NORDIC LYMPHOMA GROUP

Unmet clinical challenges in high risk hematological malignancies: from benchside to clinical practice

How I treat high risk T-cell lymphomas?

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Torino Incontra Centro Congressi

Disclosure of affiliations

- Advisory boards: Nordic Nanovector, Servier Pharmaceuticals, Takeda, Kyowa Kirin, ImmuneOncia
- Speaker's honoraria: Takeda, Servier Pharmaceuticals
- Research support: Sanofi/Genzyme, Takeda, Roche, Servier Pharmaceuticals, MSD

Structure of the talk

WHO update

- Some novel entities from the 2016/2017 WHO classification
- Newly recognized biological features relevant for patient management

Treament according to subtype and risk profile?

- What have we learned from the large upfront PTCL-specific trials?
- Treatment according to subtype and risk adapted?

New drugs

- Novel therapies tested in PTCL clinical trials

T-cell lymphomas over the last 30 years

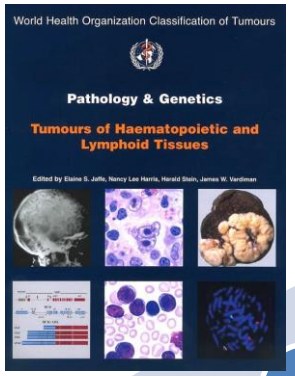
Journal of Clinical Pathology

Suchi-Lennert Classification 1987

Morphology, IH

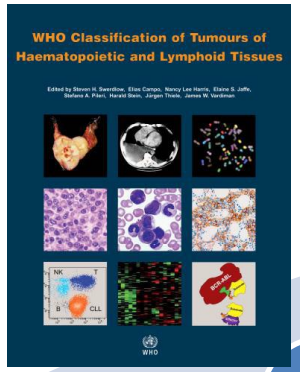
REAL Classification 1994

Morphology, IH, FISH,cytogenetics



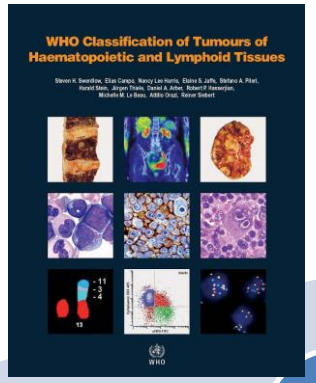
WHO Classification 2001

Morphology, IH, FISH, cytogenetics, mol. biol.



WHO Classification 2008

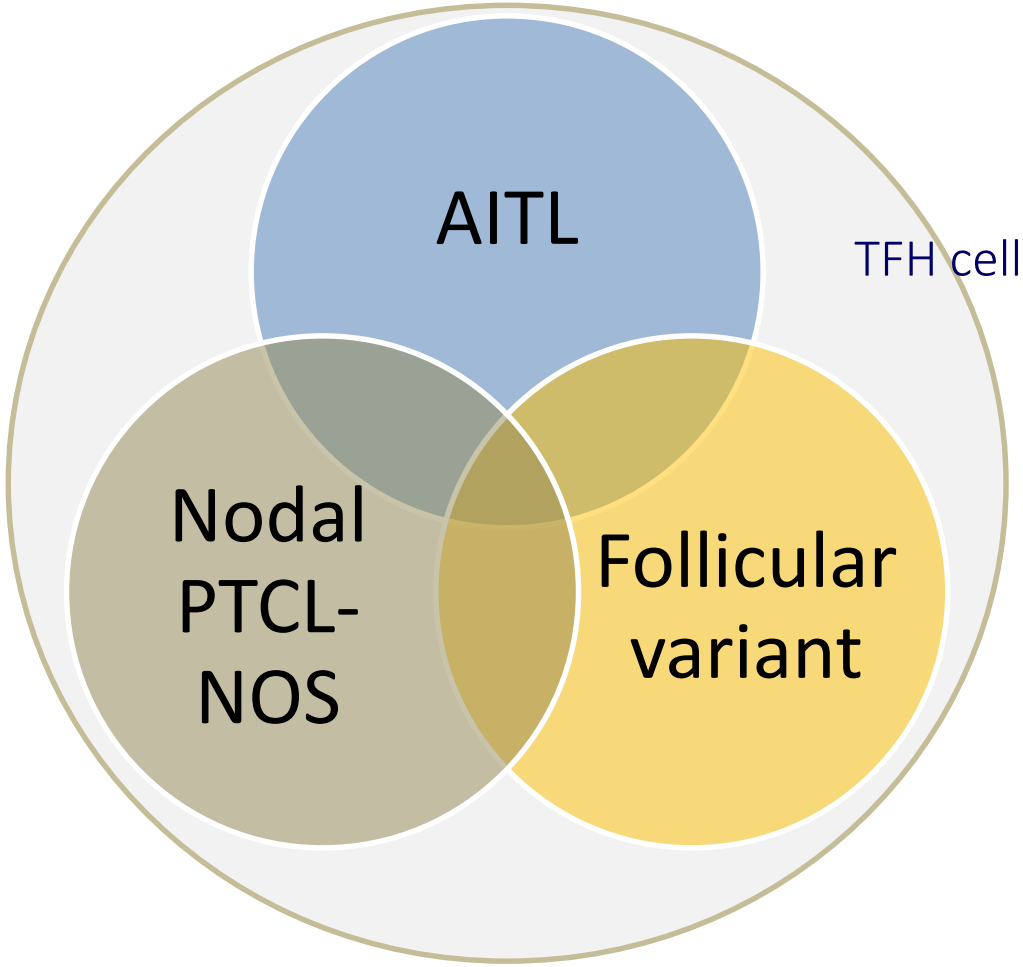
Morphology, IH, FISH,cytogenetics, mol. biol., GEP



WHO Classification 2016/2017

Morphology, IH, FISH,cytogenetics, mol. biol., GEP, NGS, Nanostring, RNA seq, high-throughput of FFPEs

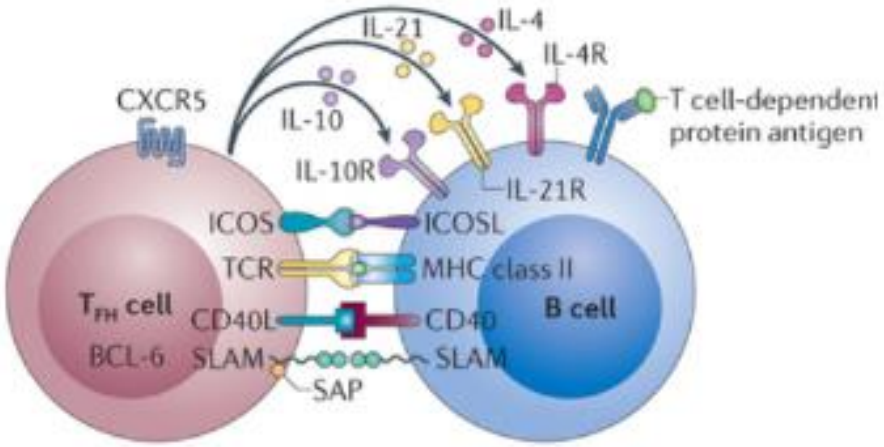
WHO 2017: Nodal PTCL of T_{FH} cell origin >> subtype migration



GEP and mutation analysis have helped to characterize the relationship between nodal PTCL entities og TFH origin

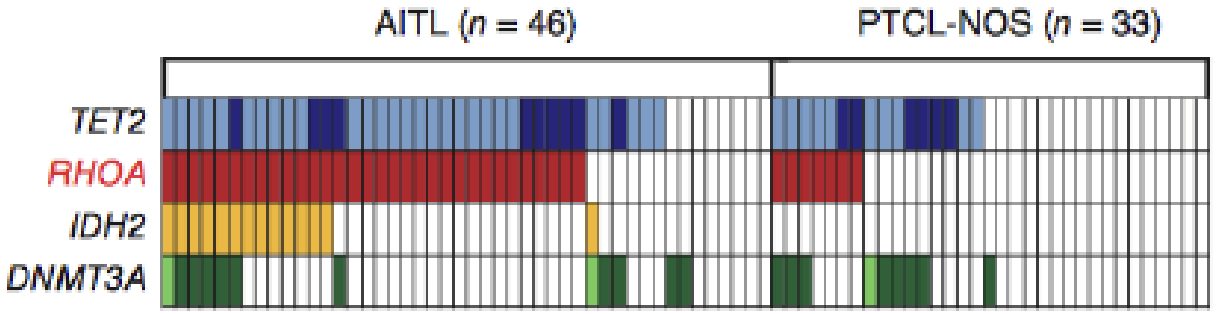
Actionable mutations in PTCL: Epigenetic modifier genes

T follicular helper CD4+ cells (TFH)



BCL6+
CXCR5+
PD1+

TFH-like lymphoma
(AITL and some PTCL-NOS)



IDH2 and TET2 mutations are mutually exclusive in AML but co-occur in TFH-derived TCL

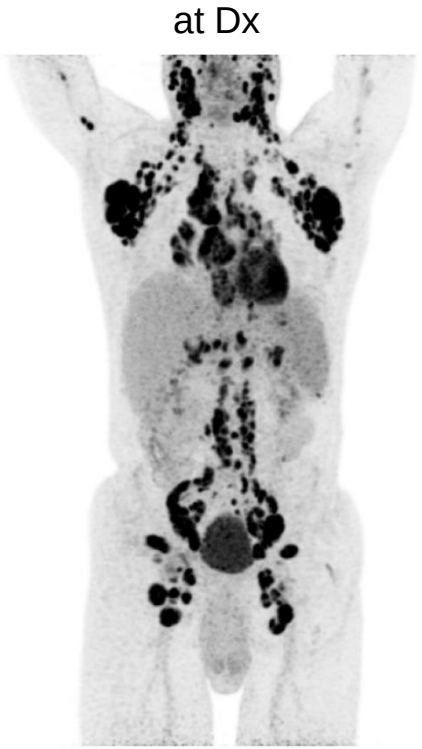
PTCL, peripheral T-cell lymphoma; IDH, isocitrate dehydrogenase; BCL, B-cell lymphoma gene; CXCR, chemokine receptor; PD-1, programmed cell death; AITL, angioimmunoblastic T-cell lymphoma, NOS, not otherwise specified; TET2, ten-eleven translocation DNMT3A, DNA (cytosine-5) methyltransferase 3 alpha; AML, acute myeloid leukemia; TFH, T follicular helper; TCL, T-cell lymphoma; mIDH2, mutant IDH

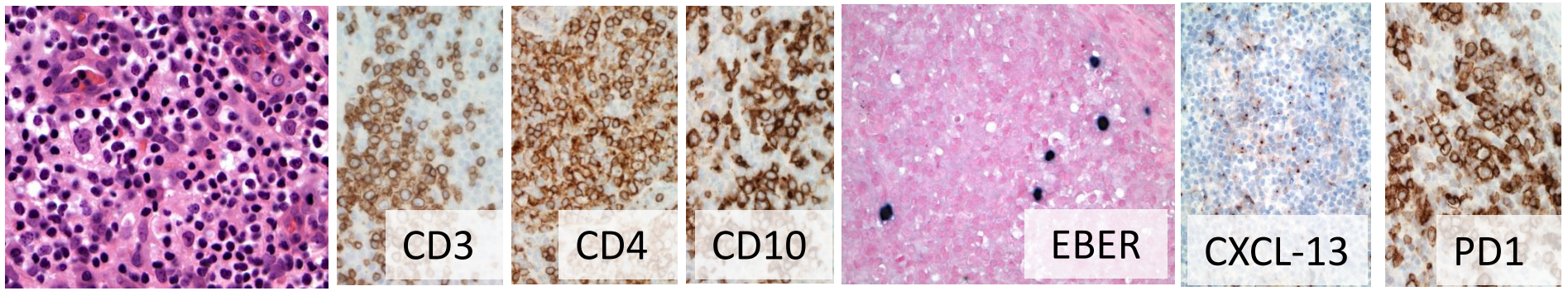
Sakata-Yanagimoto M, et al. Nat Gen 2014;46:171-5

Clinical case

2 points: (i) ET/AITL; (ii) Mutational status

- 45 y/o man with known JAK2+ ET develops fever, fatigue, drenching sweats, PS 3
- Multiple supra- and infradiaphragmatic LN involvement and BM infiltration
- Cervical LN biopsy showed AITL
- Elevated LDH (770 U/l)
- Mutations: TET2+, IDH2+, JAK2+





Lymphoproliferative and myeloproliferative malignancies occurring in the same host: A nationwide discovery cohort

AITL: **expected** occurrence among NHL (i.e. without CLL and HL) => **3%** of 64 = ca 2 => **observed**: 8 = **12,5%**

	PV	ET	MF	CML	Mastocytosis	MPN-NOS	Total
Chronic lymphocytic leukemia	8	6	2	1	-	14	31
Diffuse large B-cell lymphoma	8	2	2	2	1	5	20
Low grade lymphoma - NOS	4	-	3	-	-	4	11
Peripheral T-cell lymphoma							
- ALCL ALK-neg	-	-	1	-	-	-	1
- AITL	2	2	1	-	-	3	8
Waldenström macroglobulinemia	-	1	4	2	-	3	10
Lymphoblastic lymphoma	-	-	-	5	-	-	5
Marginal zone lymphoma	-	-	1	-	-	4	5
Hodgkin's lymphoma	-	1	-	1	-	-	2
Follicular lymphoma	-	1	-	1	-	-	2
Mantle cell lymphoma	-	-	-	-	-	1	1
Primary CNS lymphoma	-	-	-	1	-	-	1
Total	22	13	14	13	1	34	97

