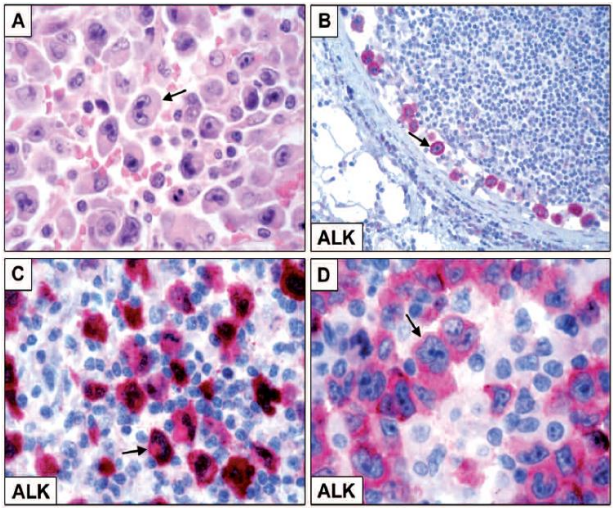
Periphere T Zell Lymphome

Aktuelle Therapiestrategien und neue Ansätze



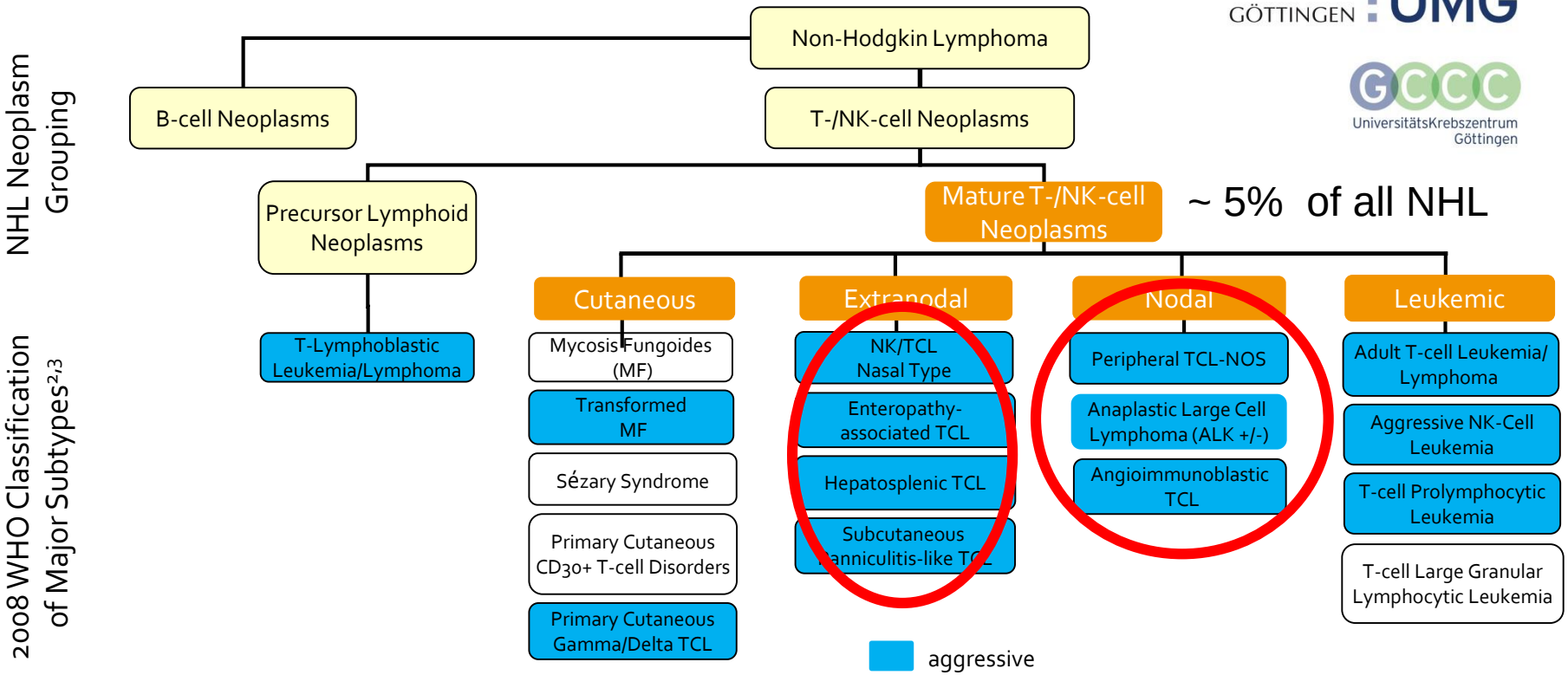
Hämatologie im Wandel 2019

Studienupdate Hämatologie und GCP Update-Kurs

Aktuelle Therapiestrategien und laufende Studien bei malignen hämatologischen Erkrankungen mit Schwerpunkt Studiendurchführung am Zentrum gemäß GCP und AMG

Lorenz Trümper, President, German Lymphoma Alliance e.V.,
UniversitätsKrebszentrum G-CCC, Universitätsmedizin Göttingen
AG T Zell Lymphome der GLA e.V./ ehem. DSHNHL
Gerald Wulf, Bertram Glaß, Thomas Weber, Bettina Altmann, Marita Ziepert, Markus Loeffler, Raphael Koch, Andreas Rosenwald, Norbert Schmitz, Michael Pfreundschuh

T-cell lymphoma: WHO classification



adapted from Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2008

WHO 2016:

new: follicular T-cell lymphoma (FTCL)

new (provisional): indolent T-cell lymphoproliferative disorder (LPD) of the GI tract and primary cutaneous acral CD8⁺ TCL

renamed: EATL-2: monomorphic epitheliotropic intestinal TCL (MEITL)

What are the challenges for diagnosis?

