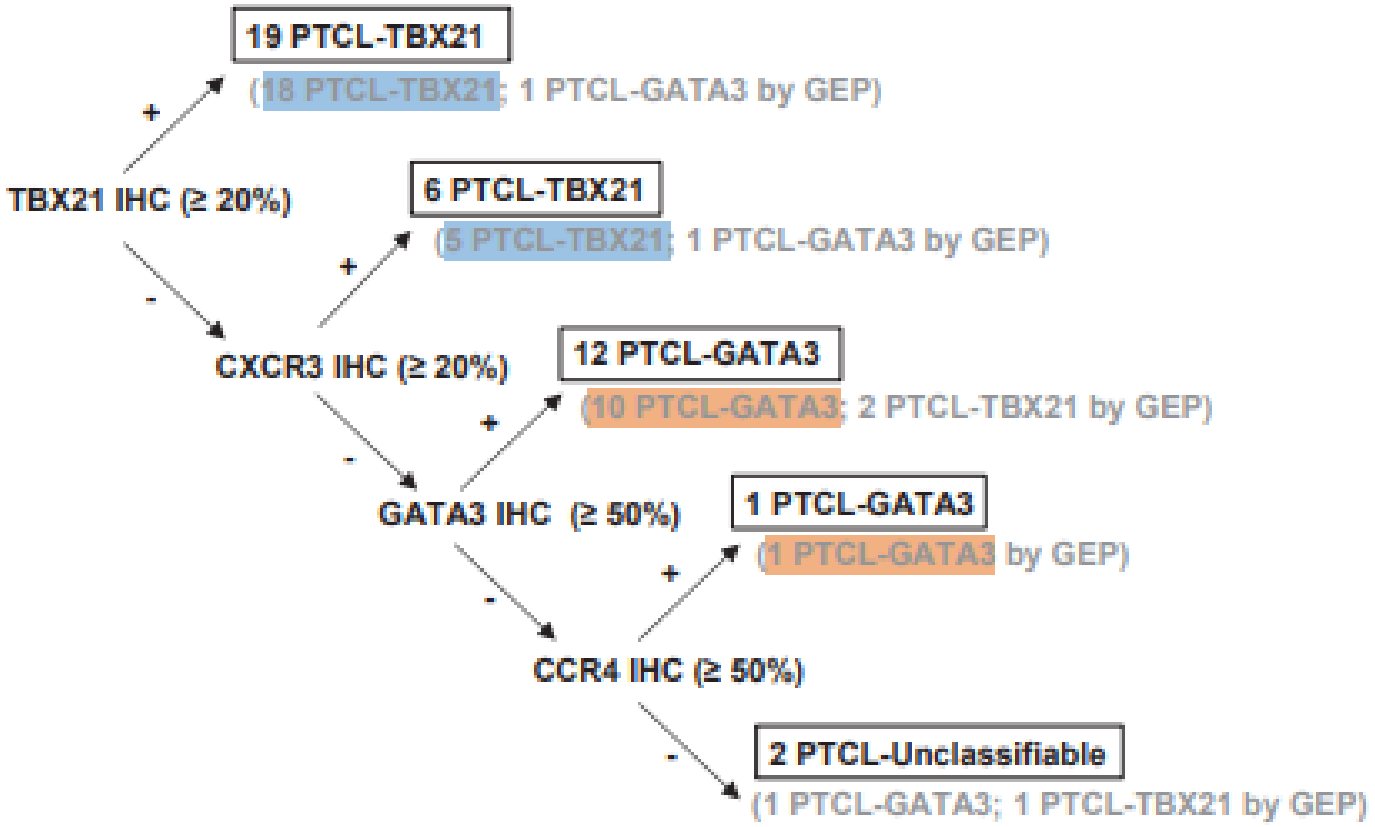
FAT1 tumor szupresszor gén mutáció PTCL-ben 39%-ban – rossz prognózis

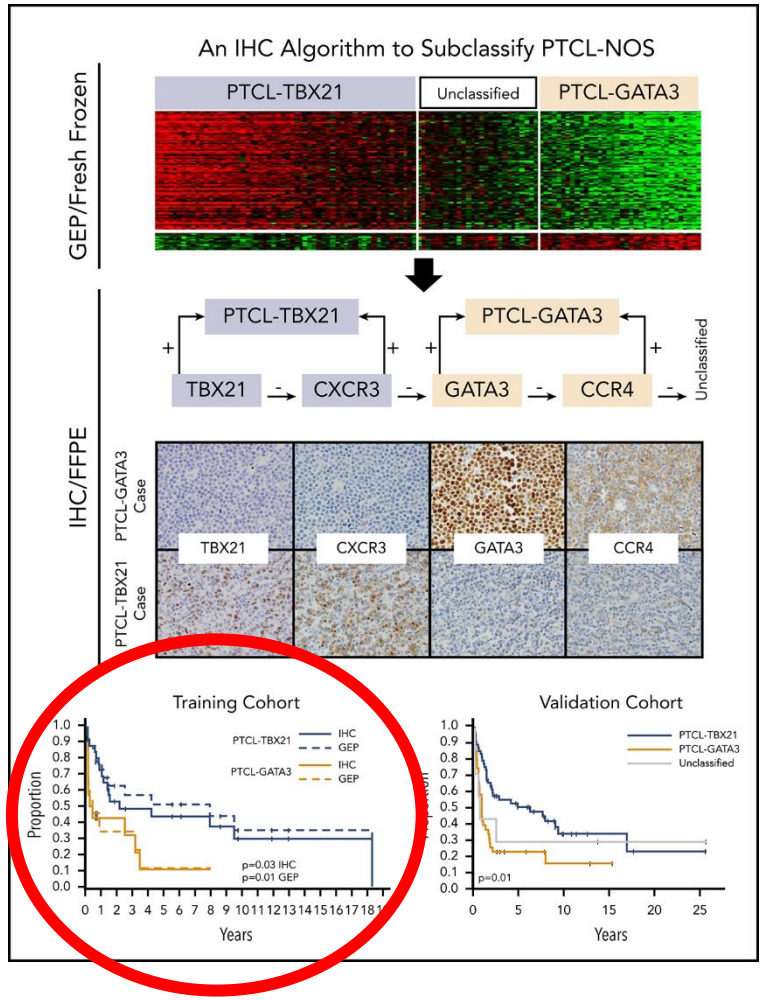
PTCL-NOS peripheral T cell lymphoma, not otherwise specified, *CHL* Classic Hodgkin lymphoma, *TBX21* T-box transcription factor 21, *GATA3* GATA binding protein 3.

[a]Based on limited data, pending validation.