Obs%: 12,5%
Exp%: 3%

collaboration AUH, DK <<>> Cornell, NY

Holst J et al. Blood 2017 130:1525

Enteropathy-associated TCL 2008-2017

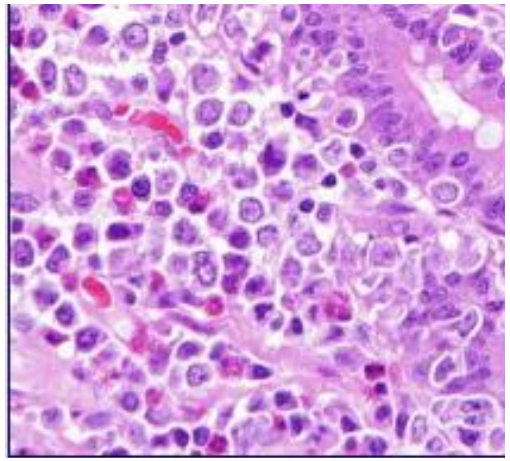
2008

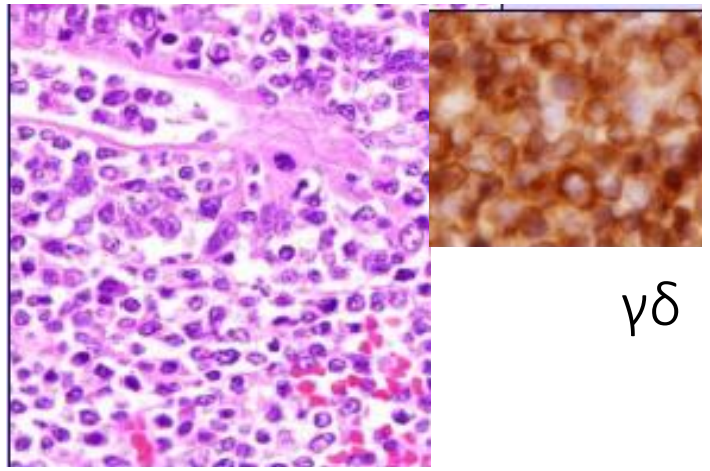
EATL type I

Usually TCR αβ rearranged, CD8+, CD56-
Coeliac disease associated
Northern European

EATL type II

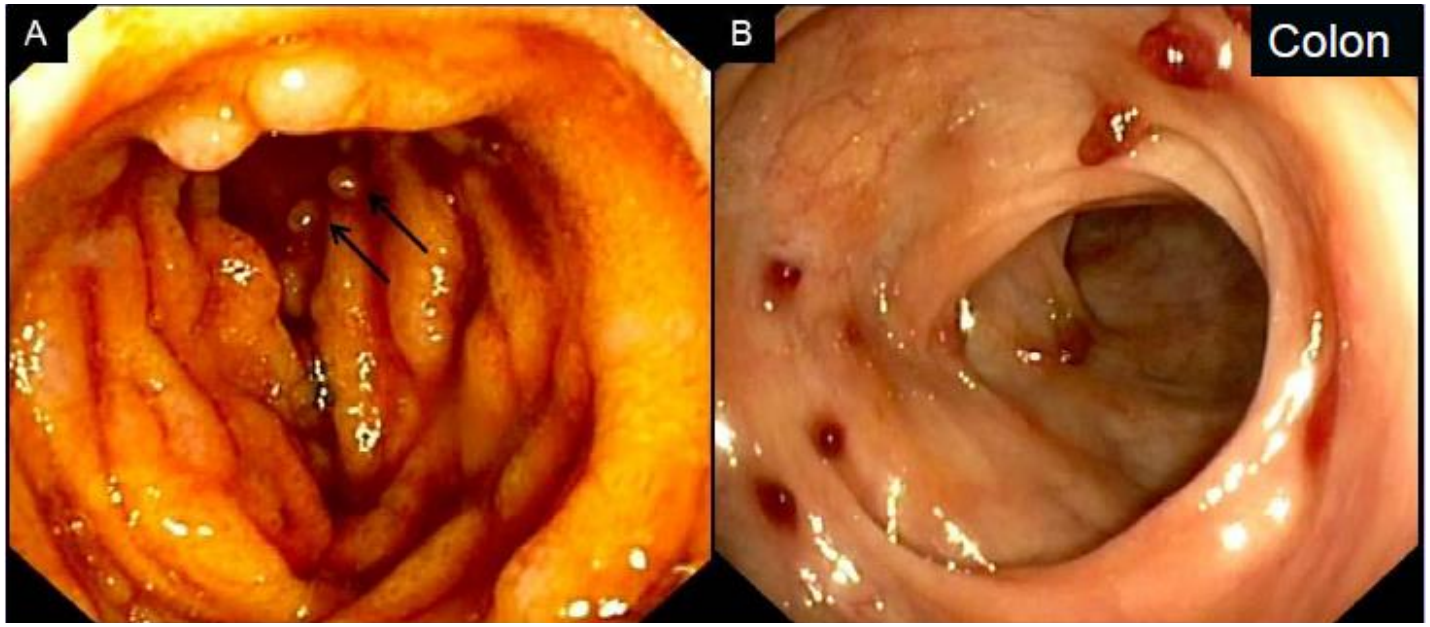
Usually TCR γδ rearranged, CD8+,CD56+
Epitheliotropic
Not associated with enteropathy
Asian, Hispanic





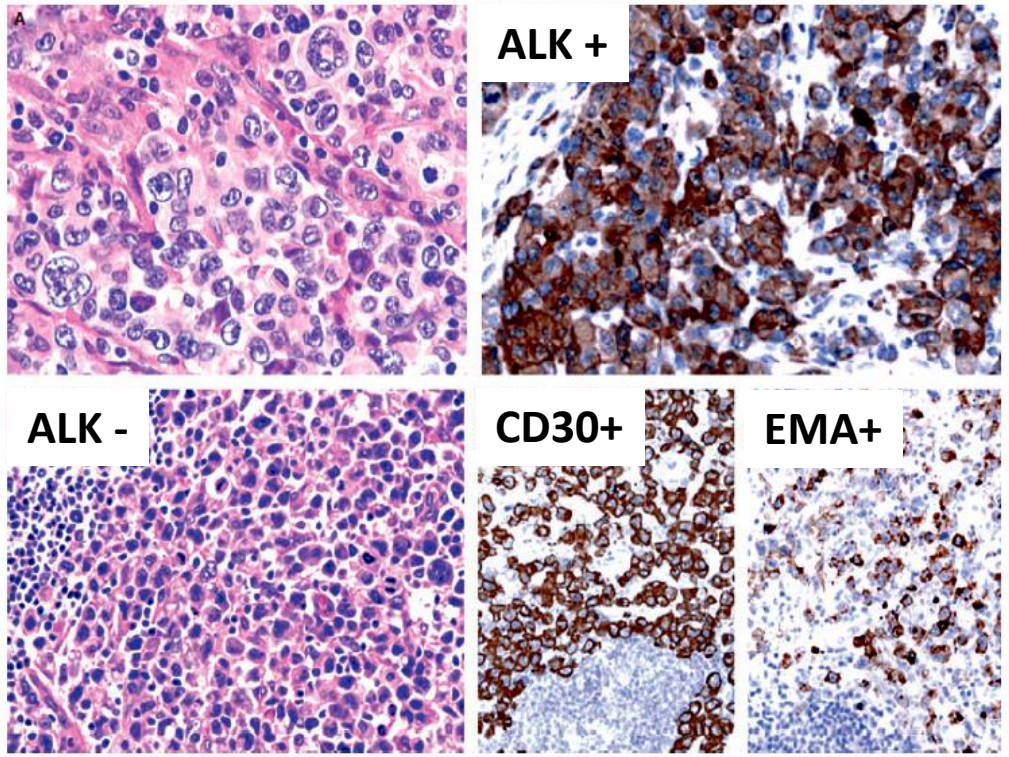
γδ

Indolent T-cell lymphoproliferative disease of the GI tract (provisional entity)
(Perry et al, Blood 2013)



- Adults, rare <20 yrs; M=F
- Clonal entity, usually cytotoxic CD8+ phenotype
- Oral cavity, stomach, small intestine, colon
- Diarrhea, pain, rectal bleeding
- Chronic, indolent course
- Usually no dissemination outside the GI-tract
- Chemotherapy not useful

Anaplastic Large Cell Lymphomas



de Leval et al, *Histopathology*, 2011

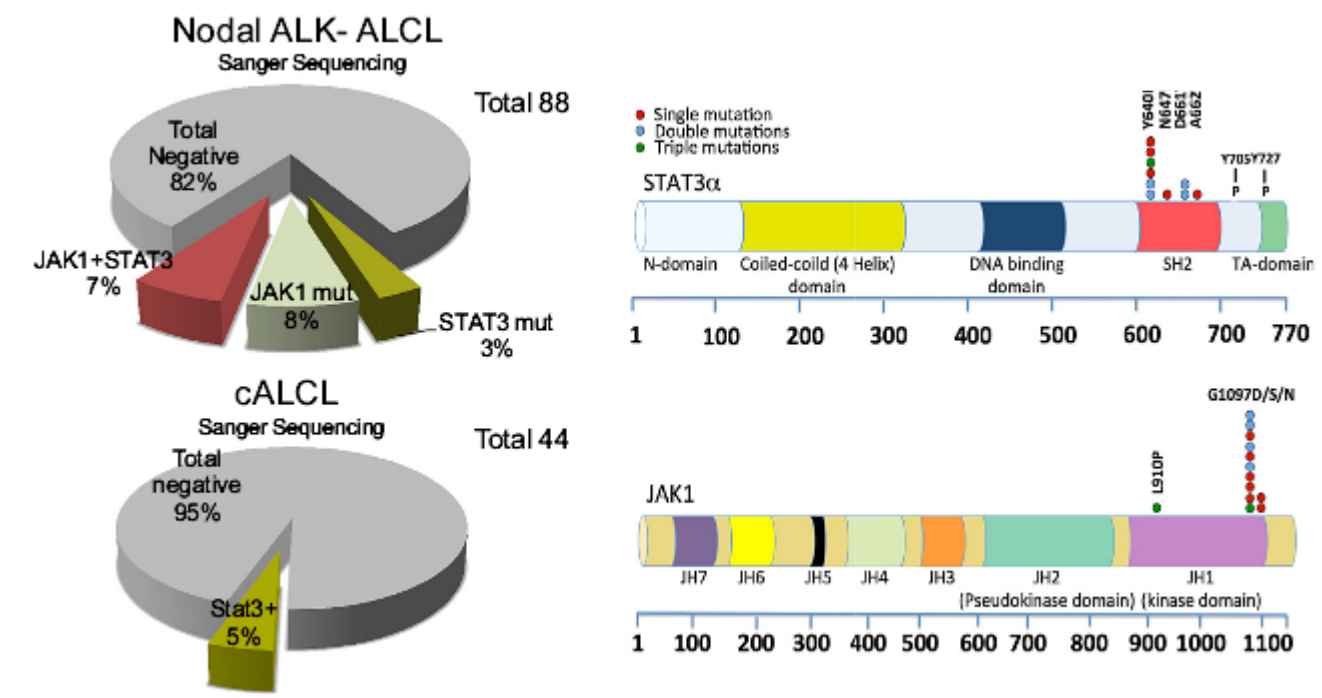
- All entities show activation of the JAK-STAT pathway
- Breast-implant associated ALCL (now entered as provisional entity)
- ALCL, ALK-positive
- ALCL, ALK-negative (no longer a provisional, but a definite entity)
- Differential diagnostic criteria vs CD30+ PTCL-NOS have been clarified
- DUSP22/IRF4 and TP63rearrangements >> prognostic implications?