- ≥10% of patients receive an incorrect diagnosis[2]
- In one analysis, diagnostic agreement between hematopathologists varied by subtype, ranging from 72% to 97%[3]
- Over 1/3 of cases cannot be further classified and are diagnosed as PTCL-NOS[4]

Diagnosis is based on evaluation of:

- Histological features[1]
  - Tumor tissue biopsy
- Immunohistochemistry
- Flow cytometry
- Molecular genetics
- Cytogenetics

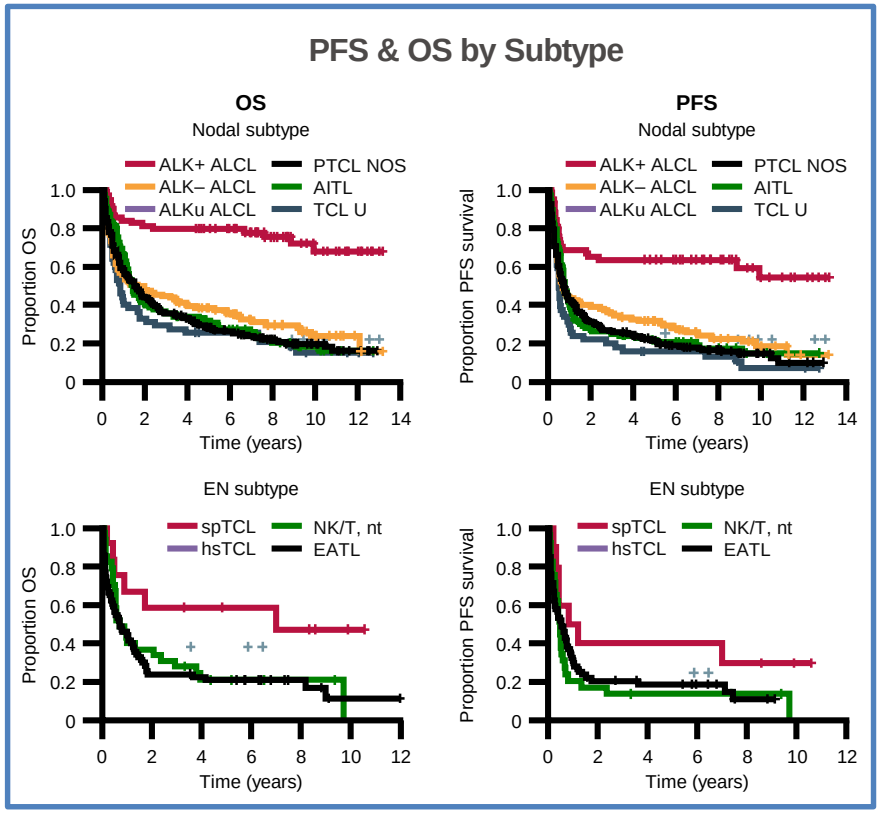
Workup to assess staging and prognosis include:[1]

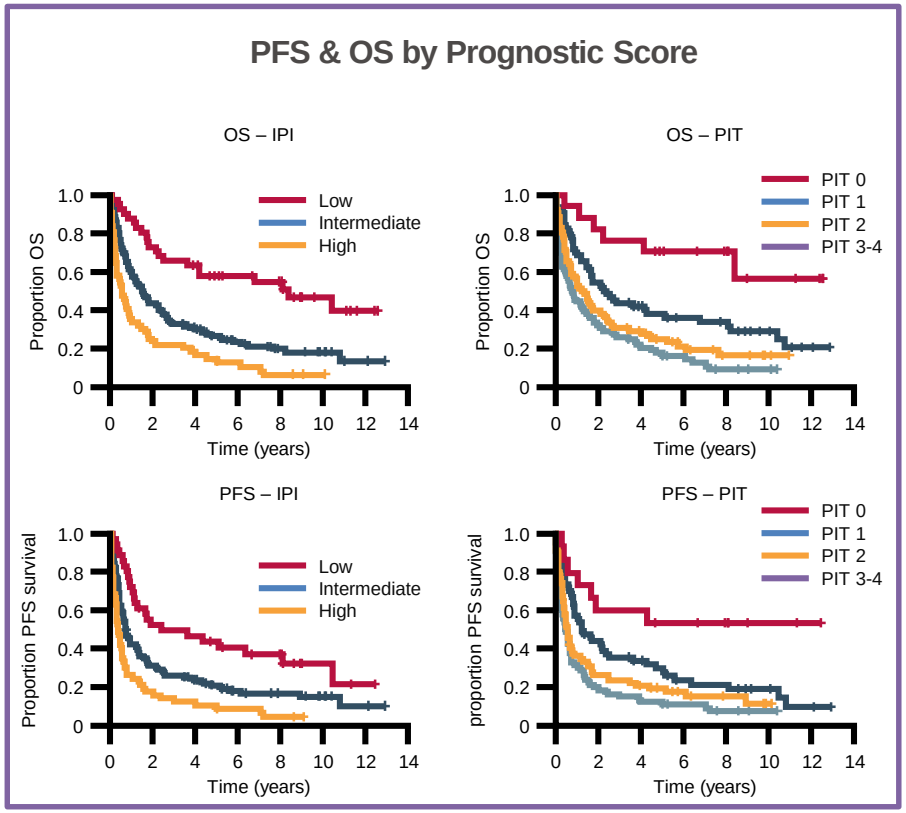
- History and physical exam
- CBC with differential
- Bone marrow biopsy ± aspirate
- LDH and uric acid
- Comprehensive metabolic panel
- PET/CT scan and/or C/A/P CT
- Tests for HIV, HTLV-1, HBV, and HBC