Vega, F. et al. Mod Pathol 2021. https://doi.org/10.1038/s41379-021-00937-0

Immunhisztokémiai (IHC) algoritmus PTCL-NOS-ban



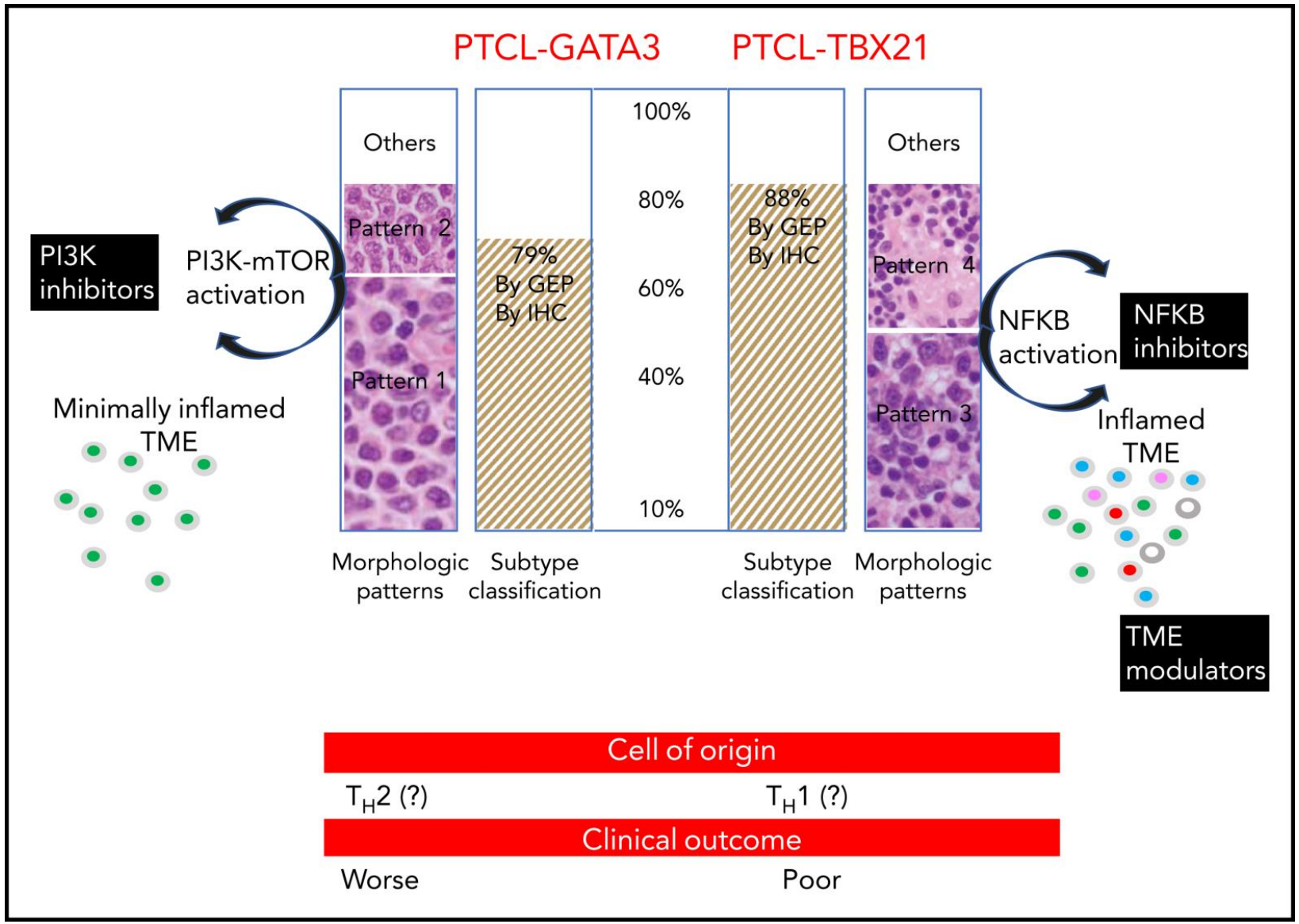


B.

	PTCL-TBX21 by GEP (n=26)	PTCL-GATA3 by GEP (n=14)	PTCL-UNC by GEP (n=9)
PTCL-TBX21 by IHC	23 (88%)	2 (14%)	6 (67%)
PTCL-GATA3 by IHC	2 (8%)	11 (79%)	2 (22%)
Unclassified by IHC	1 (4%)	1 (7%)	1 (11%)

Amador C. Blood 2019 doi: 10.1182/blood.2019000779.

Perifériás T-sejtes lymphoma NOS szubklasszifikációja



Carbone A, Gloghini, A Subclassifying peripheral T-cell lymphoma NOS, Blood, 2019, 134:2120-2121.

Table 3 Genetic findings and biomarkers with potential relevance in the work-up of AITL and other PTCL with a TFH phenotype.

From: Genetic profiling and biomarkers in peripheral T-cell lymphomas: current role in the diagnostic work-up

Biomarker	Test	Purpose	Disease	Comment
RHOA^{G17V} *mutations*[51,71,73]	NGS	Diagnosis and treatment	TFH lymphomas	Predict response to HDACi
DNMT3A mutations[51,71,73]	NGS	Diagnosis and treatment	TFH lymphomas	Predict response to HDACi
IDH2^{R172} *mutations*[57,67]	NGS and IHC	Diagnosis and treatment	AILT	Specific for AILT. Predict response to HDACi
ITK-SYK[74]	FISH	Diagnosis and treatment	FTCL	Sensitivity to SYKi
FER and *FES* translocations[73]	FISH and sequencing	Diagnosis and treatment	FTCL	Potential use of FER and FESinh or STAT3i

IDH2 isocitrate dehydrogenase 2, *DNMT3A* DNA methyltransferase, *FTCL* follicular T-cell lymphoma, *TFH* T follicular helper, *AILT* angioimmunoblastic T cell lymphoma, *HDACi* histone deacetylase inhibitors, *SYK* spleen tyrosine kinase.

Vega, F. et al. Mod Pathol 2021. https://doi.org/10.1038/s41379-021-00937-0

International prospective T-cell Project (NCT01142674) angioimmunoblastos lymphomás megfigyelései

2006-2018. között 282 beteg Életkor: 64 év >90 % előrehaladott stádium

81 % anthracyclin tartalmú kezelés 13 % ASCT konszolidációként CR1-ben

5 éves OS és PFS 44 és 32 % (transzplantáltaknál jobb)

Multivariate analízissel kedvezőtlen a kimenetel: kor>60 év, ECOG >2, emelkedett CRP és béta 2 microglobin

AITL score ezekkel: kis, intermedier és nagy rizikó, 5 éves OS: 63 %, 54 % és 21 %

Progresszív betegség 24 hónapnál (POD24) 5 éves túlélés: 63 % POD24 nélkül, vs 6 % POD24

Advani RH et al. Blood 2021;138:213-220.

CLINICAL TRIALS AND OBSERVATIONS | APRIL 22, 2021

Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study

Clinical Trials & Observations

Lorenzo Falchi, Helen Ma, Sandra Klein, Jennifer K. Lue, Francesca Montanari, Enrica Marchi, Changchun Deng, Hye A. Kim, Aishling Rada, Alice T. Jacob, Cristina Kinahan, Mark M. Francescone, Craig R. Soderquist, David C. Park, Govind Bhagat, Renu Nandakumar, Daniel Menezes, Luigi Scotto, Lubomir Sokol, Andrei R. Shustov, Owen A. O'Connor

Blood (2021) 137 (16): 2161–2170.

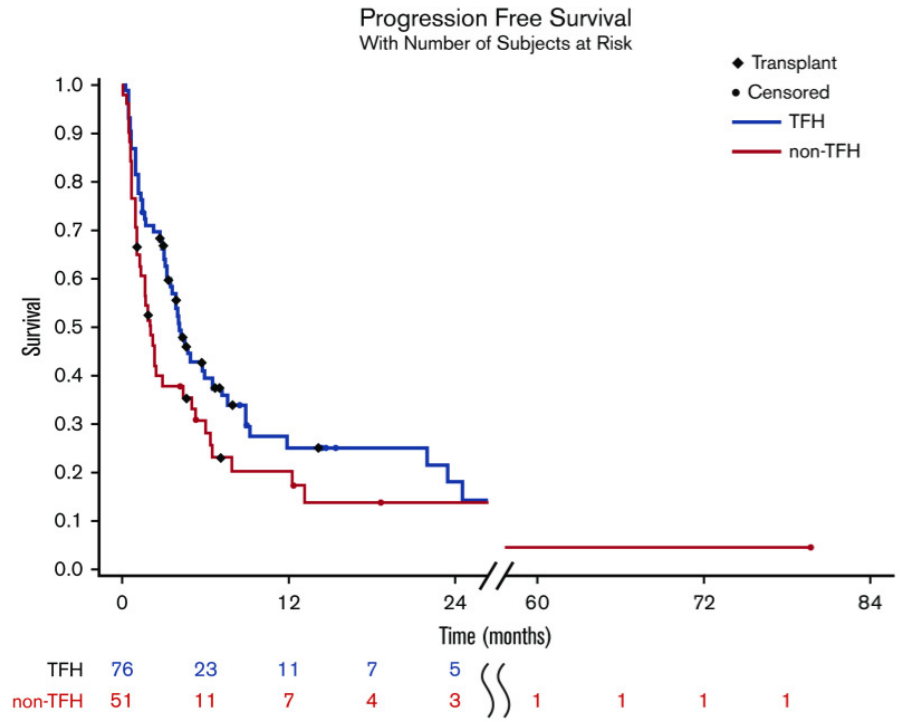
https://doi.org/10.1182/blood.2020009004 Article history

Key Points

- Combined oral azacytidine and romidepsin induced high response rates and prolonged remissions in PTCL patients, particularly those with tTFH.
- Mutations of genes involved in DNA methylation and histone deacetylation appear more frequently in patients responding to epigenetic therapy.