Actionable mutations in sALCL within the JAK/STAT pathway

CellPress

Cancer Cell
Article

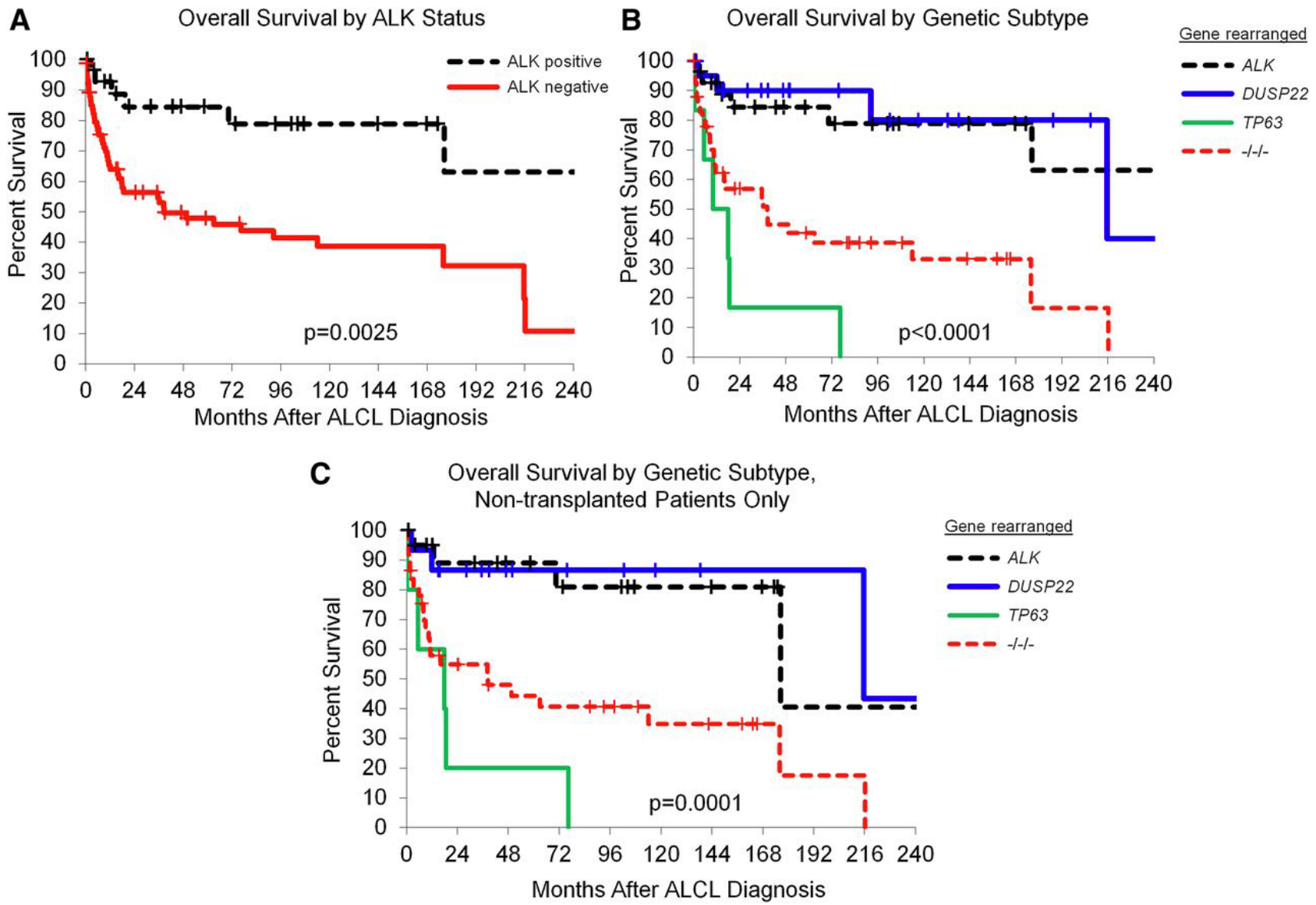
Convergent Mutations and Kinase Fusions Lead to Oncogenic STAT3 Activation in Anaplastic Large Cell Lymphoma



- Co-occurring somatic mutations and TF/TK fusions in STAT3+JAK1 in syst alk-ALCL>>oncogenic
- JAK/STAT pathway inhibitors showed therapeutic efficacy in pre-clinical models
- **Phase 2 Ruxolitinib trial is ongoing**

Crescenzo R, et al. Cancer Cell 2015;27:516-32

Prognostic impact of ALK, DUSP22 and TP63 rearrangements in adult systemic ALCL

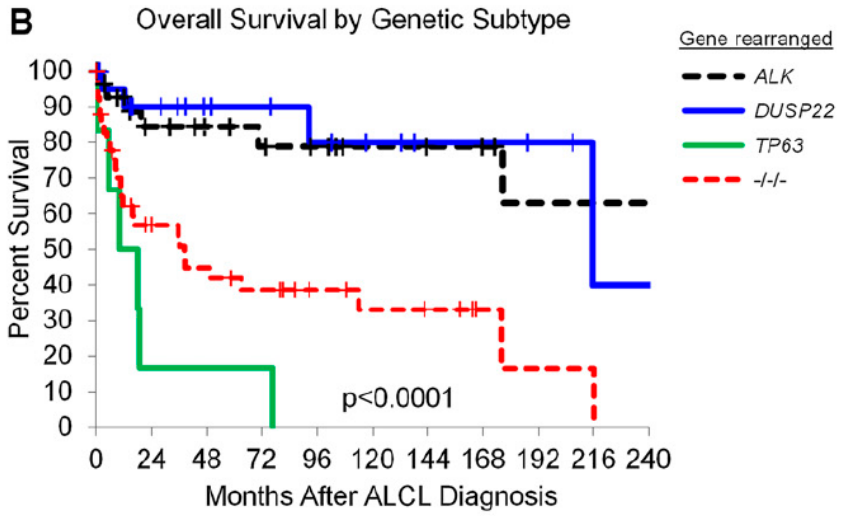


ALK, anaplastic lymphoma kinase; DUSP, dual specificity phosphatase; TP63, transformation-related protein 63; ALCL, anaplastic large cell lymphoma

Parilla Castellar ER, et al. Blood 2014;124:1473-80

Parrilla Castellar et al (Blood 2014)

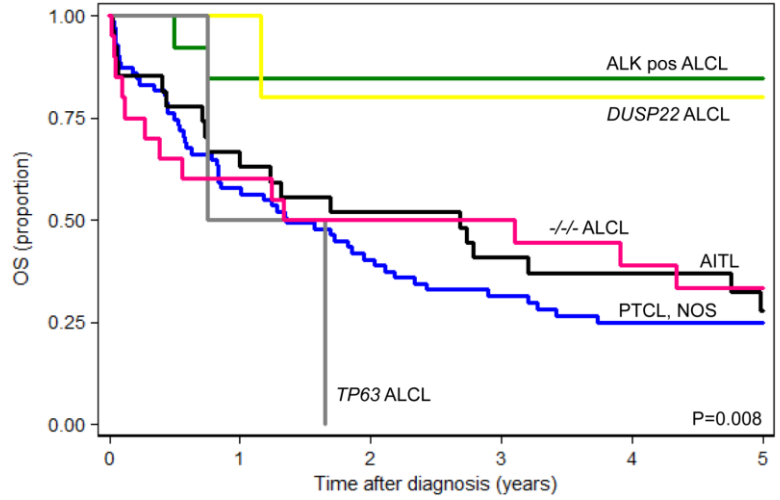
- N=105 **(ALCL, only)**
  - N= 32 ALK positive (30%)
  - N=73 ALK negative (70%)
- ALK negative
  - N= 22 DUP22+ (30%)
  - N= 6 TP63+ (8%)
  - N= 45 -/-/- (62%)



Parrilla Castellar et al, *Blood*, 2014

Pedersen et al (Blood 2017)

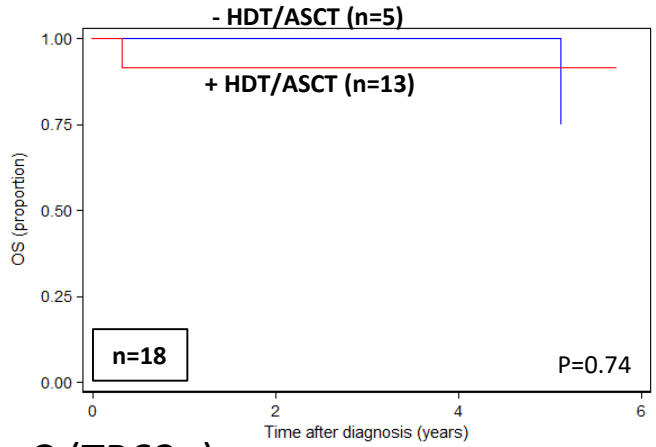
- N= 138 **(PTCL-NOS, AITL, ALCL N=40)**
  - N=13 ALK positive (32%)
  - N=27 ALK negative (68%)
- ALK negative
  - N= 5 DUP22+ (21 %)
  - N= 2 TP63+ (7%)
  - N= 20 -/-/- (74 %)



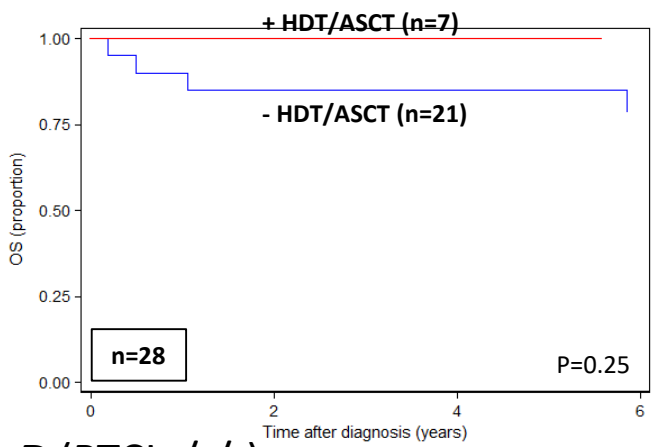
Pedersen et al, *Blood*, 2017

Tx. eligible patients - HDT/ASCT

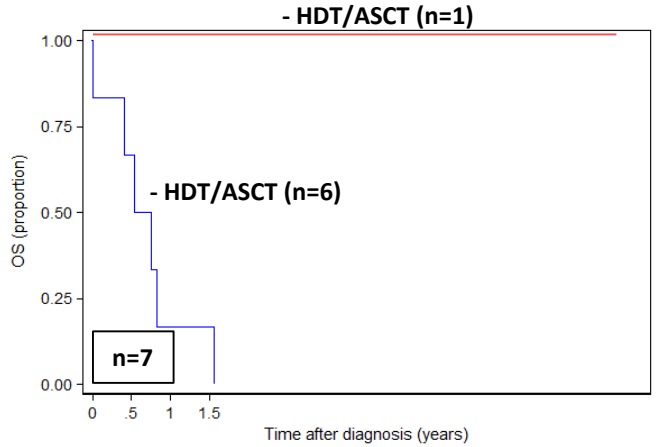
A (DUSP22+)



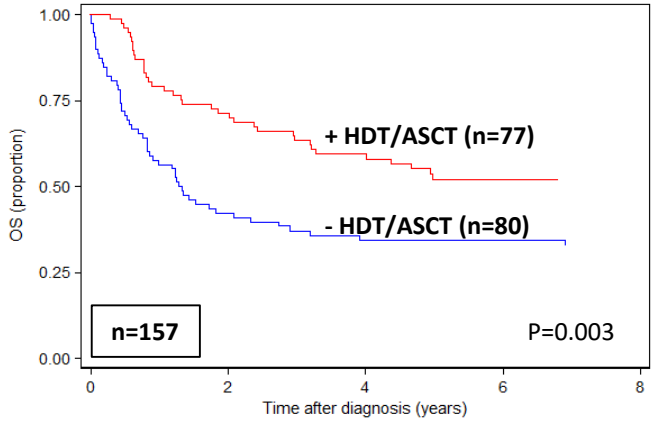
B (ALK+ ALCL)



C (TP63+)



D (PTCL-/-/-)

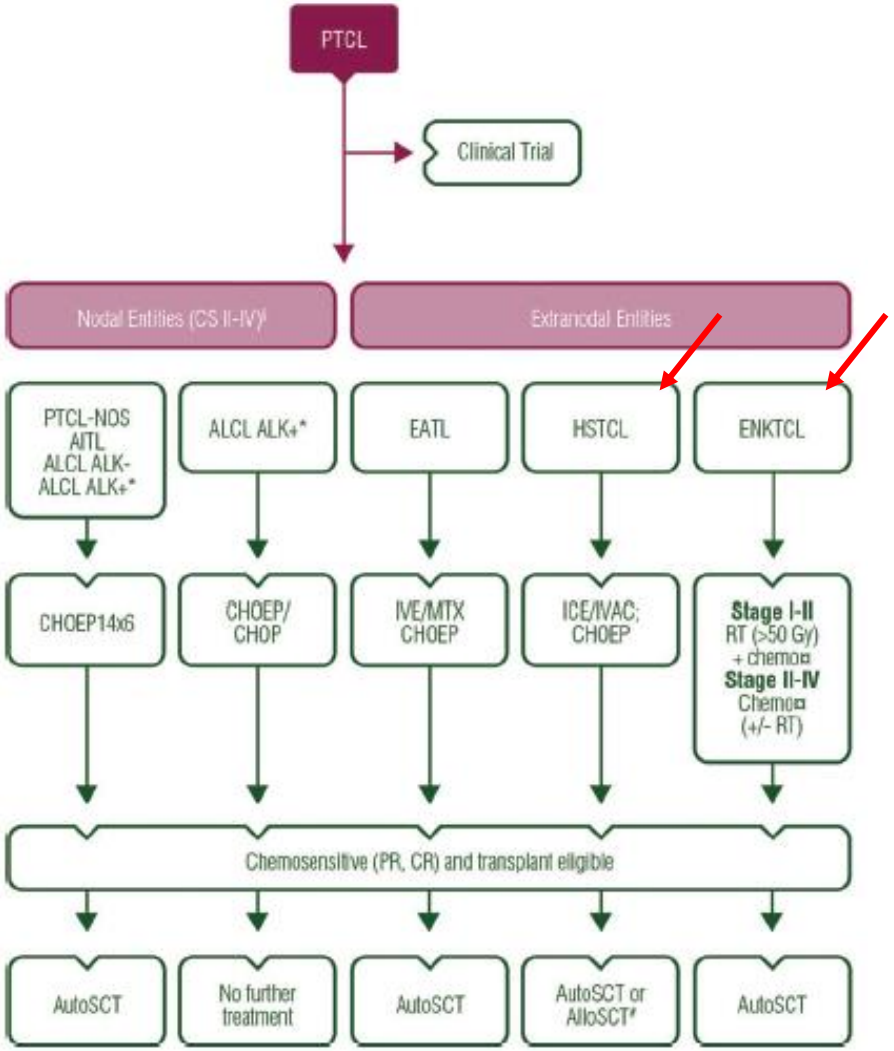


Pedersen et al, Blood 2017 130:822

Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. d'Amore[1], P. Gaulard[2], L. Trümper[3], P. Corradini[4], W.-S. Kim[5], L. Specht[6], M. Bjerregaard Pedersen[1] & M. Ladetto[7], on behalf of the ESMO Guidelines Committee*