1. NCCN Guidelines. *T cell lymphomas*. V4.2018; 2. d'Amore F, et al. *Ann Oncol.* 2015;26(suppl 5):v108-v115;
2. Cheson BD. *Clinical Advances in Hematology and Oncology.* 2011;9(suppl 26);
3. Armitage JO, et al. *Am J Hematol.* 2017;9:2706–2715;
4. Iqbal J, et al. *Blood Rev.* 2016;30:89–100.

PFS and OS vary by subtype as well as by IPI and PIT score

PTCL outcomes in the modern era: Swedish Lymphoma Registry (pts diagnosed 2000–2009)[1]

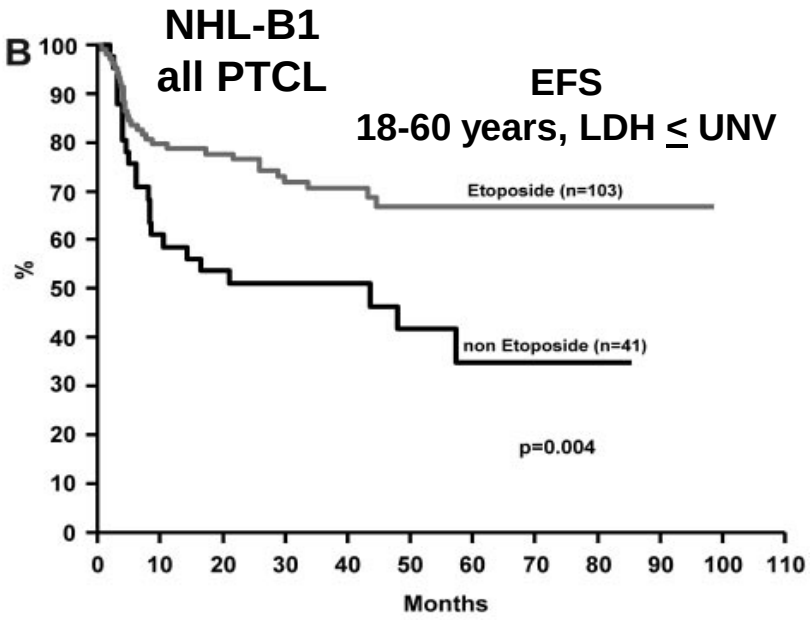




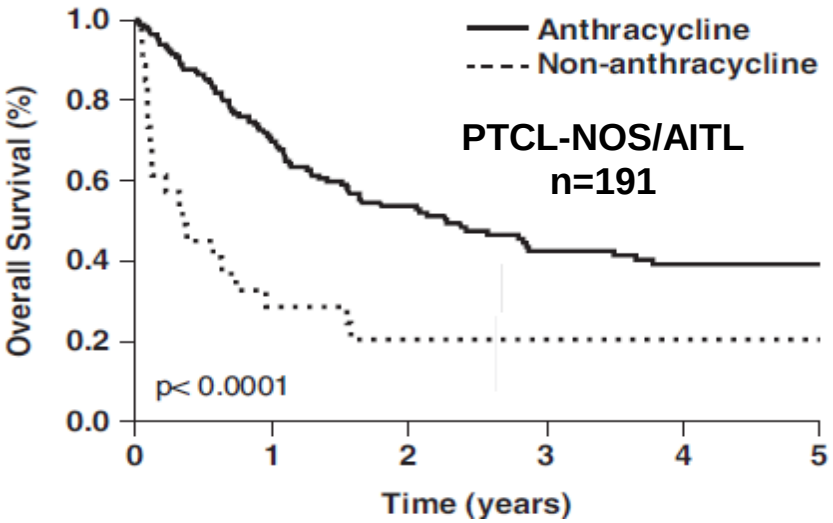
ALKu, anaplastic large cell lymphoma kinase unknown; EN, extranodal; IPI, IPI, International Prognostic Index; PFS, progression-free survival; PIT, Prognostic Index for T-cell lymphoma; pts, patients; sp, subcutaneous panniculitis-like; TCL, T-cell lymphoma

Ellin F, et al. *Blood* 2014;124:1570–7.