Abstract

Peripheral T-cell lymphomas (PTCLs) are uniquely vulnerable to epigenetic modifiers. We demonstrated in vitro synergism between histone deacetylase inhibitors and DNA methyltransferase inhibitors in preclinical models of T-cell lymphoma. In a phase 1 trial, we found oral 5-azacytidine and romidepsin to be safe and effective, with lineage-selective activity among patients with relapsed/refractory (R/R) PTCL. Patients who were treatment naïve or who had R/R PTCL received azacytidine 300 mg once per day on days 1 to 14, and romidepsin 14 mg/m^2 on days 8, 15, and 22 every 35 days. The primary objective was overall response rate (ORR). Targeted next-generation sequencing was performed on tumor samples to correlate mutational profiles and response. Among 25 enrolled patients, the ORR and complete response rates were 61% and 48%, respectively. However, patients with T-follicular helper cell (tTFH) phenotype exhibited higher ORR (80%) and complete remission rate (67%). The most frequent grade 3 to 4 adverse events were thrombocytopenia (48%), neutropenia (40%), lymphopenia (32%), and anemia (16%). At a median follow-up of 13.5 months, the median progression-free survival, duration of response, and overall survival were 8.0 months, 20.3 months, and not reached, respectively. The median progression-free survival and overall survival were 8.0 months and 20.6 months, respectively, in patients with R/R disease. Patients with tTFH enjoyed a particularly long median survival (median not reached). Responders harbored a higher average number of mutations in genes involved in



Blood Adv. 2020 Oct 13;4(19):4640-4647. doi: 10.1182/bloodadvances.2020002396.

T follicular helper phenotype predicts response to histone deacetylase inhibitors in relapsed/refractory peripheral T-cell lymphoma

Paola Ghione [1 2], Promie Faruque [1], Neha Mehta-Shah [1 3], Venkatraman Seshan [4], Neval Ozkaya [5], Shakthi Bhaskar [3], James Yeung [6], Michael A Spinner [7], Matthew Lunning [1 8],

Table 4 Genetic findings and biomarkers with potential relevance in the work-up of ENKTL.

From: Genetic profiling and biomarkers in peripheral T-cell lymphomas: current role in the diagnostic work-up

Biomarker	Test	Purpose	Disease	Comment
TCR gene rearrangements	PCR	Diagnosis	ENKTL	NK versus T-cell origin
EBER	ISH	Diagnosis	ENKTL	Important for diagnosis
Del14q11.2[83]	FISH	Diagnosis	ENKTL	Potential indicator of T-cell origin
JAK3 mutations[a,80,84,85,86]	NGS	Therapy?	ENKTL	Potentially targetable
STAT3 mutations[a,80,84,85,86]	NGS	Therapy?	ENKTL	Potentially targetable
TP53 mutations[a,80]	NGS	Prognosis	ENKTL	Associated with extranasal or lymph node involvement
BCOR[b] mutations[80,84,85,86]	NGS	Therapy?	ENKTL	Potential role of NOTCH inhibitors
DDX3X mutations[86]	NGS	Prognosis	ENKTL	Poor prognosis

JAK3 janus kinase 3, *STAT3* signal transducer and activator of transcription 3, *BCOR* BCL6 co-repressor, *DDX3X* EAD-Box Helicase 3 X-Linked.

[a]Non-specific for diagnosis; they are seen in other T-cell lymphomas.

[b]Based on limited data, pending validation. BCOR mutations are rare in lymphomas; reported also in splenic diffuse red pulp small B-cell lymphoma.

Vega, F. et al. Mod Pathol 2021. https://doi.org/10.1038/s41379-021-00937-0

PINK [15]	
Low risk (0)	Age (>60 years vs. ≤60 years)
Intermediate risk (1)	Ann Arbor stage (III/IV vs. I/II)
High risk (≥2)	Distant lymph node involvement (yes vs. no)
	Nonnasal disease (yes vs. no)

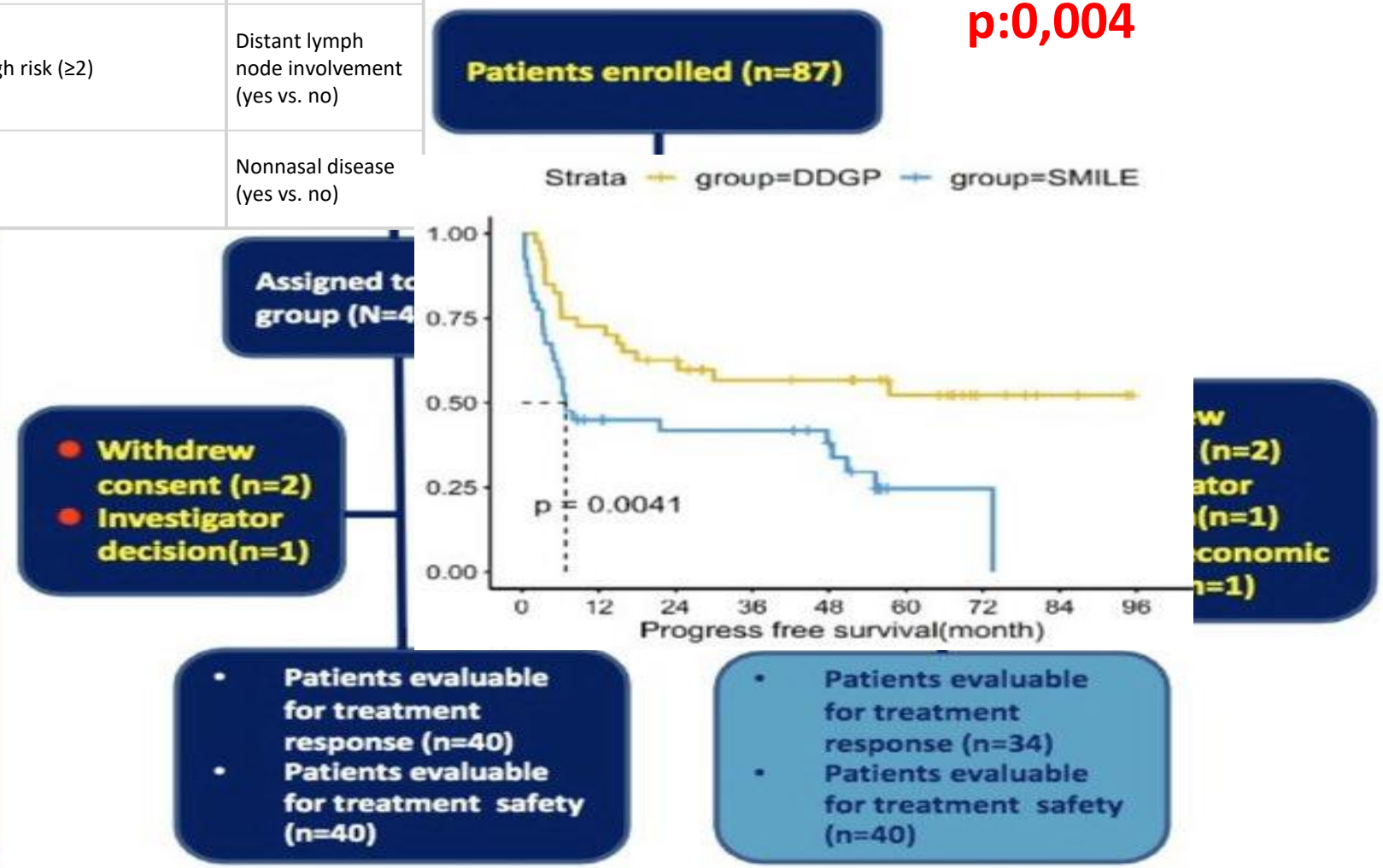
3 éves PFS: **DDGP: 56,6 %**
SMILE: 41,8 %
p:0,004