1st line



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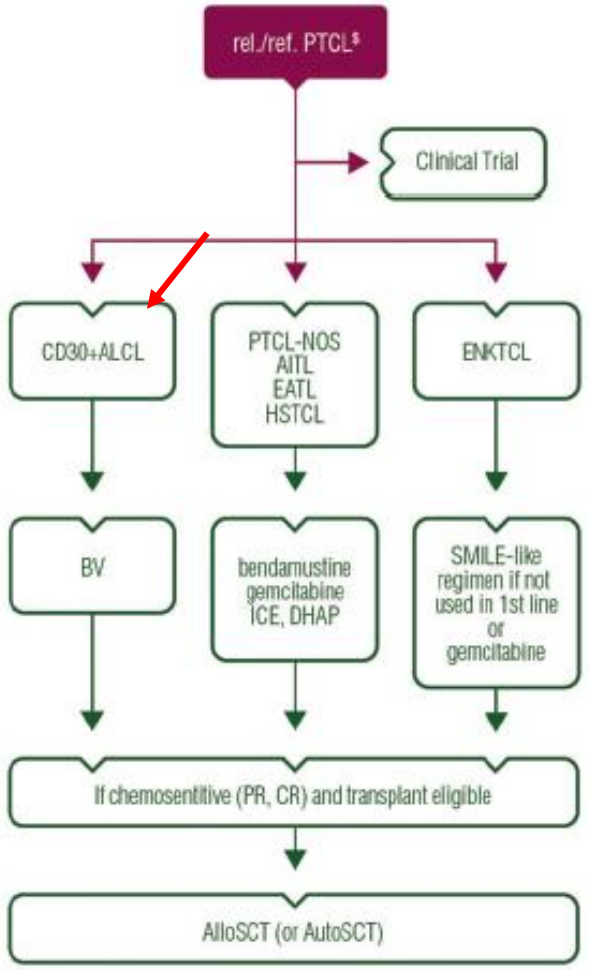
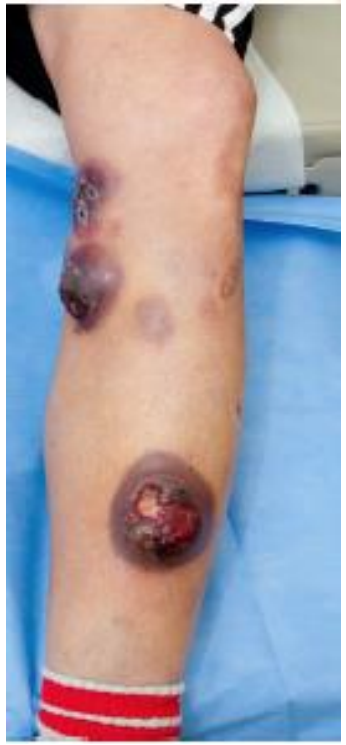
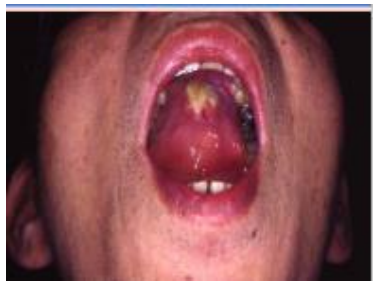


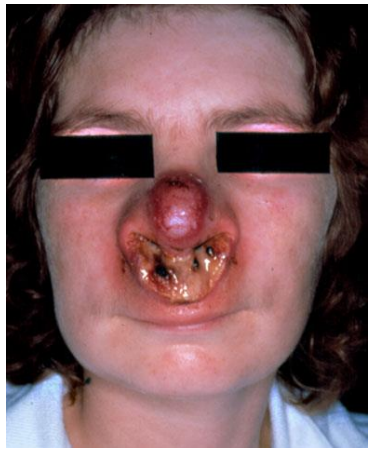
d'Amore F, et al. Ann Oncol 2015;26 Suppl. v108-v115

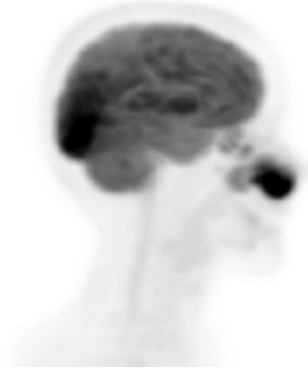
Extranodal NK/T cell lymphoma, nasal type

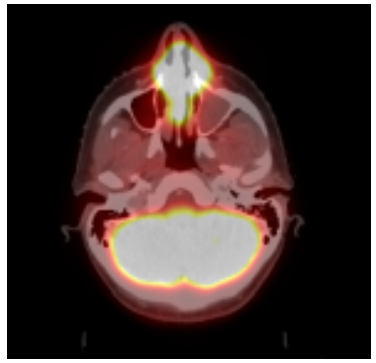
Epidemiological and clinical features	
Frequency	North America and Europe: 1-5% Asia/Central-South America: >20%
Most common site	Nasal cavity/rhinopharynx
Less common	Waldeyer ring, tonsils, sinuses
Other sites	Skin, GIT, testes, sal.glands
EBV	Strongly associated/driven Quantitative p-EBVDNA is prognostic (PINK-E index, Lancet Oncol 2016)











NK/T, natural killer T-cell lymphoma; p-EBVDNA, Epstein Barr Virus deoxyribose nucleic acid; PINK-E, prognostic index of natural killer lymphoma plus EBV DNA data; GIT, gastrointestinal tract; sal, salivary

Kim SJ, et al. Lancet Oncology 2016;17:389-400

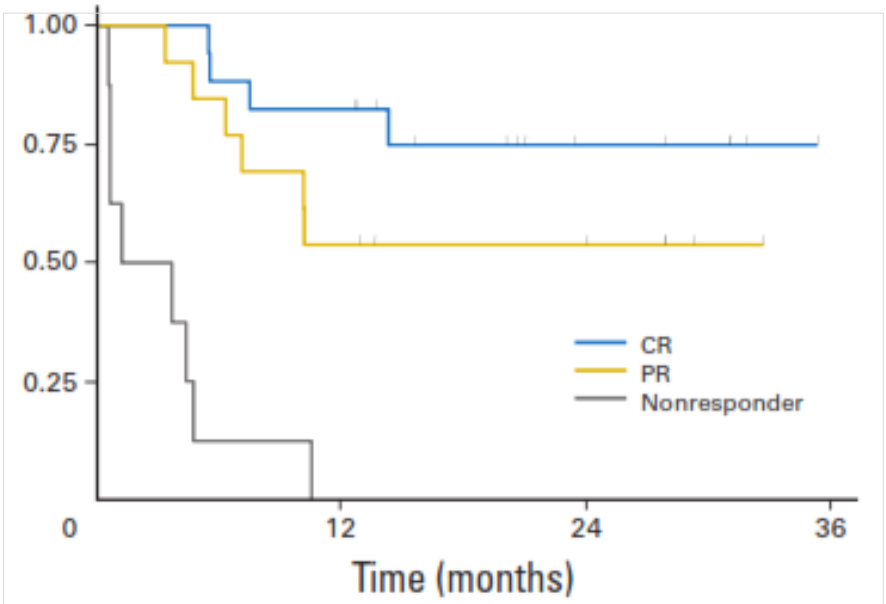
L-asparaginase in ENKTCL: The SMILE regimen

Agent	Dose/d
Methotrexate	2 g/m^2*
Leucovorin	15 mg × 4
Ifosfamide	1,500 mg/m^2
Mesna	300 mg/m^2 × 3
Dexamethasone	40 mg/d
Etoposide	100 mg/m^2*
L-asparaginase (*Escherichia coli*)	6,000 U/m^2
G-CSF	

Response After Two Cycles of SMILE

Response	All Patients (N = 38) No.	%
CR	17	45
PR	13	34
NR	1	3
PD	4	10
ED	3	8

79%



	1-yr OS	3-yr OS	3-yr PFS
All pts	55%	50%	45%

ENKTCL, extranodal natural killer T-cell lymphoma; d, day; G-CSF, granulocyte colony-stimulating factor; SMILE, dexamethasone, methotrexate, ifosamide, L-aspraginase, etoposide; CR, complete response; PR, partial response; NR, non responder; PD, progressive disease; ED, early death; OS, overall survival; PFS, progression free survival, pts, patients

Yamaguchi M, et al. J Clin Oncol 2011;29:4410-6

ENKTL – CD38

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CORRESPONDENCE

Targeting CD38 in Refractory Extranodal Natural Killer Cell–T-Cell Lymphoma

N Engl J Med 2016; 375:1501-1502 | October 13, 2016 | DOI: 10.1056/NEJMc1605684

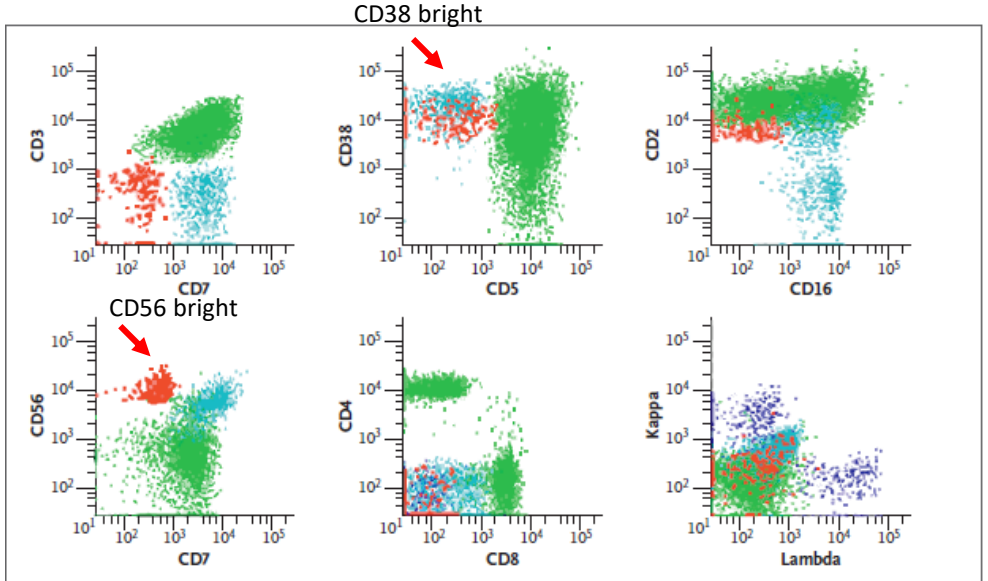


Figure 1. Flow-Cytometric Analysis of a Peripheral-Blood Sample in a Patient with a Recurrence of Leukemic Extranodal Natural Killer (NK) Cell–T-Cell Lymphoma (Nasal Type).

Aberrant NK cells (red) were positive for CD2, CD16 (dim), CD38, and CD56 (bright) and negative for surface CD3, CD4, CD5, CD7, and CD8. Normal NK cells (cyan), T cells (green), and B cells (blue) are shown for comparison. Both normal and abnormal NK cells are negative for surface light chains (kappa and lambda).