CHOP as back-bone chemotherapy in aggressive lymphoma: still valid in PTCL



Schmitz et al., Blood 2010;116(18):3418-3425



Mayo Clinic 1994-2009; U Michigan 1988-2011

Briski et al., Blood Cancer Journal 2014; 4; e214

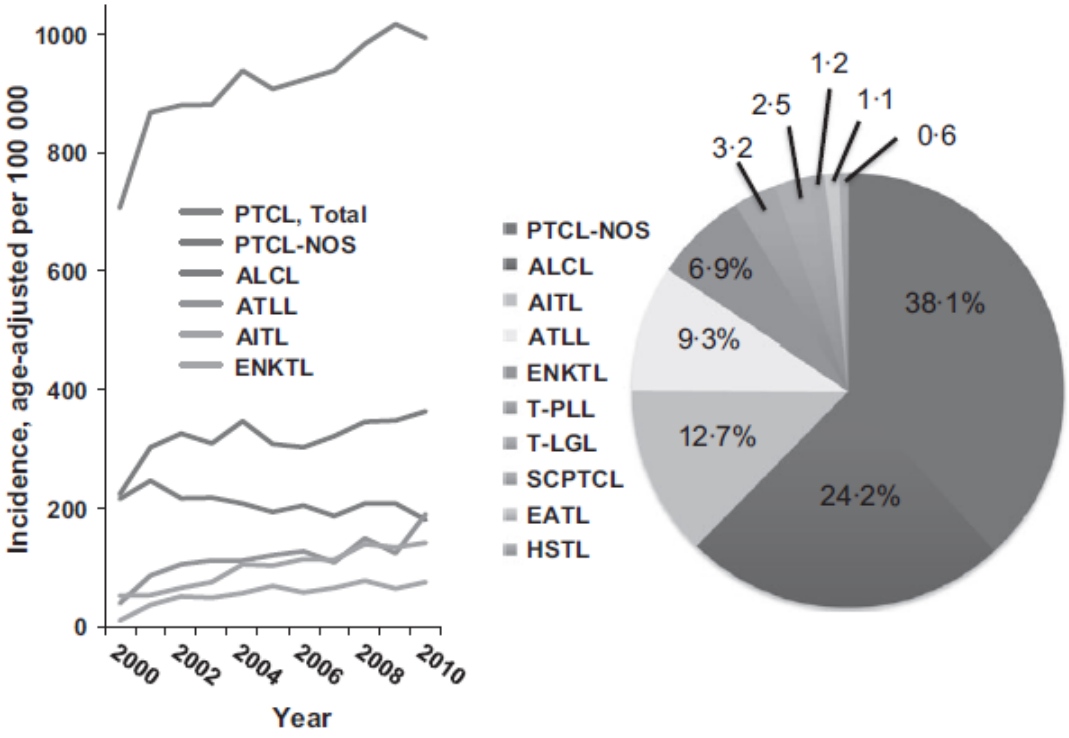
McKelvey et al.
Cancer 1976 Oct;38(4):1484-93

Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma

Study undertaken by the Southwest Oncology Group Supported by Operations Office Grant—CA16943 and Statistical Office Grant—CA12014.

	n	**ORR** [%]	**CRR [%]**
Morabito	297	**76**	56
Savage	199	**76-90**	55-70
Lee	84	**59**	47
Lopez-G.	174	**64**	49
Sung	52	**63**	17
Delmer	57		46

pTNHL – very few data…



Petrich et al., Br.J.Hematol. 168:708-718, 2014

Clinical data sets ?

retrospective analyses (subgroups)
phase I/II clinical trials (relapse)