STUDY DESIGN

Data were collected from January 2011 to February 2019

- **DDGP regimen:**
  cisplatin 20 mg/m² d 1-4
  dexamethasone 15mg /m² d 1-5
  gemcitabine 800mg/m² d1,8
  pegaspargase 2500 IU/m² d1
  21 days per cycle

- **SMILE regimen:**
  methotrexate 2g/m² d1
  dexamethasone 40mg/m² d2-4
  ifosfamide 1500mg/m² d2-4
  L-asparaginase 6000 U/m² d3-9
  etoposide 100 mg/m² d2–4
  21 days per cycle



Zhang M et al. ASH 2019; ASH News 01. March. 2020.

THE LANCET
Haematology
Volume 7, Issue 4, April 2020, Pages e284-e294

Articles

Survival outcomes of patients with extranodal natural-killer T-cell lymphoma: a prospective cohort study from the international T-cell Project

Christopher P Fox MD [a], Monica Civallero PhD [b], Young-Hyeh Ko MD [c], Martina Manni PhD [b], Tetiana Skrypets MD [b], Prof Stefano Pileri MD [d], Seok Jin Kim MD [e], Maria Elena Cabrera MD [f], Andrei R Shustov MD [g], Carlos S Chiattone MD [h, i], Steven M Horwitz MD [j], Ivan Dlouhy MD [k], Michele Spina MD [l], Felicitas Hitz MD [m], Silvia Montoto MD [n], Arnon Nagler MD [o], Virginia Martinez MD [p], Carmino A De Souza MD [q] ... Won Seog Kim MD [e]

166/1553 (11%) ENKTL
98 nasal – 54 % OS
68 extranasal – 34 % OS
St I: 55 %
St II: 42 % OS
St III-IV: 24 %

THE LANCET
Haematology

I-II st-ban P-GemOx (pegaspargase, gemcitabine, oxaliplatin) OS: 85 %
PFS: 74% - SMILE helyett DDGP

CORRESPONDENCE | VOLUME 7, ISSUE 6, E441, JUNE 01, 2020

Extranodal natural-killer T-cell lymphoma: experience from China

Liang Wang • Jing-wen Wang

Published: June, 2020 • DOI: https://doi.org/10.1016/S2352-3026(20)30103-4

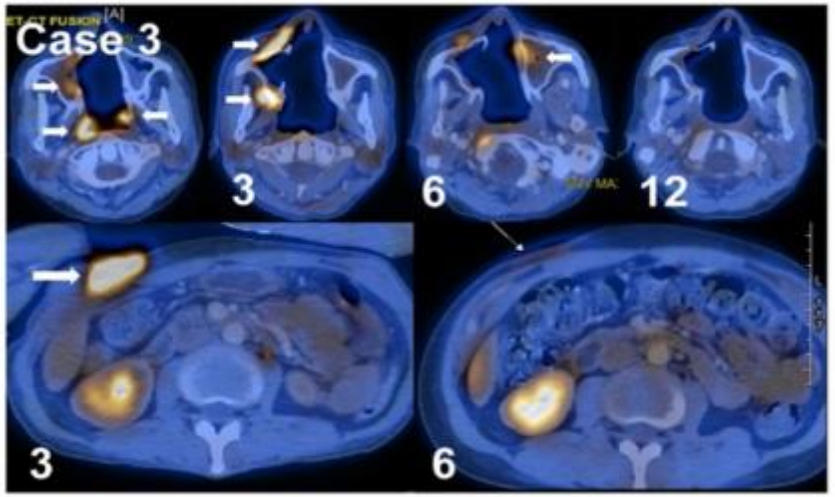
1582 beteg (1531 kínai)

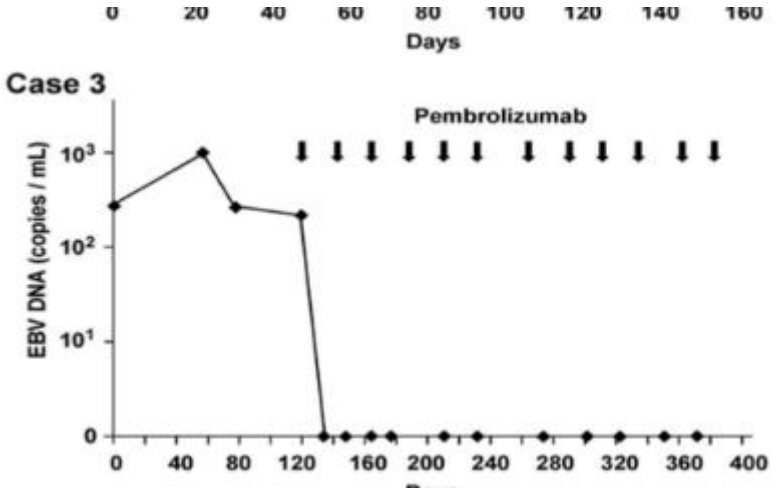
78·9% stage I, 67·8% stage II,
53·3% stageIII, 29·7% stage IV.

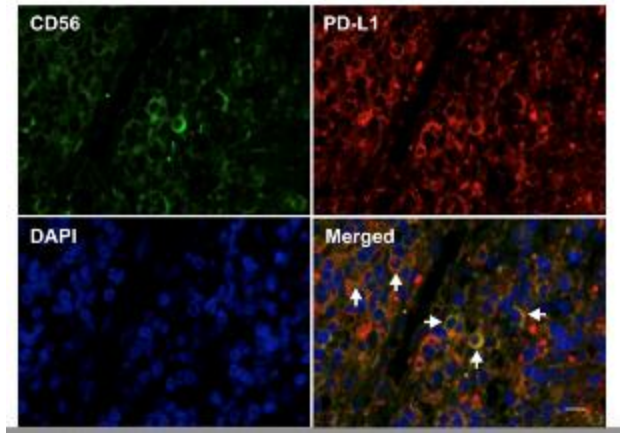
OS

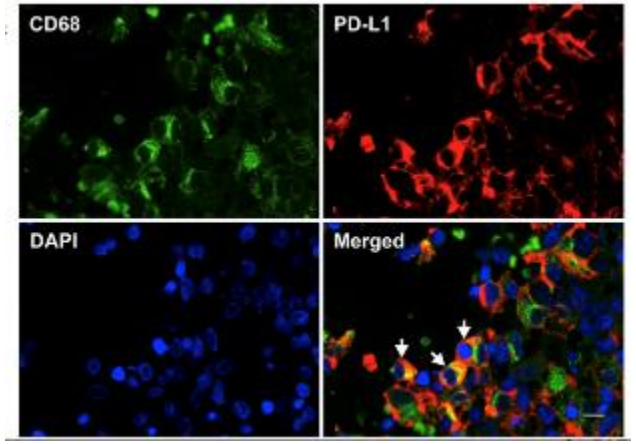
Az NK/T-sejtes lymphomák egyedi érzékenységgel rendelkeznek a checkpoint blokádra

Pembrolizumab in NK/T cell lymphoma[1]