- Short DoR
- Loss of target
- Maybe useful to improve QoR in combination regimens within a ‘bridging-to-allo’ strategy

A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis

Seok Jin Kim, Dok Hyun Yoon, Arnaud Jaccard, Wee Joo Chng, Soon Thye Lim, Huangming Hong, Yong Park, Kian Meng Chang, Yoshinobu Maeda, Fumihiro Ishida, Dong-Yeop Shin, Jin Seok Kim, Seong Hyun Jeong, Deok-Hwan Yang, Jae-Cheol Jo, Gyeong-Won Lee, Chul Won Choi, Won-Sik Lee, Tsai-Yun Chen, Kiyeun Kim, Sin-Ho Jung, Tohru Murayama, Yasuhiro Oki, Ranjana Advani, Francesco d'Amore, Norbert Schmitz, Cheolwon Suh, Ritsuro Suzuki, Yok Lam Kwong, Tong-Yu Lin, Won Seog Kim

Lancet Oncology 2016

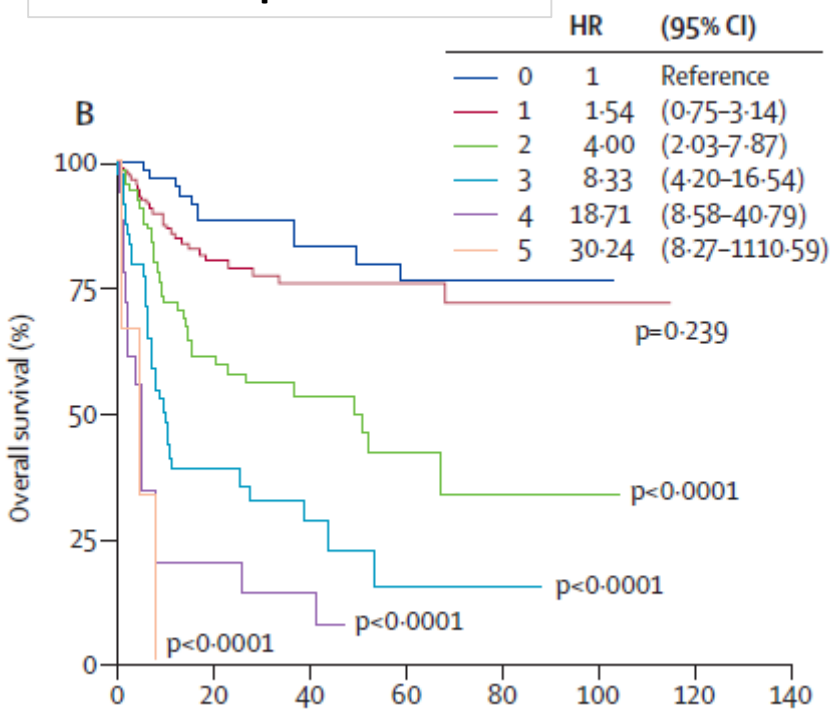
➢ PINK

- Age >60
- St III-IV
- Distant l.nodes
- Non-nasal sites

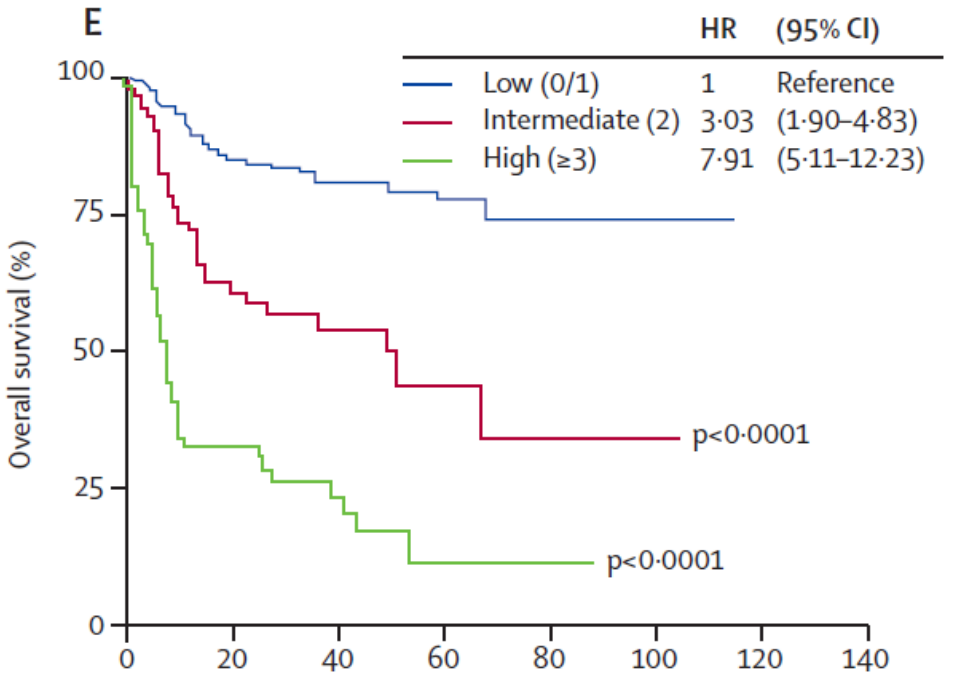
➢ PINK-E

- PINK factors
- p-EBV DNA detectable

PINK-E: OS pr N of factors



PINK-E: OS pr risk group



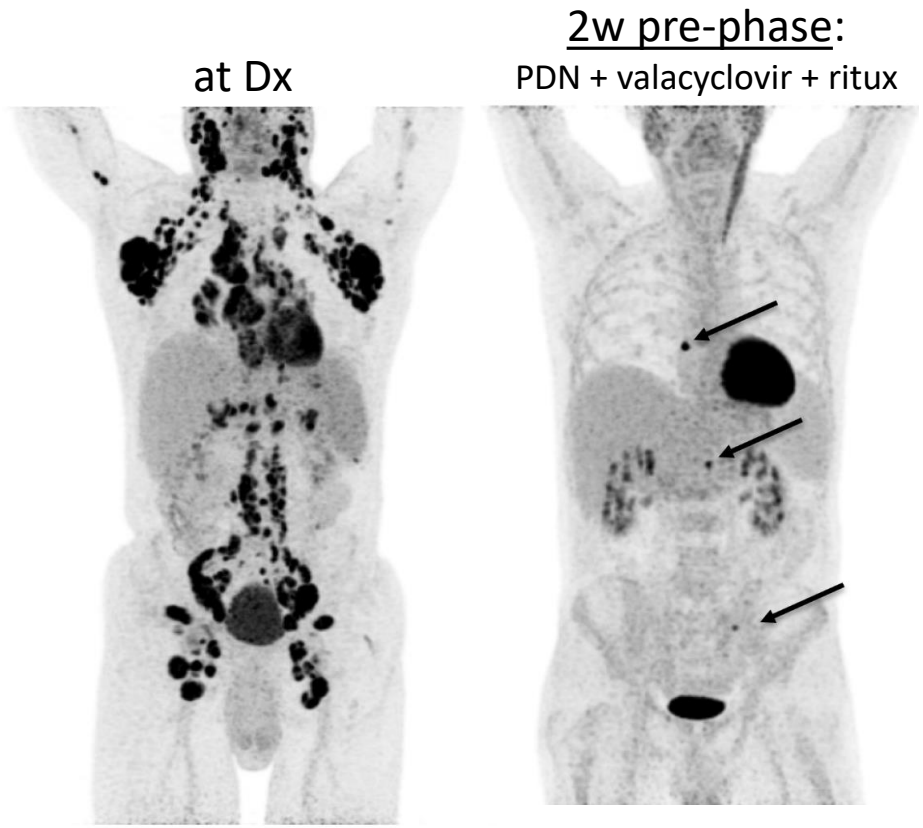
PINK, prognostic index of natural killer lymphoma; PINK-E, prognostic index of natural killer lymphoma plus EBV DNA data; OS, overall survival; pr N, prognostic number; HR, hazard ratio; CI, confidence interval; St, stage; l.nodes, lymph nodes; EBV, Epstein Barr Virus

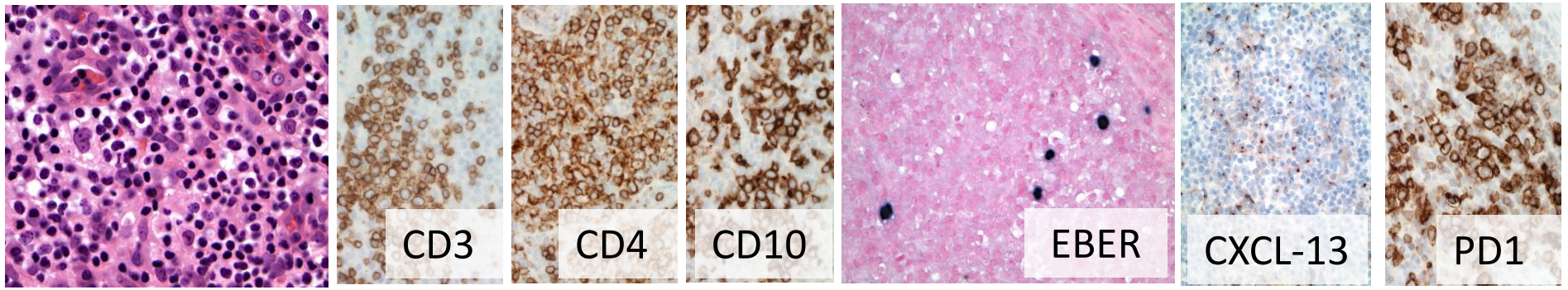
Kim SJ, et al. Lancet Oncology 2016;17:389-400

Clinical case

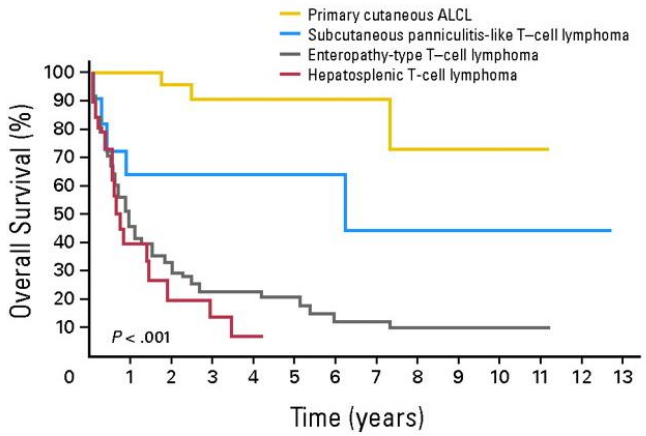
2 points: (i) EBV viremia; (ii) response to antiviral pre-phase

- 45 y/o man with known JAK2+ ET develops fever, fatigue, drenching sweats, PS 3
- Multiple supra- and infradiaphragmatic LN involvement and BM infiltration
- Cervical LN biopsy showed AITL
- Elevated LDH (770 U/l)
- Mutations: TET2+, IDH2+, JAK2+
- At Dx: EBV-DNA copy n: 440.000
- After pre-phase: EBV-DNA CN: 6400

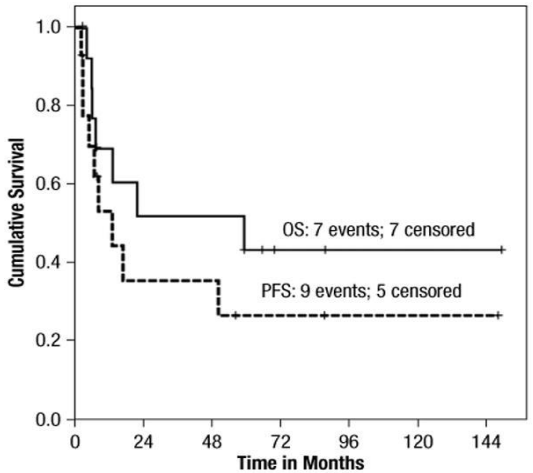




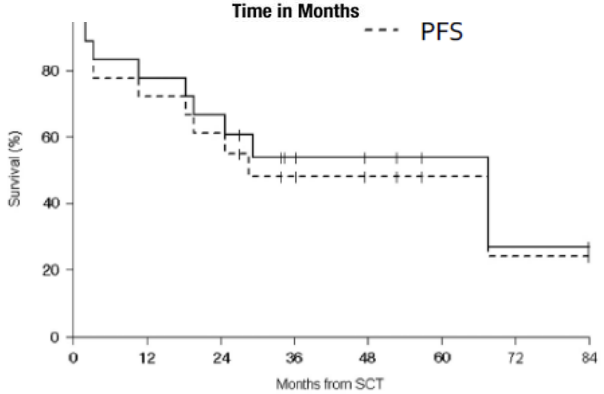
HSTCL: if in CR1/(PR1) allo upfront



- Younger males
- Often prior IBD and immunosuppression
- Very aggressive clinical course
- Marked hepato-splenomegaly
- Bone marrow infiltration
- Strong elevation of LDH and LFT's
- Isochromosome 7



- ICE/IVAC induction preferred (MSKCC)
- Median follow-up 5.5 yrs
- Median PFS 13.3 mos
- Median OS 59 mos



- N=25
- Allo SCT N=18 >> 3-yrs PFS: 48%
- Auto SCT 5 of 7 relapsed

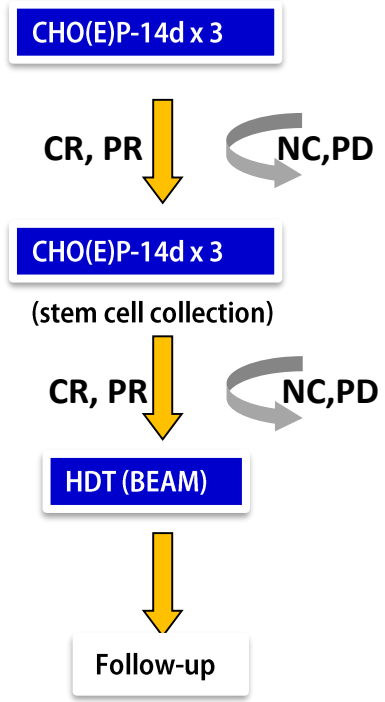
International T-Cell Lymphoma Project J Clin Oncol 2008;26:4124-30
Voss MH, et al. Clin Lymphoma Myeloma Leuk 2013;13:8-14
Tanase A, et al. Leukemia 2015;29:686-8

NLG-T-01: 1st PTCL-specific trial – Does upfront HDT improve outcome?