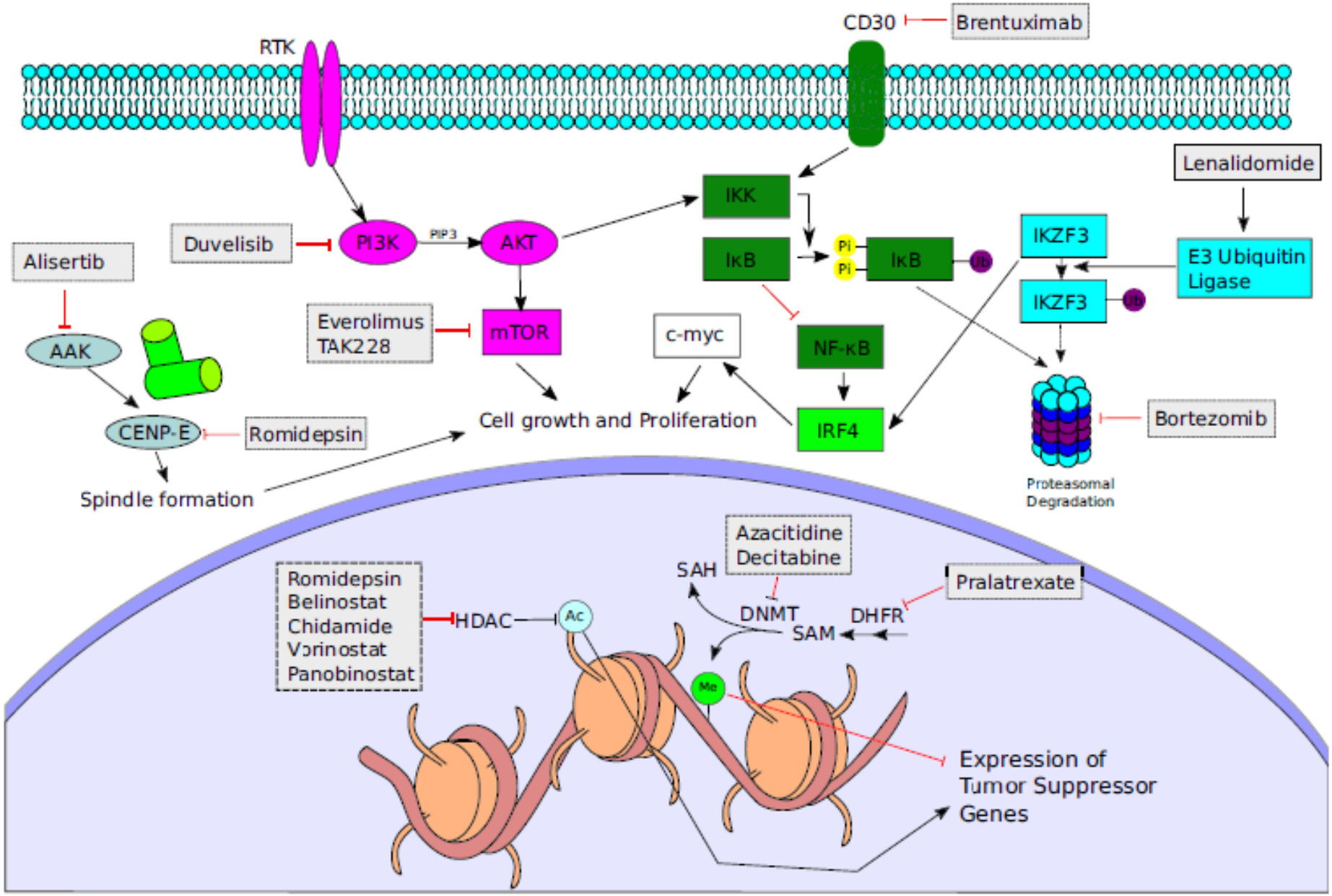
Few „true“ phase III clinical trials

ACT-1 (NLG)
DSHNHL 2006 1A (in coop w. LYSA)
ACT-2 / DSHNHL 2006 1B (w. NLG)
GEM-P (UK) vs CHOP

Ro-CHOP (LYSA)

2 large international registries

Kombinationstherapie mit innovativen Substanzen bei peripheren T NHL



Ma et al. Current Hematologic Malignancy Reports (2018) 13:13–24

DSHNHL
DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN LYMPHOME

ACT-2 study

Response and progression rates according to treatment arm

Treatment arm	**OR rate**	95% CI	**CR/u rate**	**PD**
6 x CHOP - 14 (n =58)	35/58 (60%)	(47% ; 73%)	25/58 (43%)	13/58 (22%)
6 x CHOP - 14 + A (n =58)	42/58 (72%)	(59% ; 83%)	35/58 (60%)	9/58 (16%)
Total (n =116)	77/116 (66%)	(57% ; 75%)	60/116 (52%)	22/116 (19%)

DSHNHL 07-DEC-2015

ACT-2 trial

Types of infections during chemotherapy (grade 3-5)

Type of infection	6 x CHOP-14 (n=17)	6 x CHOP-14 + A (n=38)	Total (n=55)
Bacterial	10/ 17 (59%)	12/ 38 (32%)	22/ 55 (40%)
Fungal	1/ 17 (6%)	4*/ 38 (11%)	5*/ 55 (9%)
Viral	**0/ 17 (0%)**	**19**/ 38 (50%)**	19**/ 55 (35%)