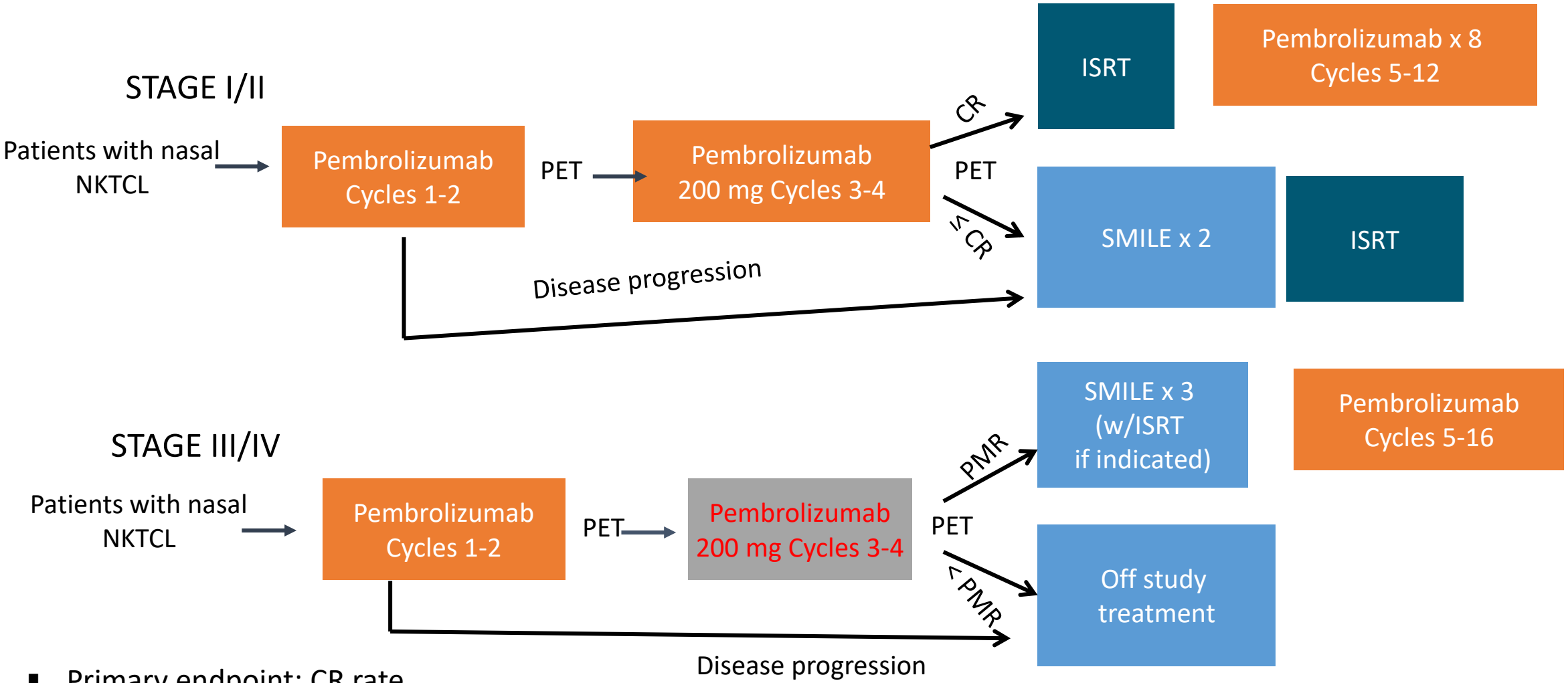




Sintilimab, human anti-PD-1 mab[2]
N=28; ORR 68%
1-year OS rate was 82.1%

1. Kwong. Blood. 2017;129:2437. 2. Taol. ASCO 2019. Abstr 7504. 3. Nagato. Cancer Immunol Immunother. 2017;66:877.

Pilot Study (N = 19): Pembrolizumab kezeletlen, Extranodal NK/T-sejtes Lymphoma, Nasal Type



- Primary endpoint: CR rate

NCT03728972

Table 5 Genetic findings and biomarkers with potential relevance in the work-up of HSTCL.

Biomarker	Test	Purpose	Disease	Comment
i(7q)	FISH	Diagnosis	HSTCL	FISH is more sensitive than karyotyping
SETD2 mutations[a,100]	NGS	Diagnosis	HSTCL	Could help in the diagnosis
STAT5B mutations[a,100,106]	NGS	Diagnosis	HSTCL	Potentially targetable
STAT3 mutations[a,100,106]	NGS	Diagnosis	HSTCL	Potentially targetable

SETD2 SET domain containing 2, histone lysine methyltransferase, *STAT3* signal transducer and activator of transcription 3.

[a]Non-specific; they are seen in other T-cell lymphomas but in the right clinical setting could support the diagnosis of HSTCL.

Vega, F. et al. Mod Pathol 2021. https://doi.org/10.1038/s41379-021-00937-0

JNCCN

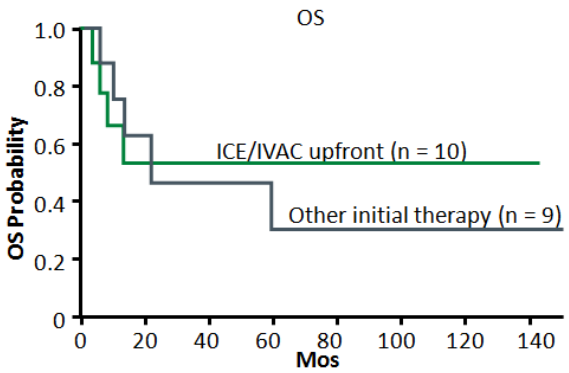
JOURNAL OF THE NATIONAL COMPREHENSIVE CANCER NETWORK

Supplemental online content for:

NCCN Guidelines Insights: T-Cell Lymphomas, Version 1.2021

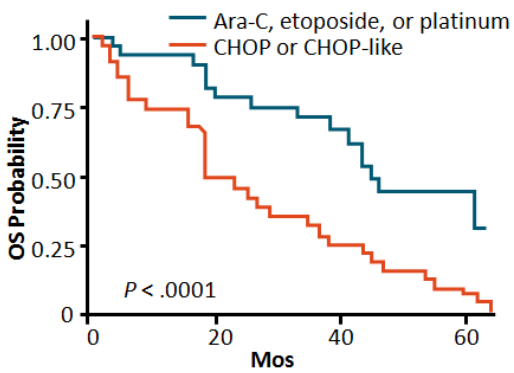
Horwitz SM et al. JNCCN 2020;18:1460-1467.

Induction[1]



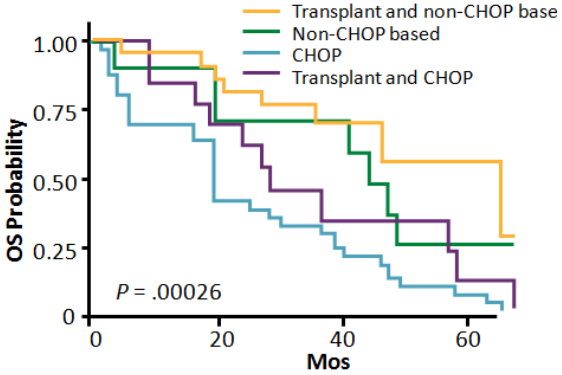
- Median OS: 59.2 mos
  - ICE/IVAC upfront: not reached
  - Other: 21.7 mos
  - Allogeneic SCT (n = 8)
  - Autologous SCT (n = 4)

Induction[2]



- Median OS (n =84)
  - Non-CHOP: 36.5 mos
  - CHOP/CHOP-like: 18 mos

CHOP/non-CHOP ± Transplant[2]



- Median OS (n = 84)
  - Non-CHOP + transplant: 35 mos
  - Non-CHOP only: 38 mos
  - CHOP + transplant: 25 mos
  - CHOP only: 18 mos

1. Voss. Clin Lymphoma Myeloma Leuk. 2013;13:8 (Updated data). 2. Klebaner. Clin Lymphoma Myeloma Leuk. 2019;October 21:[Epub].