Excluded:
- Precursor TCL
- alk+ ALCL
- CTCL
- Primary leukemic PTCL

CHO(E)P :
18-60 yrs: CHOEP-14 (n=118)
61-67 yrs: CHOP-14 (n=42)

60 mo median follow-up

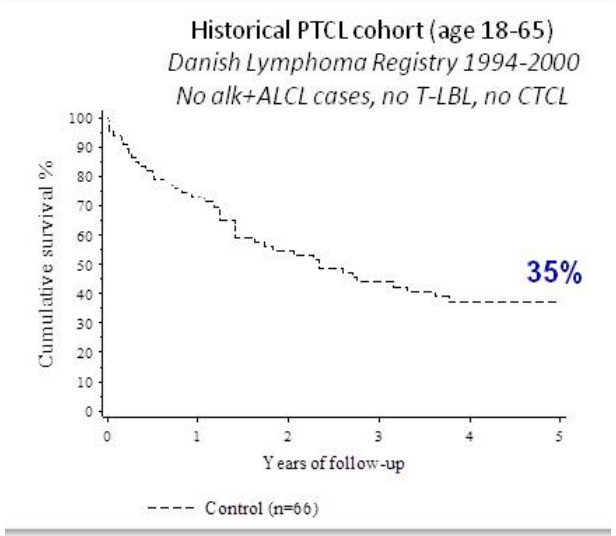


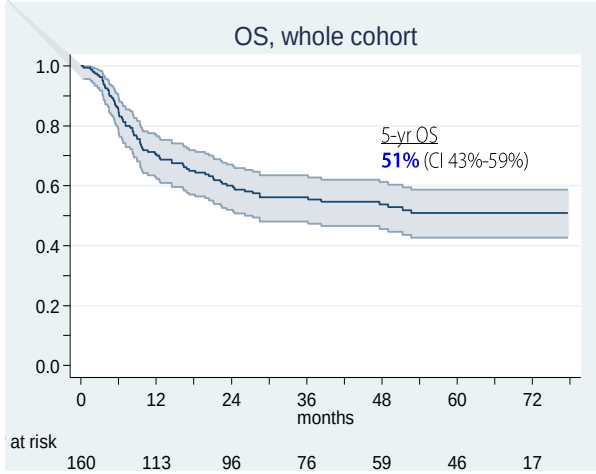
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Upfront Autologuos Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01

Francesco d'Amore, Thomas Relander, Grete F. Lauritzsen, Esa Jantunen, Hans Hagberg, Harald Anderson, Harald Holte, Anders Österborg, Mats Merup, Peter Brown, Outi Kuittinen, Martin Erlanson, Bjørn Østenstad, Unn-Merete Fagerli, Ole V. Gadeberg, Christer Sundström, Jan Delabie, Elisabeth Ralfkiaer, Martine Vornanen, and Helle E. Toldbod

JCO 2012;30(25):3093-9





Histology	5-yr OS	95% CI	5-yr PFS	95% CI
ALCL	**70%**	50%-83%	**61%**	42%-76%
AILT	**52%**	33%-69%	**49 %**	30%-65%
EATL	**48%**	26%-67%	**38 %**	18%-57%
PTCL-NOS	**47%**	34%-59%	**38 %**	25%-50%

A doxo-void backbone alternative to CHOP/CHOEP?

CEOP-Pralatrexate
Gemcytabine-Methylprednisolone-Cisplatin (GEM-P)

Design	Regimen	Outcome	Authors' statement	Reference
Phase 2	CHOP+Pralatrexate	2yr PFS: 39%	No obvious improvement on historical CHOP data	Advani R et al. Br J Haem 2015, 172:535-44
Phase 2 rand	CHOP vs GEM-P Hypothesis: GEM-P>CHOP EOT-CR 70% vs 50%	EOT-CR: CHOP 53% GEM-P 47% (p=0.24)	1) No efficacy difference 2) GEM-P had a higher rate of study withdrawals	Gleeson M et al. 14th ICML, Lugano 2017 (abstr#64)

AlloTx (RIC) in PTCL with chemosensitive relapse

- 32 pts
- Previous ASCT: 17 pts (53%)
- Conditioning regimen: fludarabine, thiotepa, cyclophophamide

median f/u 30 mo (6-86)	5 yr OS	62%	(95% CI, 42-82%)
22 pts (69%) alive (16 in CR)	5 yr PFS	53%	(95% CI, 35-71%)

Upfront Auto or AlloTx (RIC) in PTCL ≤60yrs

Intensified chemo-immunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma

Total eval.pts: 61	Outcome (4 yr-OS, PFS)
Not TX: 24	OS >> auto vs allo: 92% vs 69% (p=0.10) PFS >> auto vs allo: 70% vs 69% (p=0.92)
AlloTx: 23	
AutoTx: 14	[Both auto and allo better than noTx]

AlloTx, allogeneic stem cell transplantation; RIC, reduced intensity conditioning; PTCL, peripheral T-cell lymphoma; pts, patients; ASCT/autoTX, autologous stem cell transplantation; f/u, follow up; mo, months; yr, years; OS, overall survival; CI, confidence interval; CR, complete response; PFS, progression free survival; TX, transplantation

Corradini P, et al. J Clin Oncol 2004;22:2172-6
Corradini P, et al. Leukemia 2014;28:1885-91

German auto vs allo trial (AATT)

ALLOGENEIC OR AUTOLOGOUS TRANSPLANTATION AS FIRSTLINE THERAPY FOR YOUNGER PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA—RESULTS OF THE INTERIM ANALYSIS OF THE **AATT** TRIAL

Trial cohort			
	All	Auto	Allo
Randomized (tot)	104	---	---
Interim analysis	58	30	28

Efficacy			
	All	Auto	Allo
ORR	51%	53%	50%
1y EFS	41%	48%	48%
1y OS	69%	61%	55%

Main problems:

1) 38% not reaching consolidative SCT
2) GvL-effect of allo counterbalanced by high TRM

Authors' statement

This analysis showed no significant differences in survival for pts randomized to autoSCT or alloSCT. After interim futility analysis,…the DSMB/PIs decided to prematurely stop patient accrual.

AATT, autologous allogeneic, transplantation trial; auto, autologous; allo, allogeneic; tot, total; ORR, overall response rate; y, year; EFS, event free survival; OS, overall survival; SCT, stem cell transplantation; GvL, graft verses lymphoma; TRM, treatment related mortality; pts, patients; DSBM, Data and Safety Monitoring Board, PI, principal investigators

Schmitz N, et al. ICML 2015;abstract 33

HCT in PTCL

Biology of Blood and Marrow Transplantation

The Official Journal of the American Society for Blood and Marrow Transplantation

Article in Press

Clinical Practice Recommendations on Indication and Timing of Hematopoietic Cell Transplantation in Mature T Cell and NK/T Cell Lymphomas: An International Collaborative Effort on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation

Mohamed A. Kharfan-Dabaja, Ambuj Kumar, Ernesto Ayala, Mehdi Hamadani, Peter Reimer, Christian Gisselbrecht, Francesco d'Amore, Esa Jantunen, Takashi Ishida, Ali Bazarbachi, Francine Foss, Ranjana Advani, Timothy S. Fenske, Hillard M. Lazarus, Jonathan W. Friedberg, Mahmoud Aljurf, Lubomir Sokol, Kensei Tobinai, Eric Tse, Linda J. Burns, Julio C. Chavez, Nishitha M. Reddy, Ritsuro Suzuki, Sairah Ahmed, Auayporn Nademanee, Mohamad Mohty, Ajay K. Gopal, Michelle A. Fanale, Barbara Pro, Alison J. Moskowitz, Anna Sureda, Miguel Angel Perales, Paul A. Carpenter, Bipin N. Savani

http://dx.doi.org/10.1016/j.bbmt.2017.07.027

Largest prospective upfront PTCL trials

Study b	Design	N pts	Median FU	Efficacy (5 y OS/PFS)	Reference
Nordic/German[1] +/-ALZ & auto (y)	phase 3	217	30 mo	---	ACT1: Final analysis ASH 2018 ACT2: Final analysis ASCO 2016
Nordic auto[2]	phase 2	160	54 mo	51%/44%	J Clin Oncol 2012
German auto[3]	phase 2	83	33 mo	40%/36%	J Clin Oncol 2009
German allo[4]	phase 3	104	12 mo	1y 69%/41% (EFS) No difference auto/allo >>premature STOP	ICML 2015 (Interim analysis)

PTCL, peripheral T-cell lymphoma; SCT, stem cell transplantation; pts, patients; FU, follow up; OS, overall survival; PFS, progression free survival; ALZ, alemtuzumab; auto, autologous stem cell transplantation; y, year; mo, months; EFS, event free survival; allo, allogeneic stem cell transplantation

[1] d'Amore F, et al. ASH 2012;abstract 57
[2] d'Amore F, et al. J Clin Oncol 2012;30:3093-9
[3] Reimer P, at al. J Clin Oncol 2009;27:106-13
[4] Schmitz N, et al. ICML 2015;abstract 33

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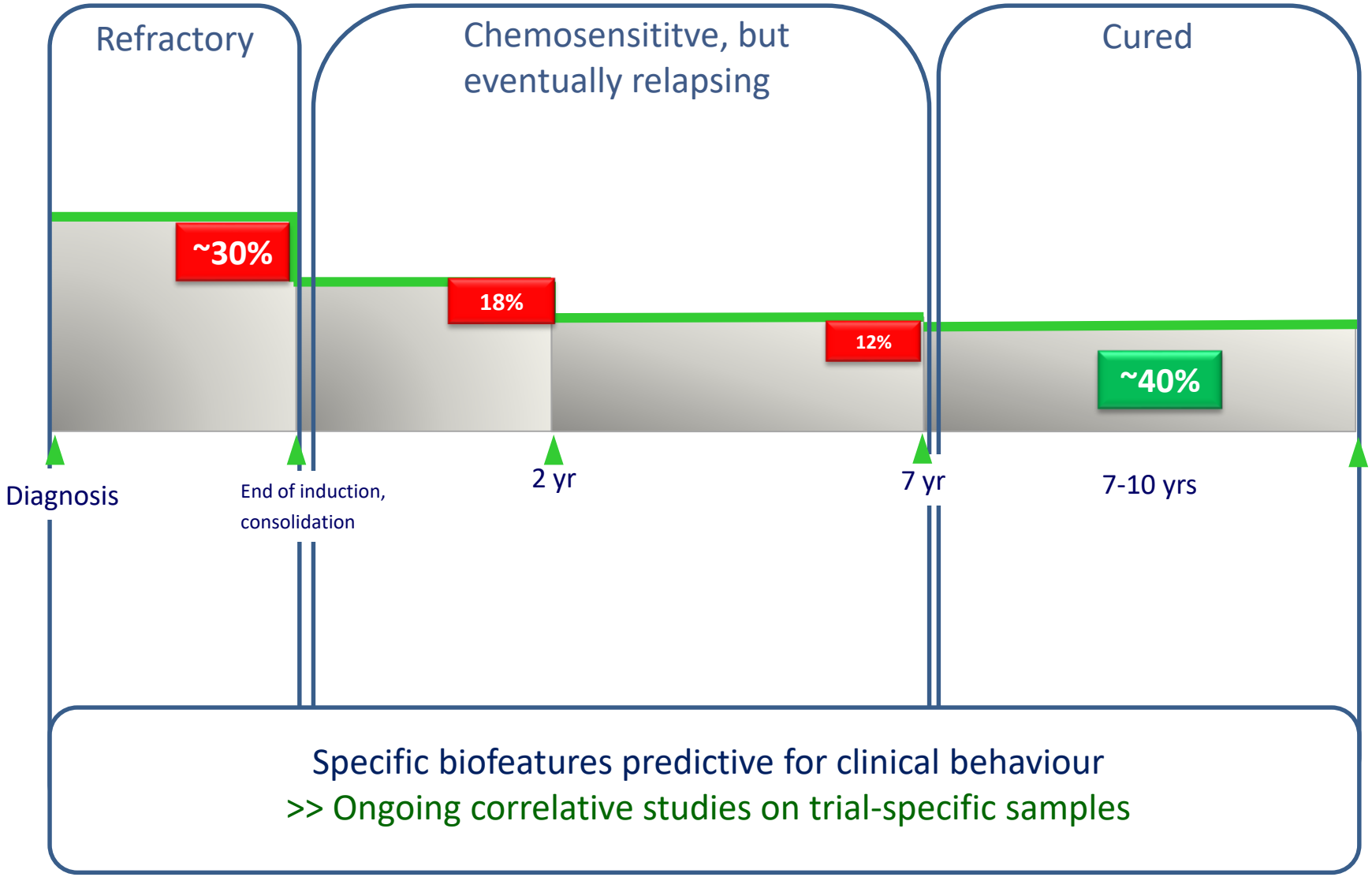
1st line treatment of PTCL

What have we learned from the large upfront PTCL-specific trials?