Note: several types of infections can be specified for one infectious event

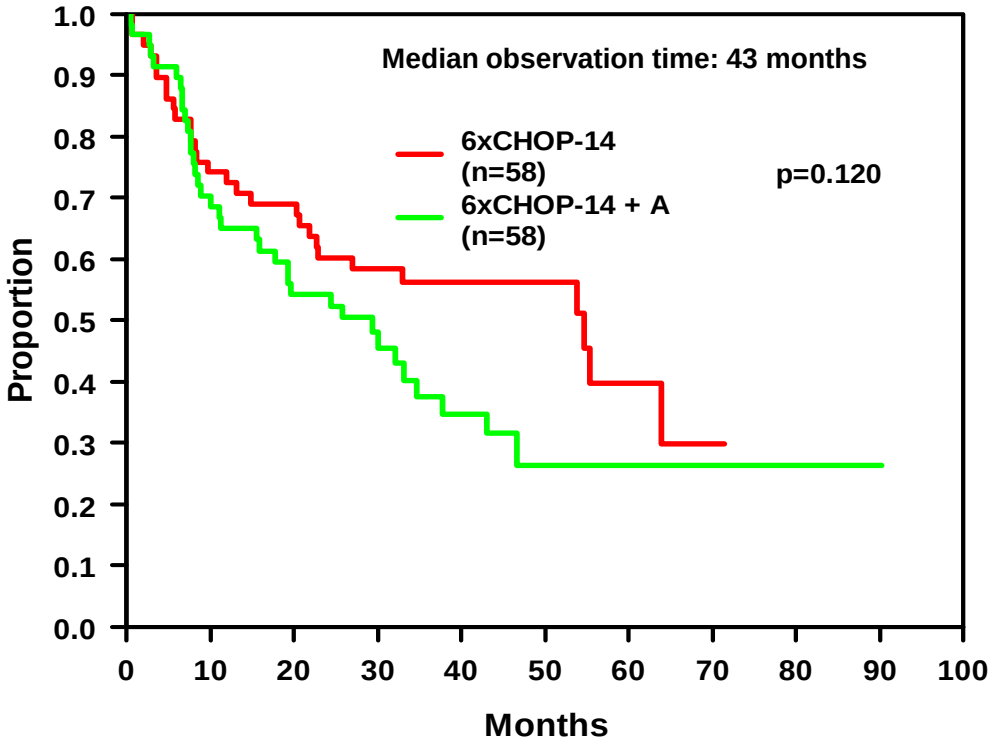
*** 1 Aspergillus**
**** 14 CMV**

DSHNHL 07-DEC-2015

DSHNHL
DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN LYMPHOME

ACT-2 trial

OS according to treatment arm



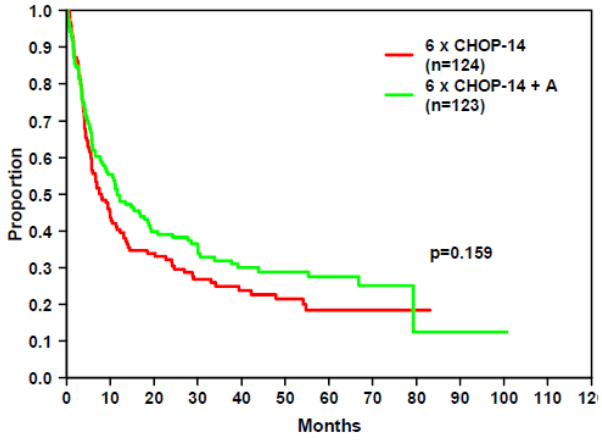
DSHNHL 07-DEC-2015

CHOP+ Alemtuzumab

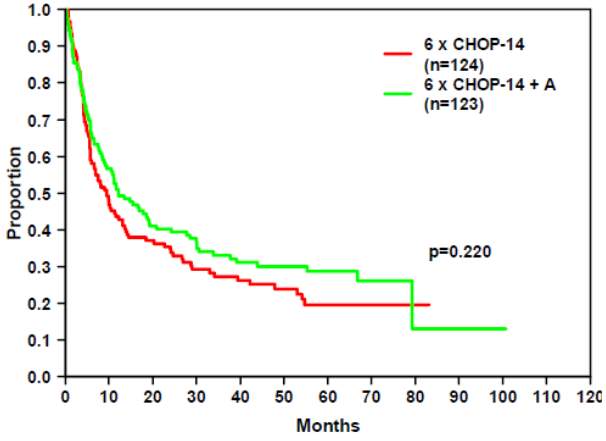
- Endauswertung der ACT-1 + ACT-2 Studie
- 252 Patienten, 18-80 Jahre; CHOP vs A-CHOP

Figure 1:

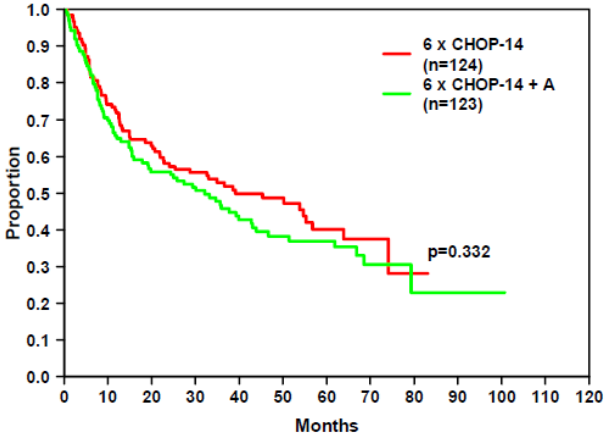
Event free survival



Progression free survival



Overall survival



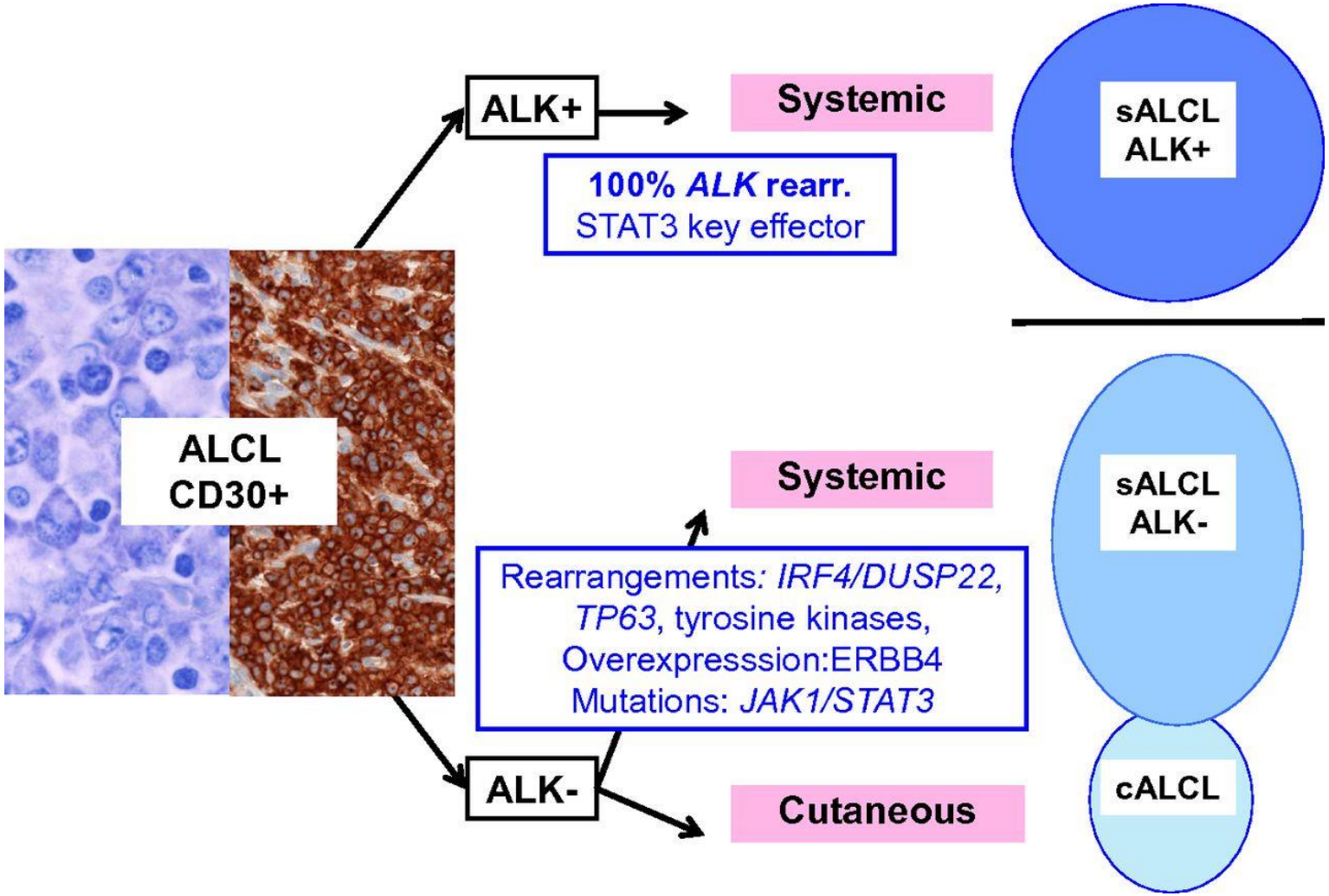
ACT-1/2 Final Analysis

- Bulky Disease & Male gender: Signifikante RF in multivariater Analyse

Table 2: Multivariate analysis (Hazard Ratio, [95% CI], p-value) adjusting for IPI risk factors, bulky disease and gender

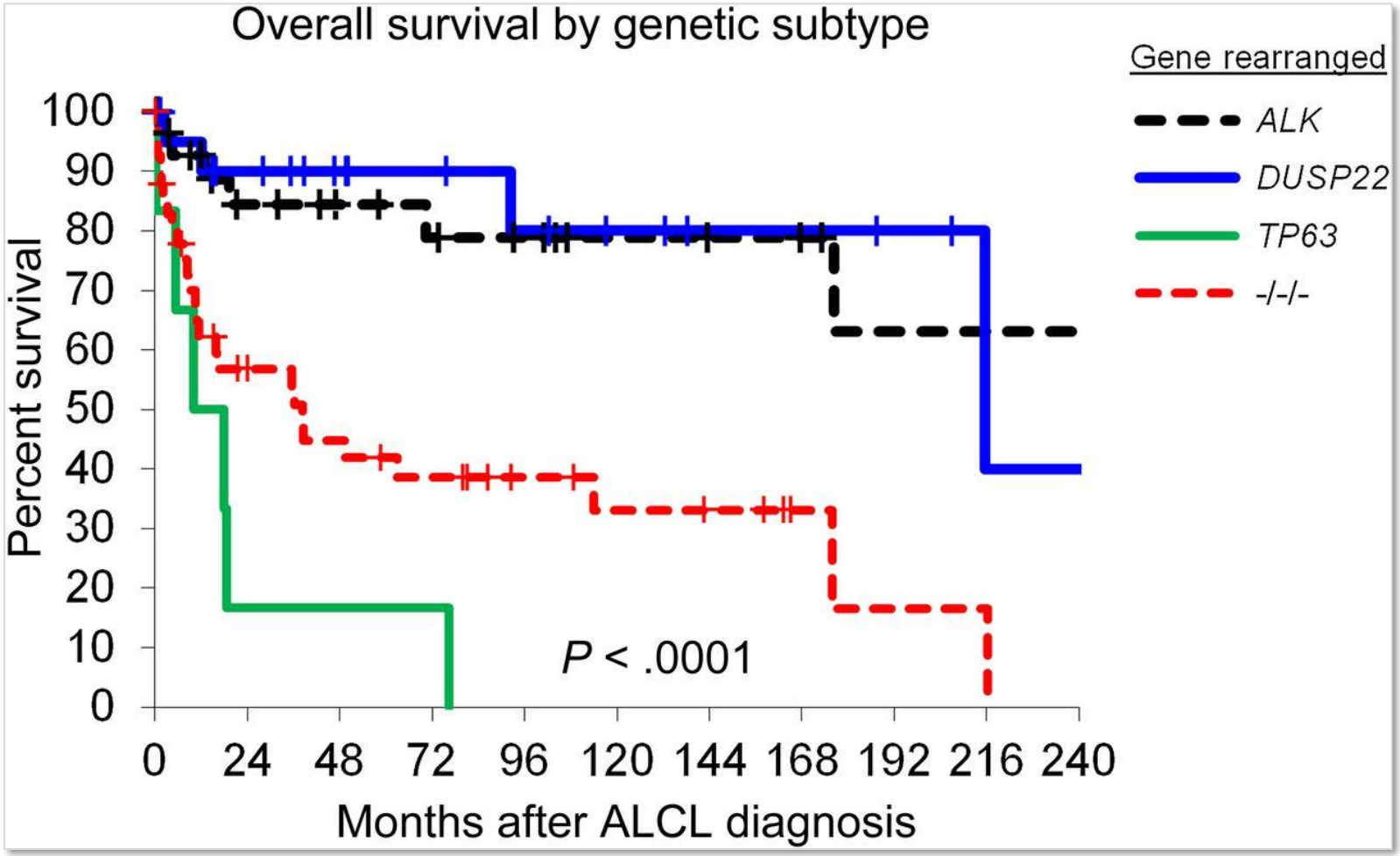
Factor	EFS	PFS	OS
6 x CHOP-14 + A vs. 6 x CHOP-14	0.8 ([0.6 – 1.1]; 0.196)	0.8 ([0.6 – 1.1]; 0.246)	1.2 ([0.8 – 1.6]; 0.370)
Age > 60	1.4 ([1.0 – 1.9]; 0.046)	1.3 ([0.9 – 1.8]; 0.128)	1.5 ([1.1 – 2.2]; 0.018)
LDH > UNV	1.1 ([0.8 – 1.5]; 0.621)	1.1 ([0.8 – 1.5]; 0.599)	1.1 ([0.8 – 1.6]; 0.535)
ECOG > 1	2.1 ([1.5 – 3.1]; <0.001)	2.3 ([1.6 – 3.3]; <0.001)	2.7 ([1.8 – 4.0]; <0.001)
Stage III/IV	1.1 ([0.7 – 1.8]; 0.722)	1.4 ([0.8 – 2.5]; 0.179)	1.6 ([0.9 – 3.1]; 0.137)
Extralymph. involvem. > 1	1.5 ([1.1 – 2.2]; 0.010)	1.4 ([1.0 – 2.0]; 0.042)	1.4 ([1.0 – 2.1]; 0.048)
Bulky disease	2.1 ([1.4 – 3.2]; 0.001)	2.0 ([1.3 – 3.1]; 0.002)	3.0 ([1.9 – 4.7]; <0.001)
Male gender	2.5 ([1.8 – 3.5]; <0.001)	2.6 ([1.9 – 3.7]; <0.001)	2.6 ([1.8 – 3.7]; <0.001)