Slide credit: clinicaloptions.com

Table 5. Suggested indications for HCT in rare PTCL

	Up-front consolidation		Salvage consolidation		Refractory
	autoHCT	alloHCT	autoHCT	alloHCT	alloHCT
Extranodal NK/T-cell lymphoma[65,66]					
Localized	-	-	+	+	+
Disseminated	+	-	+	+	+
Adult T-cell leukemia/lymphoma[33]					
Chronic/smoldering	-	-	-	E	E
Acute/lymphoma	-	+	-	+	+
Enteropathy-associated T-cell lymphoma[47,48]	+	-	E	E	E
Hepatosplenic T-cell lymphoma[32]	E	+	-	+	+

+ Recommendation based on evidence from registry studies and expert opinion.

E Recommendation based on expert opinion only.

- Not recommended.

Partly adapted from Kharfan-Dabaja et al.[3]

Dreger P és Schmitz N
Hematology Am Soc Hematol Educ Program (2024) 2024 (1): 69–77.
https://doi.org/10.1182/hematology.2024000670

Romidepsin[20,21]	2	NCT00426764	R/R PTCL	130	ORR 25% CR/CRu 15% mDOR 17 mo mPFS 4 mo	AITL (*n* = 27): ORR 30%, CR/CRu 19% PTCL-NOS (*n* = 69): ORR 29%, CR/CRu 14% ALK- ALCL (*n* = 21): ORR 24%, CR 19%
Belinostat[23]	2	BELIEF (CLN-19)	R/R PTCL	129	ORR 26% CR 11% mDOR 13.6 mo mPFS 1.6 mo, mOS 7.9 mo	AITL (*n* = 10): ORR 45% PTCL-NOS (*n* = 18): ORR 23% ALK- ALCL (*n* = 13): ORR 15%
Azacitidine*[25]	3	ORACLE (NCT03593018)	R/R AITL or nodal TFH lymphoma	86	3-mo ORR 33% 3-mo CR 12% mPFS 5.6 mo mOS 18.4 mo	N/A
Valemetostat*[30]	2	VALENTINE-PTCL01 (NCT04703192)	R/R PTCL (including ALCL with prior BV exposure)	133	ORR 44% CR 14% mDOR 11.9 mo mPFS 5.5 mo mOS 17.0 mo	AITL (*n* = 42): ORR 55%, CR 19% PTCL-NOS (*n* = 41): ORR 32%, CR 10% PTCL-TFH (*n* = 8): ORR 50%, CR 12%
Brentuximab vedotin[17]	2	NCT01421667	R/R CD30+ PTCL excluding ALCL	34	ORR 41% CR 24% mDOR 7.6 mo mPFS 2.6 mo	AITL (*n* = 13): ORR 54%, CR 38% PTCL-NOS (*n* = 21): ORR 33%, CR 14%
Crizotinib[18]	2	NCT02419287	R/R ALK+ ALCL	12	ORR 83% CR 58% mDOT 16.5 mo mPFS NR mOS NR	N/A
Duvelisib*[26]	2	PRIMO (NCT03372057)	R/R PTCL	101	ORR 49% CR 34% mPFS 3.6 mo	AITL (*n* = 30): ORR 67%, CR 53% PTCL-NOS (*n* = 52): ORR 48%, CR 27% ALCL (*n* = 15): ORR 13%, CR 13%
Pralatrexate[12]	2	PROPEL (NCT00364923)	R/R PTCL	109	ORR 29% CR/CRu 18% mDOR 10.1 mo mPFS 3.5 mo mOS 14.5 mo	AITL (*n* = 13): ORR 8% PTCL-NOS (*n* = 59): ORR 32% ALCL (*n* = 17): ORR 35%
Golidocitinib*[29]	2	JACKPOT8 (NCT04105010)	R/R PTCL	88	ORR 44% CR 24% mDOR 20.7 mo mPFS 5.6 mo mOS 19.4 mo	AITL (*n* = 16): ORR 56% PTCL-NOS (*n* = 46): ORR 46% ALCL (*n* = 10): ORR 10%

Refrakter/relapszusos PTCL-ben „single agent” tanulmányok

Nizamuddin IA és Mehta-Shah N
http://ashpublications.org/hematology/article-pdf/2024/1/54/2344172/54

Combination therapies						
Romidepsin + pralatrexate*[37]	1	NCT01947140	R/R lymphoma	23	ORR 57% CR 17% mPFS 3.7 mo mOS 13.8 mo	TCL ($n = 14$): ORR 71% mDOR 4.29 mo mPFS 4.4 mo mOS 12.4 mo
Romidepsin + duvelisib*[38]	1b/2	NCT02783625	R/R PTCL	48	ORR 56% CR 44% mDOR 12 mo mOS 12 mo	AITL ($n = 12$): ORR 71% PTCL-NOS ($n = 8$): ORR 47% ALCL ($n = 3$): ORR 100%

Refrakter/relapszusos PTCL-ben „kombinációs” tanulmányok

Agent(s)	Study phase	Trial	Patient population	# evaluable patients	Efficacy: overall	Efficacy: subgroups
Romidepsin + azacitidine*[39]	2	NCT01998035	Treatment-naïve or R/R PTCL	23	ORR 61% CR 48% mDOR 20.3 mo mPFS 8 mo mOS NR	R/R PTCL ($n = 13$): ORR 70%, CR 50% mDOR 13.5 mo mPFS 8 mo mOS 20.6 mo TFH ($n = 15$) ORR 80%, CR 60% mPFS 8.9 mo mOS NR
Romidepsin + lenalidomide*[40]	1b/2	NCT01755975	R/R NHL or HL	45	ORR 49% CR 18% mDOR 15.7 mo mPFS 5.7 mo mOS 24 mo	R/R PTCL ($n = 15$) ORR 53% CR 13% PTCL-NOS ($n = 5$) ORR 40% ATLL ($n = 6$): ORR 50% AITL ($n = 2$): ORR 100%
Romidepsin + lenalidomide + carfilzomib*[40]	1b/2	NCT02341014	R/R NHL or HL	27	ORR 48% CR 20% mDOR 10.6 mo mPFS 3.4 mo mOS 26.5 mo	R/R PTCL ($n = 13$) ORR 54% CR 39% PTCL-NOS ($n = 7$): ORR 29% AITL ($n = 5$): ORR 100%

*Not currently approved by the Food and Drug Administration for treatment of PTCL

Nizamuddin IA és Mehta-Shah N
:p://ashpublications.org/hematology/arti
cle-pdf/2024/1/54/2344172/54

From: Enteropathy-Associated T cell Lymphoma

Study	Type	Surgery	Chemo-therapy	Combination of surgery and chemotherapy	Consolidation	PFS	OS
L J Egan (1995) [56]	Retrospective *n* = 31	-	-	Yes *n* = 14	-	-	1-year OS 31% 5-year OS 11%
J Gale (2000) [7]	Retrospective *n* = 31 patients	*n* = 7 Surgery alone	*n* = 24 Chemotherapy alone	-	-	-	Actuarial 1-year survival 38.7% Actuarial 5-year survival 19.7%
Daum et al. (2003) (German Study group) [47]	Retrospective *n* = 56 *n* = 35, ITCL	-	-	Surgery + chemotherapy (CHOP).	-	-	2-year cumulative survival 28% In ITCL.
S Wohrer et al. (2004) [51]	Prospective *n* = 10	-	CHOEP *n* = 8.	*n* = 2.			2 patients only alive at median follow-up of 7 months
BJ Novakovic (2006) [50]	Retrospective *n* = 15 10 patients EATL	-	-	Surgery + CHOP	-	-	Actuarial 1-year survival rate 33%, 5-year survival 9%
Sieniawski (2010) [5]	Prospective CHOP arm *n* = 54 IVE/MTX-ASCT arm *n* = 26	CHOP arm *n* = 19.	-	CHOP *n*=35	IVE/MTX-ASCT Conditioning regimens : Melphalan + TBI, or BEAM	CHOP arm 5-year PFS 18% IVE/MTX –ASCT arm 5-year PFS 52%.	CHOP arm 5-year OS 20% IVE/MTX-ASCT arm 5-year OS 60 %
J Delabie (2011) [2]	Retrospective *n* = 62. EATL type 1 *n* = 38.	-	CHOP *n* = 28.	-	-	5-year PFS 4%	5-year OS 20%
F d'Amore (2012) [46]	Prospective *n* = 21	-	CHOEP CHOP if age>60.	-	BEAM	5-year PFS 38%.	5-year OS 48%
E Jantunen (2013) [45]	Retrospective *n* = 44	-	Multiple regimens	-	BEAM or TBI	4-year PFS 54%	4-year OS 59%