PTCL, peripheral T-cell lymphoma; yr, years

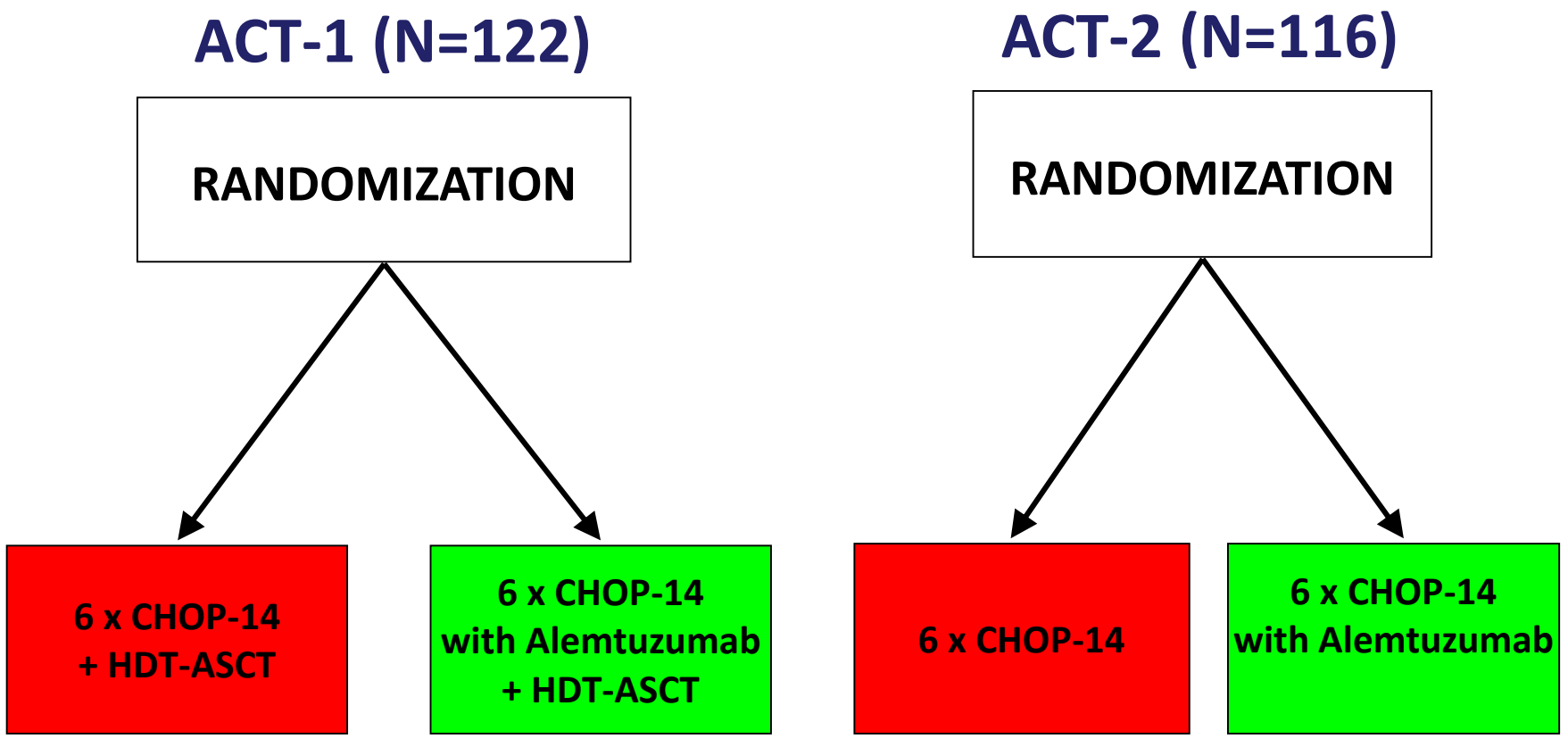
d'Amore F, et al. J Clin Oncol 2012;30:3093-9
d'Amore F, et al. Ann Oncol 2015; 26 Suppl 5:v108-15

Monotherapy with biological agents in R/R PTCL (last decade)

Ref	Compound	ORR	Approved (cond.)	Upfront phase3 trials
Enblad G, et al, Blood 2004;103:2920-4	Alemtuzumab (CD52)	36%	-	ACT-1+2
O'Mahony D, et al, CCR 2009;15:2514-22	Siplizumab (CD2)	31%	-	
O'Connor OA, et al, ASCO 2013;abstract 8507	Belinostat	26%	US	BEL-CHOP
d'Amore F, et al, BJH 2010;150:565-73	Zanolimumab (CD4)	26%	-	
O'Connor OA, et al, JCO 2011;29:1182-9	Pralatrexate	29%	US	
Coiffier B, et al, JCO 2012;30:631-6	Romidepsin	25%	US	RO-CHOP
Foss F, et al, ASCO 2010;abstract 8045	Denileukin Diftitox	40%	-	
Pro B, et al, JCO 2012;30:2190-6	Brentuximab vedotin (CD30)	86% (ALCL)	(ALCL) US, EU	CH[O]P+/-BV
Ogura M, et al, JCO 2014;32:1157-63	Mogamulizumab	34%	-	
O'Connor OA, et al, ASH 2015;abstract 341	Alisertib	24%	-	
Horwitz S, et al, ASH 2014;abstract 803	Duvelisib	47%	-	
Gambacorti Passerini C, et al, JNCI 2014;106: djt378. doi: 10.1093/jnci/djt378	Crizotinib	90% (alk+ALCL)	-	

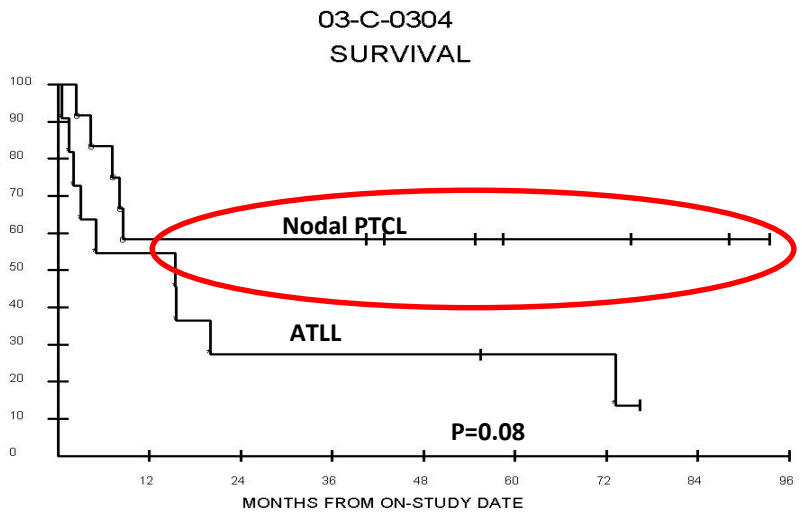
ACT trials

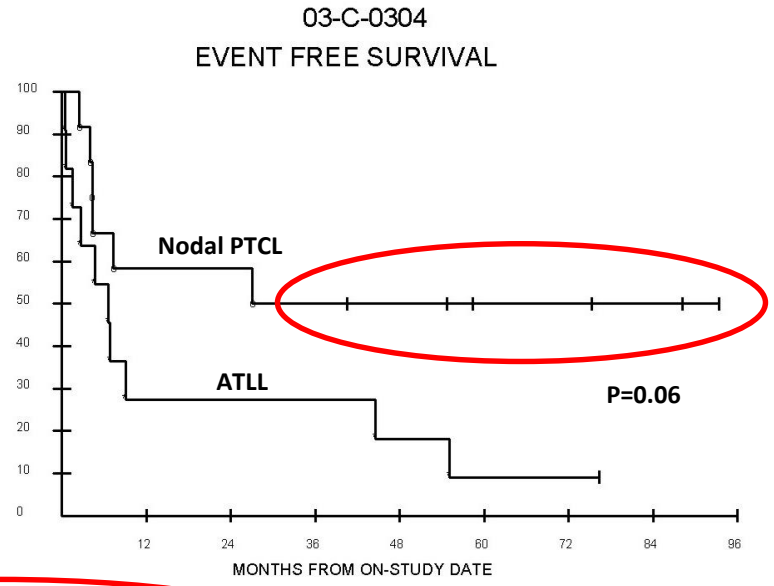
Trial design



CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; HDT-ASCT, high dose therapy-autologous stem cell transplantation

Efficacy of Alemtuzumab in combination with dose-adjusted EPOCH in untreated nodal PTCL





45 mo median follow-up

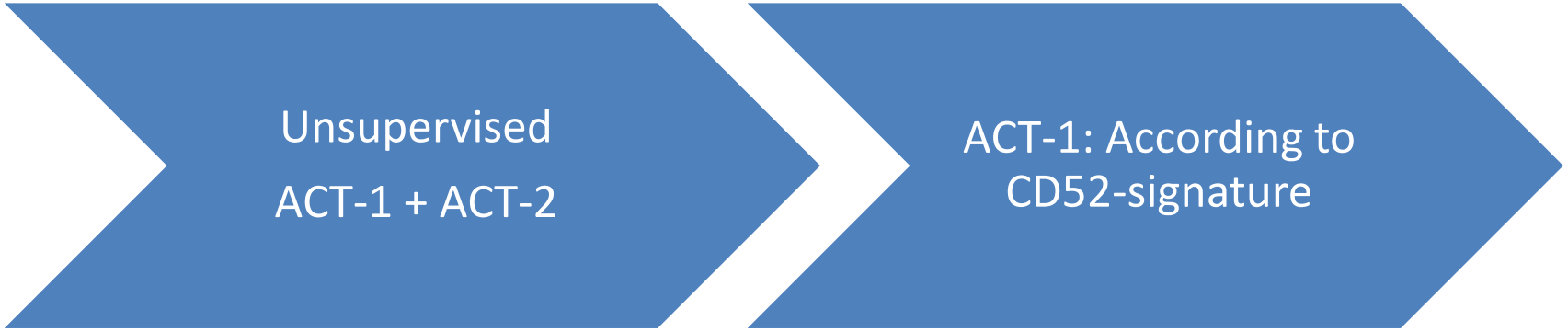
Flowcytometry-assessed CD52 expression required for protocol entry

EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; PTCL, peripheral T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; mo, months

Grant C, et al. ASCO 2012;abstract 8051
Courtesy of Dr. Cliona Grant (adapted)

ACT-1: Final analysis submitted to ASH 2018

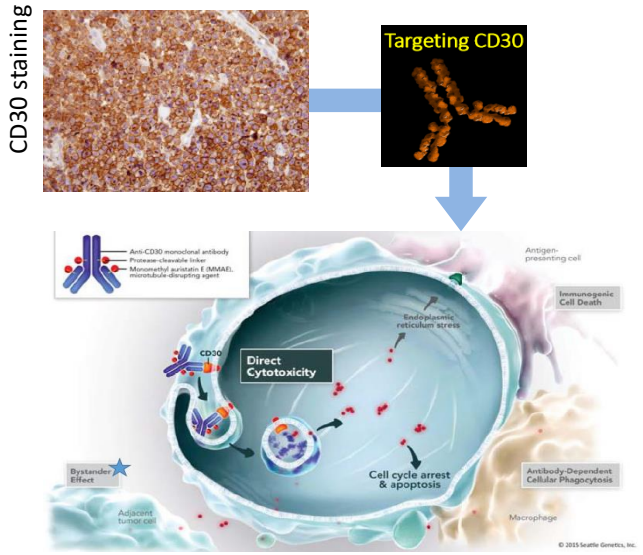
ACT-1: Total 122 pts



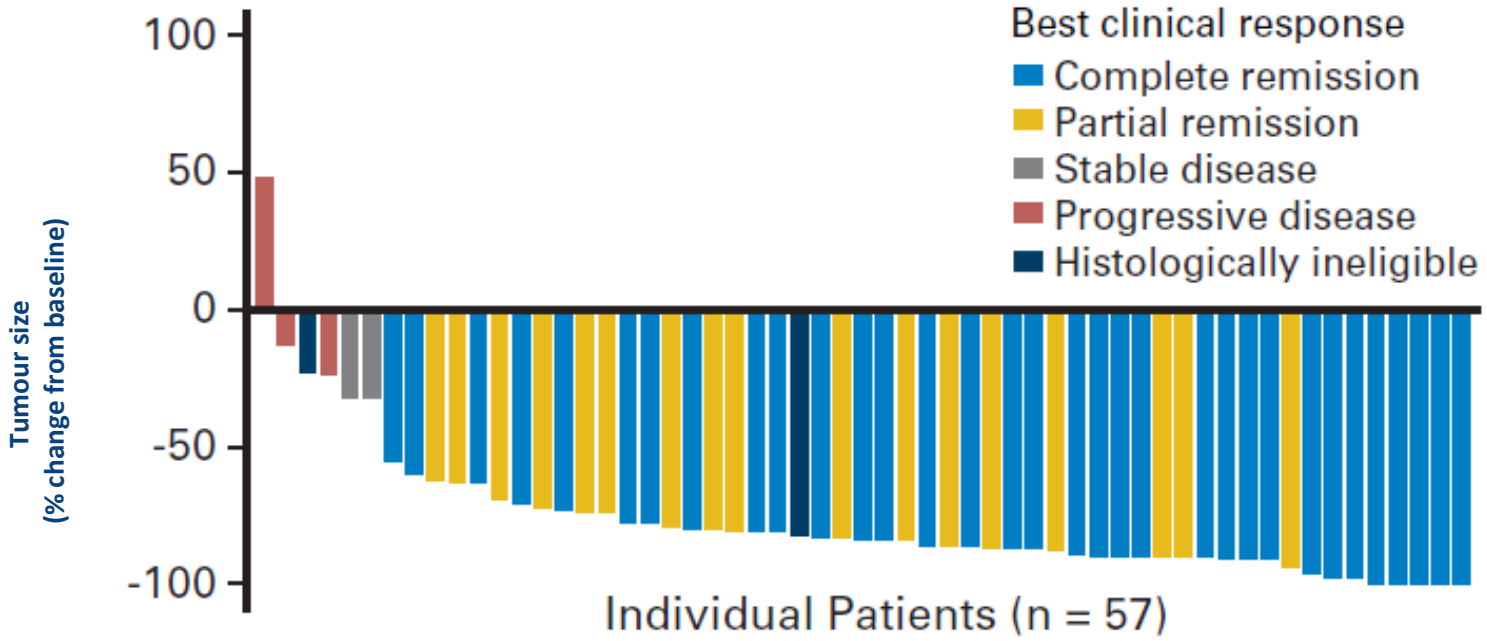
92 samples collected for CD52-signature analysis
RNAseq: BCCA
Bioinformatics: Iqbal (UNMC)-Chan (COH) lab