Al-Somali Z et al. Curr Hematol Malig Rep. 2021;16:140-147

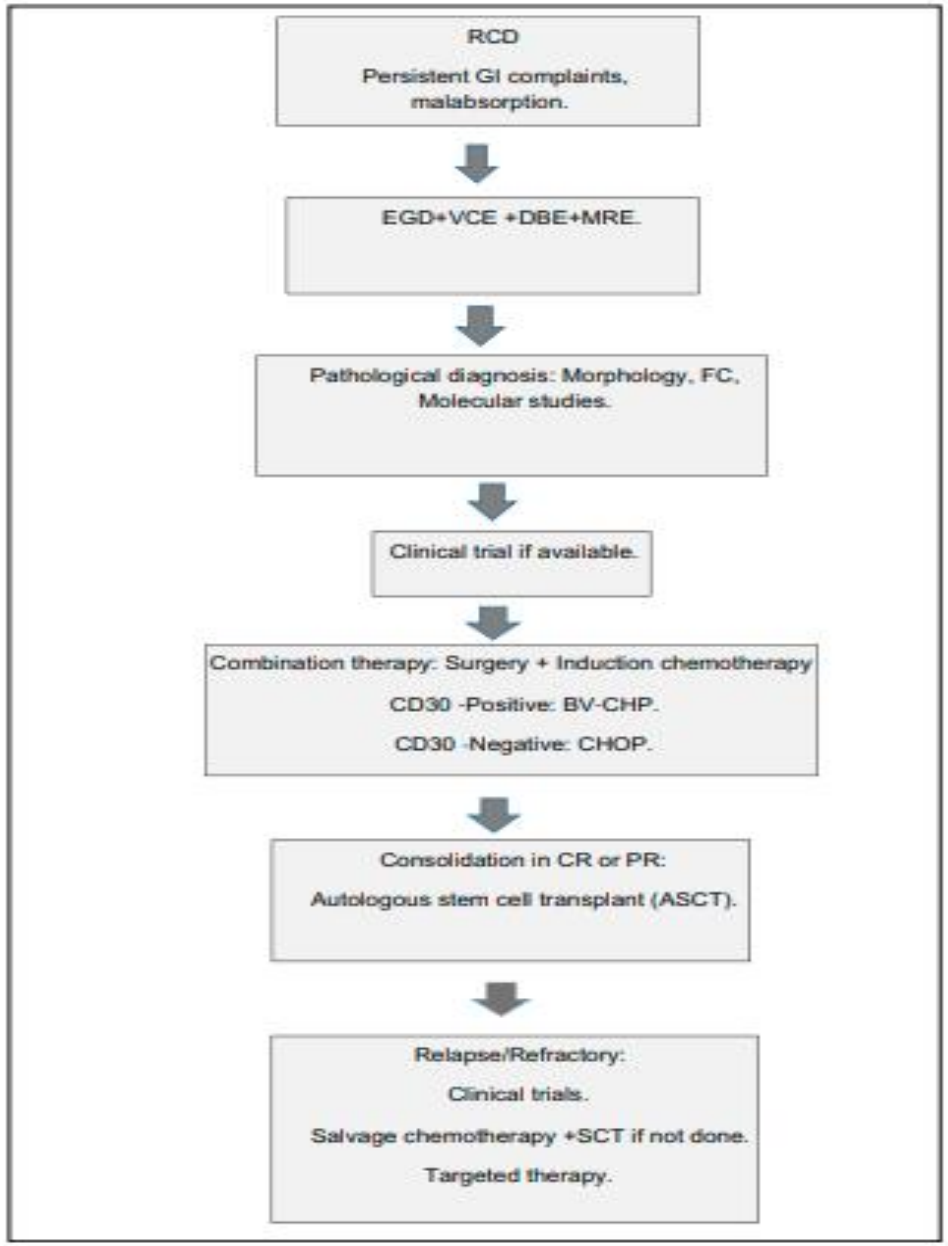
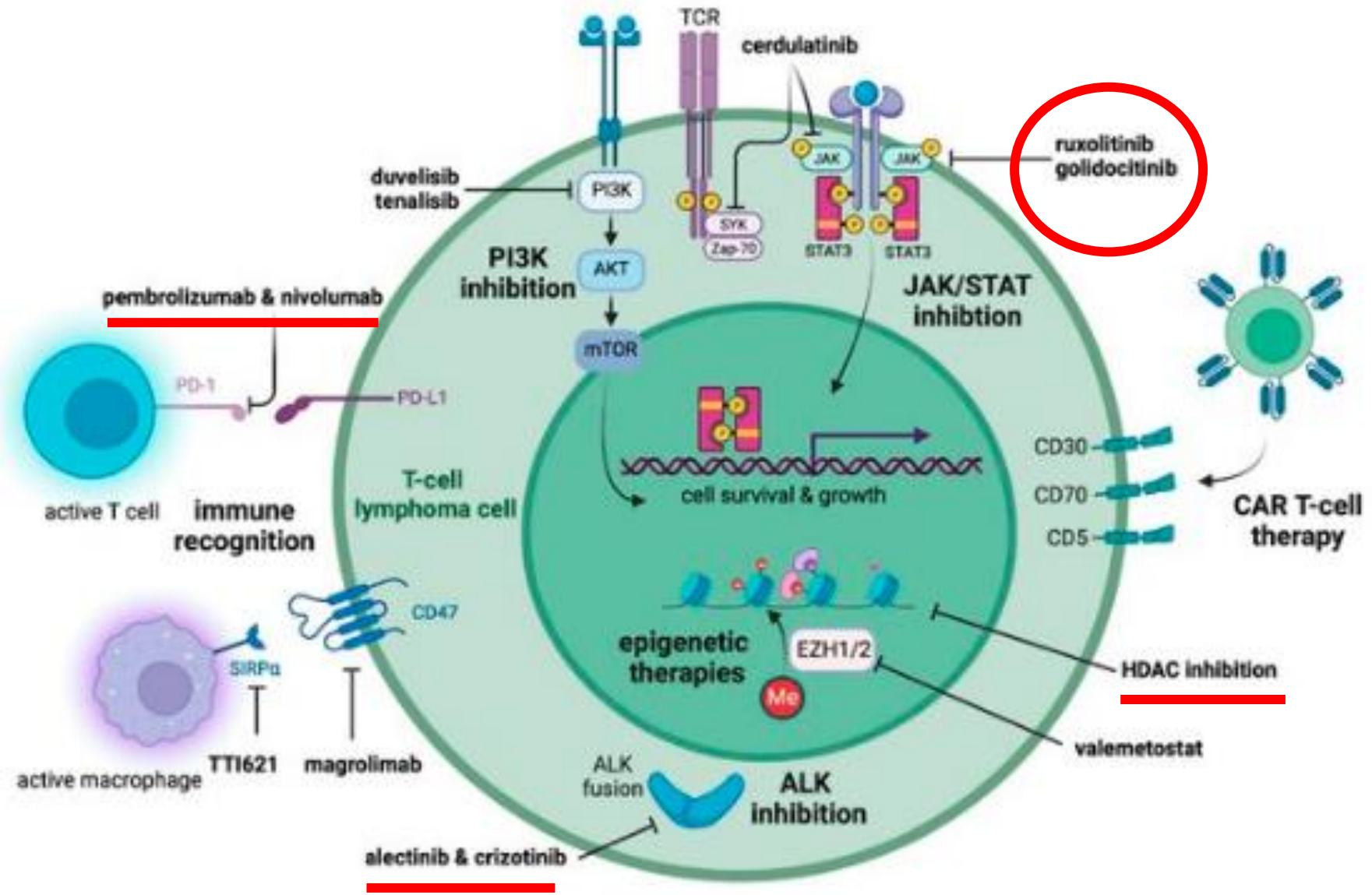