Pts, patients; RNA, ribonucleic acid; seq, sequence; BCCA, British Columbia Cancer Agency

Targeting CD30: Brentuximab vedotin in R/R ALCL



ORR 86% in R/R ALCL

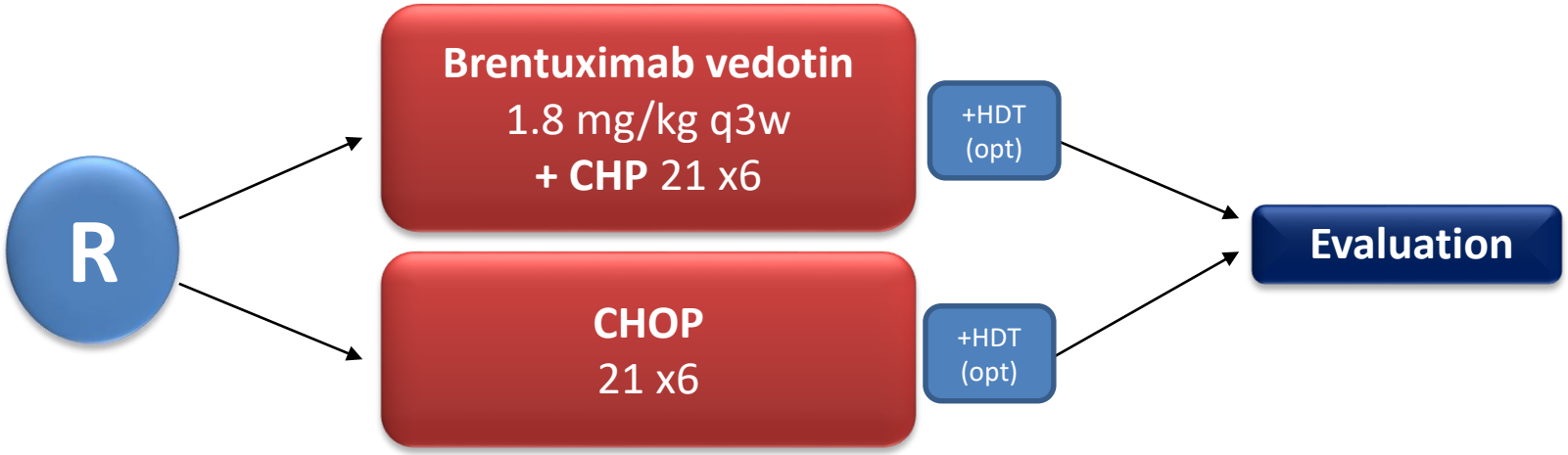


BV, brentuximab vedotin; R//R, relapsed/refractory; ALCL, anaplastic large cell lymphoma; ORR, overall response rate

Pro B, et al. J Clin Oncol 2012;30:2190-6

BV-CHP vs CHOP

Study Design: Patients with newly diagnosed CD30+ ALCL and mature TCL



Endpoints:

- **Primary**: PFS per IRF
- **Secondary**
  - PFS per IRF for patients with sALCL
  - others: CR rates per IRF following completion of treatment, OS, ORR per IRF, safety and tolerability

TCL, T-cell lymphomas.

O'Connor OA, et al. J Clin Oncol. 2013;31:Abstract TPS8611.

Crizotinib – ALK inhibitor

R/R ALCL ALK+: t(2;5) (NPM/ALK)
Crizotinib monotherapy

Parameter	N
N	11
type	R/R ALCL ALK+
Med prior lines of therapy	3
ORR	10/11 (91%)
2 yr OS and PFS	73% and 64%

Ph 1-2 in combination with chemotherapy
–> only ALK+ ALCL

ALK, anaplastic lymphoma kinase; R/R, relapsed/refractory; ALCL, anaplastic large cell lymphoma; NPM, nucleophosmin; med, median; ORR, overall response rate; yr, year; OS, overall survival; PFS, progression free survival; ph, phase

Gambacorti-Passerini C, et al. JNCI 2014; 106:2:djt378. doi: 10.1093/jnci/djt378

FDA approved drugs in PTCL: subtype-specific responses – **Epigenetic modifiers**

PTCL subtype	Pralatrexate	Romidepsin	Belinostat	Brentuximab vedotin
All subtypes	29	25	26	---
PTCL-NOS	31	29	23	33
AITL	8	30	46	54
ALCL	29	24	15	86

Mutations in epigenetic regulators are more frequent in TF_H- derived PTCL

PTCL subtype	IDH2R140	IDH2R172	TET2
PTCL-NOS	0/43	0/43	22/58 (40%) (FH 58% non-FH 24%)
AITL	25/101 (25%)	1/101	40/86 (47%)
ALCL	0/50	0/50	0/18

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;
Horwitz, S et al ICML 2013
Pro B, et al. J Clin Oncol. 2012;30:2190-2196
Horwitz S M et al. Blood 2014;123:3095-3100

Romidepsin-CHOP vs CHOP

ICML, Lugano 2013: Median Follow-up: 10 months

- n=27 evaluable
- CR 15/27 (55.6%)
- ORR 20/27 (74%)

Delarue R, et al. ICML 2013;abstract OT02;

THE LANCET
Haematology

Articles

Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: a non-randomised, phase 1b/2 study

Jehan Dupuis, MD, Prof Franck Morschhauser, MD, Hervé Ghesquières, MD, Prof Hervé Tilly, MD, Prof Olivier Casasnovas, MD, Prof Catherine Thieblemont, MD, Vincent Ribrag, MD, Céline Bossard, MD, Fabien Le Bras, MD, Emmanuel Bachy, MD, Bénédicte Hivert, MD, Emmanuelle Nicolas-Virelizier, MD, Prof Fabrice Jardin, MD, Jean-Noel Bastie, MD, Sandy Amorim, MD, Julien Lazarovici, MD, Prof Antoine Martin, MD, Prof Bertrand Coiffier, MD

- Romidepsin MTD (phase 1b): 12mg/m2 x6 d1+8 at each cycle of CHOP
- Target population: 420 pts
- Enrolled pr Feb 2015: 108 pts
- 1st interim analysis at 84 events (30% of the total expected)

Dupuis J, et al. Lancet Haematol 2015;2:e160-5

Randomized Phase 3 Study Evaluating the Efficacy and the Safety of Oral Azacitidine (CC-486) Compared to Investigator's Choice Therapy in Patient With Relapsed or Refractory Angioimmunoblastic T Cell Lymphoma

The ORACLE trial

Sponsor: LYSARC – PI: R.Delarue
External partnership: Celgene
EudraCT number: 2017-003909-17
European centers
Asian centers
NLG participates with 4 centers: Aarhus, Copenhagen, Lund, Helsinki

NORDIC LYMPHOMA GROUP

Lumière trial – Aurora A kinase inhibitor

Phase 3 in R/R PTCL: Alisertib vs physician's best choice

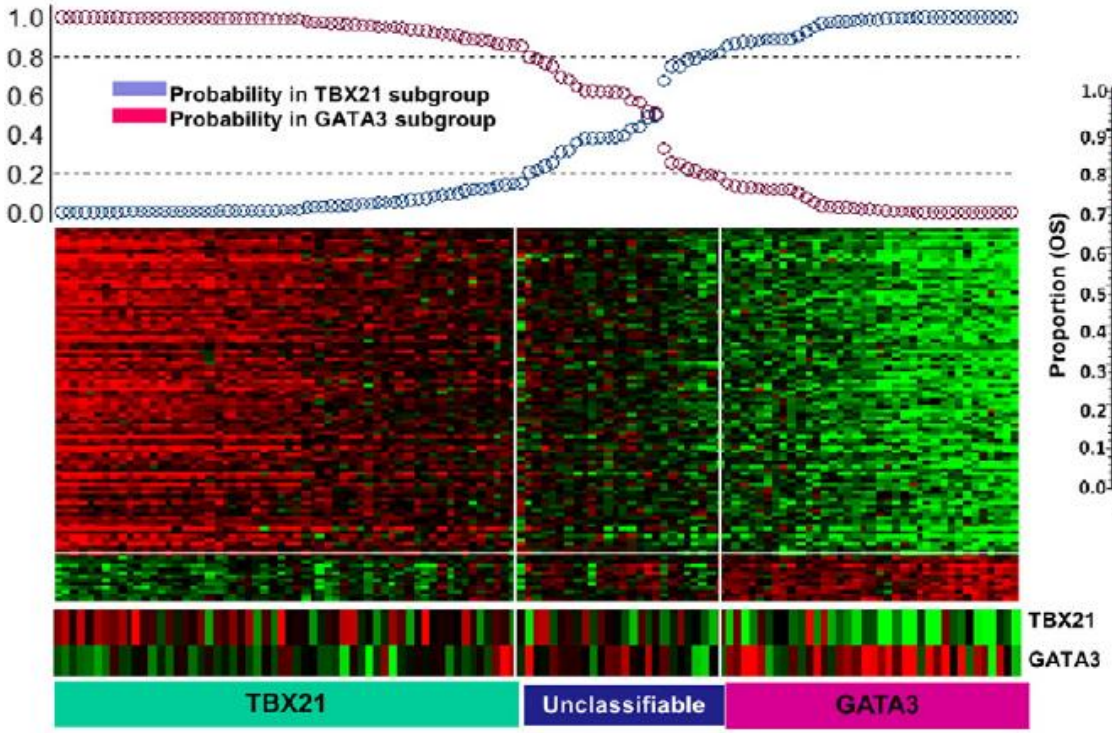
Response (%)	Alisertib (N=96)	Comparator			
		All pts (n=85)	Pralatrexate (n=45)	Gemcitabine (n=22)	Romidepsin (n=18)
ORR	36	46	44	36	61
CR	19	28	29	23	33
PR	17	18	16	14	28
SD	30	20	24	14	17
PD	34	34	31	50	22

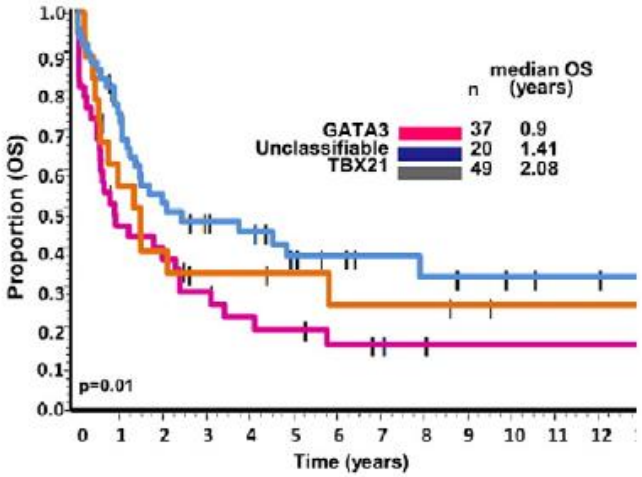
R/R, relapsed/refractory; PTCL, peripheral T-cell lymphoma; pts, patients; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease

O'Connor OA, et al. ASH 2015;abstract 341

Rationale for pathway targeting in TCL: PI3K

Evidence of molecular subsets in PTCL-NOS





GATA3	TBX21
33% of tested cases	49% of tested cases
TH2 TrFact signature	➢ TH1 TrFact sign (good outcome) ➢ Cytotoxic sign (poor outcome)
PI3K and mToR pathways	
Poor clinical outcome	NFKB and STAT3 pathways

Iqbal J, et al. Blood Reviews 2016;30:89-100

PI3Kγδ inhibitor: Duvelisib
Evidence of clinical activity in T-cell lymphomas

Study cohort	Best response – N(%)					
	N	CR	PR	SD	PD	ORR
All pts	33	2 (6)	12 (36)	7 (21)	12 (36)	14 (42)
PTCL	15	2 (13) 1 EATL, 1 PTCL-NOS	6 (40)	1 (7)	6 (40)	8 (53)
CTCL	18	0 (-)	6 (33)	6 (33)	6 (33)	6 (33)

P13K, phosphoinositide 3-kinase; pts, patients, PTCL, peripheral T-cell lymphoma; CTCL, cutaneous T-cell lymphoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; EATL, enteropathy associated T-cell lymphoma; NOS, not otherwise specified; GATA3, GATA binding protein 3

Horwitz S, et al. ASH 2014;abstract 803

Summary

Entity/subtype	Treatment option
BIA-ALCL	Surgery
Indolent GIT PTCL	Watchful waiting
NK/T	L-asparaginase
HSTCL	alloTx upfront in Tx eligible pts
ALK+ALCL	Etoposide, @CD30, crizotinib
ALK-ALCL	@CD30, DUSP22, TP63,JAK/STAT
ALCL triple neg	CHOEP+HDT
AITL/T_{FH}	5-aza, HdAC
PTCL with significant EBV viremia at Dx	Role for antiviremic prephase? Work in progress

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