Fig. 1 Suggested approach to patients with EATL. RCD refractory celiac disease, EGD esophagogastroduodenoscopy, VCE video capsule endoscopy, DBE double balloon enterography, MRE magnetic resonance enterography, PET positron emission tomography, FC flow cytometry, CR complete remission, PR partial remission, SCT stem cell transplantation

EATL kivizsgálási és kezelési javaslat

Al-Somali Z et al. Curr Hematol Malig Rep. 2021;16:140-147

Terápiás célpontok T-sejtes lymphomában



Stuver R et al. Cancer 2023;15:589-606

Valemetostat tosylate (DS-3201b; also known as valemetostat) is a novel, potent, and selective dual inhibitor of EZH2 and EZH1. A first-in-human phase 1 study was conducted for pts with R/R NHL in Japan and the US. Valemetostat demonstrated clinical antitumor activity in pts with NHL, including R/R PTCL and R/R ATL. Treatment with valemetostat 150 or 200 mg/day led to overall response rates (ORRs) of 54.5% (95% CI, 38.8%-69.9%) and 57.1% (95% CI, 28.9%-82.3%) in pts with R/R PTCL (n=44) or R/R ATL (n=14), respectively (EHA 2021. Abstract S218). Durability of response was demonstrated by a median duration of response (DOR) of 56.0 weeks (range, 44.43- -) in PTCL pts. Based on these encouraging efficacy results, a global phase 2 study was designed.

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 5, 2021

A Global Phase 2 Study of Valemetostat Tosylate (Valemetostat) in Patients with Relapsed or Refractory (R/R) Peripheral T-Cell Lymphoma (PTCL), Including R/R Adult T-Cell Leukemia/Lymphoma (ATL) - Valentine-PTCL01

Francine M. Foss, Pierluigi Porcu, Steven M. Horwitz, Koji Izutsu, Kenji Ishitsuka, Kazunobu Kato, Jin Jin, Yining Du, Ai Inoue

Blood (2021) 138 (Supplement 1): 2533.

https://doi.org/10.1182/blood-2021-144676

A phase 2 biomarker-driven study of ruxolitinib demonstrates effectiveness of JAK/STAT targeting in T-cell lymphomas

45 R/R PTCL-es és 7 Mycosys Fungoides-es beteg

3 biomarker-definiált cohort: (1) aktiváló JAK és/vagy STAT mutáció jelen van

(2) ≥30% pSTAT3 expresszió a tumorsejtekben immunohisztokémiával

(3) semmi kimutatható eltérés

Kezelés: ruxolitinib 20 mg per os 2x naponta progresszióig

Elsődleges végpont: CBR „clinical benefit rate” (CR, PR, SD 6 hónapig)

Th válasz: 1/7 MF betegnél volt csak CBR (> 18 hónapig PR)

PTCL: 53 %, 45 %, 13 % az 1, 2 és 3. cohortban.

–T-LGL leukémiában a legjobb válasz

Moskowitz AJ et al. Blood 2021;138:2828-2837. #NCT02974647.

Összefoglalás

T-sejtes lymphomák – kedvezőtlen kimenetel

CHOEP választandó 60 év alatt

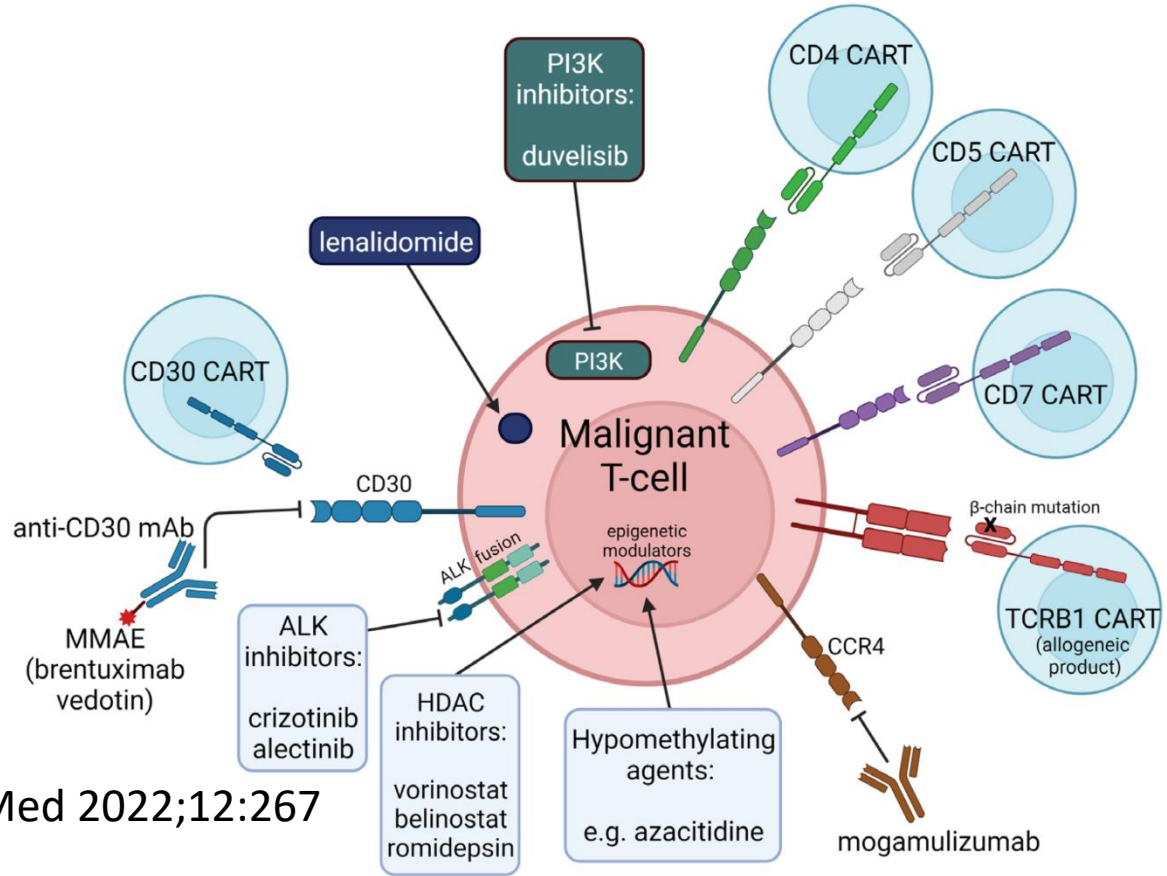
Brentuximab vedotin CD30+ esetben első vonalban javasolt (A-CHP)

ALK negatív DUSP22+ és ALK pozitív ALCL-en kívül egyéb esetekben első vonalban ASCT javallt

Relapszusos esetek kezelési eredménye kiábrándító – allogén transzplantáció adhat reményt a reagáló betegeknek

Gyógyszertanulmány javasolt (új, célzott kezelés)

CAR T-sejt terápia itt is alkalmazható lesz



Angelos M et al. J Pers Med 2022;12:267