Schematic representation of ALCL entities and their genetic-associated aberrations.



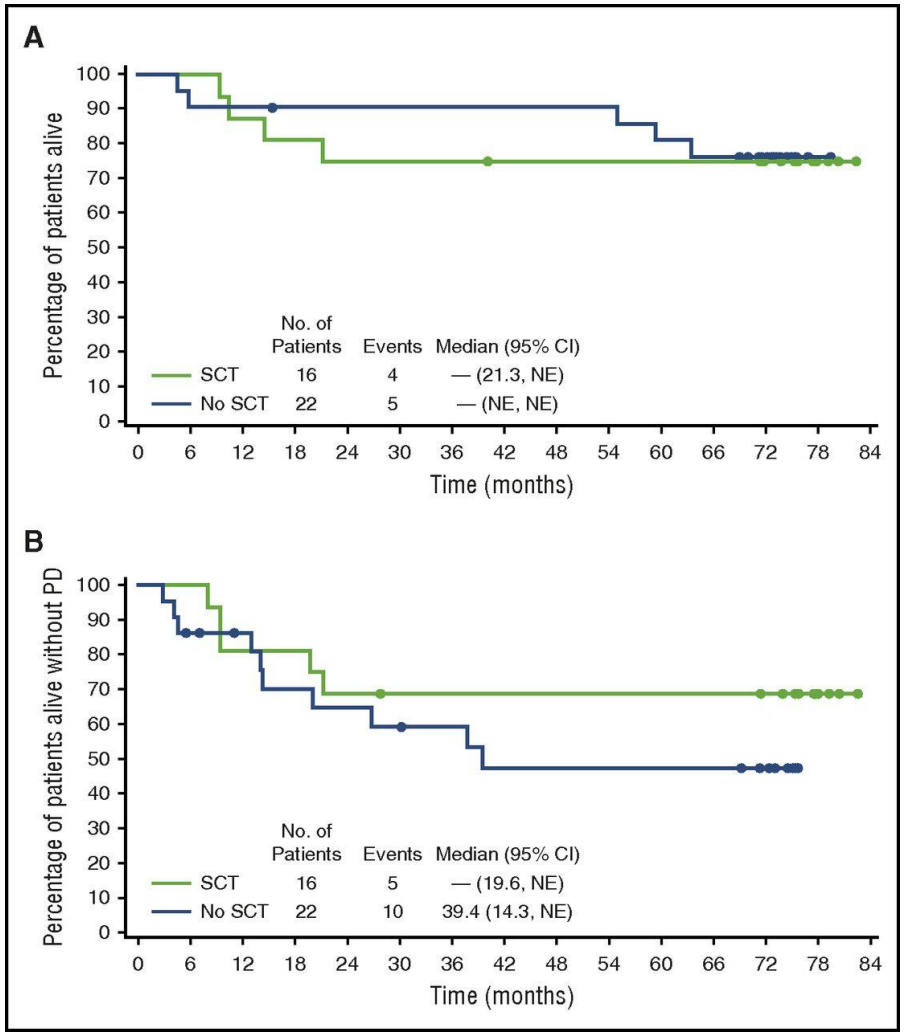
Philippe Gaulard, and Laurence de Leval Blood 2016;127:175-177

Overall survival in patients with ALCL, stratified by rearrangements of ALK, DUSP22, and TP63. −/−/−, triple-negative cases lacking all 3 rearrangements



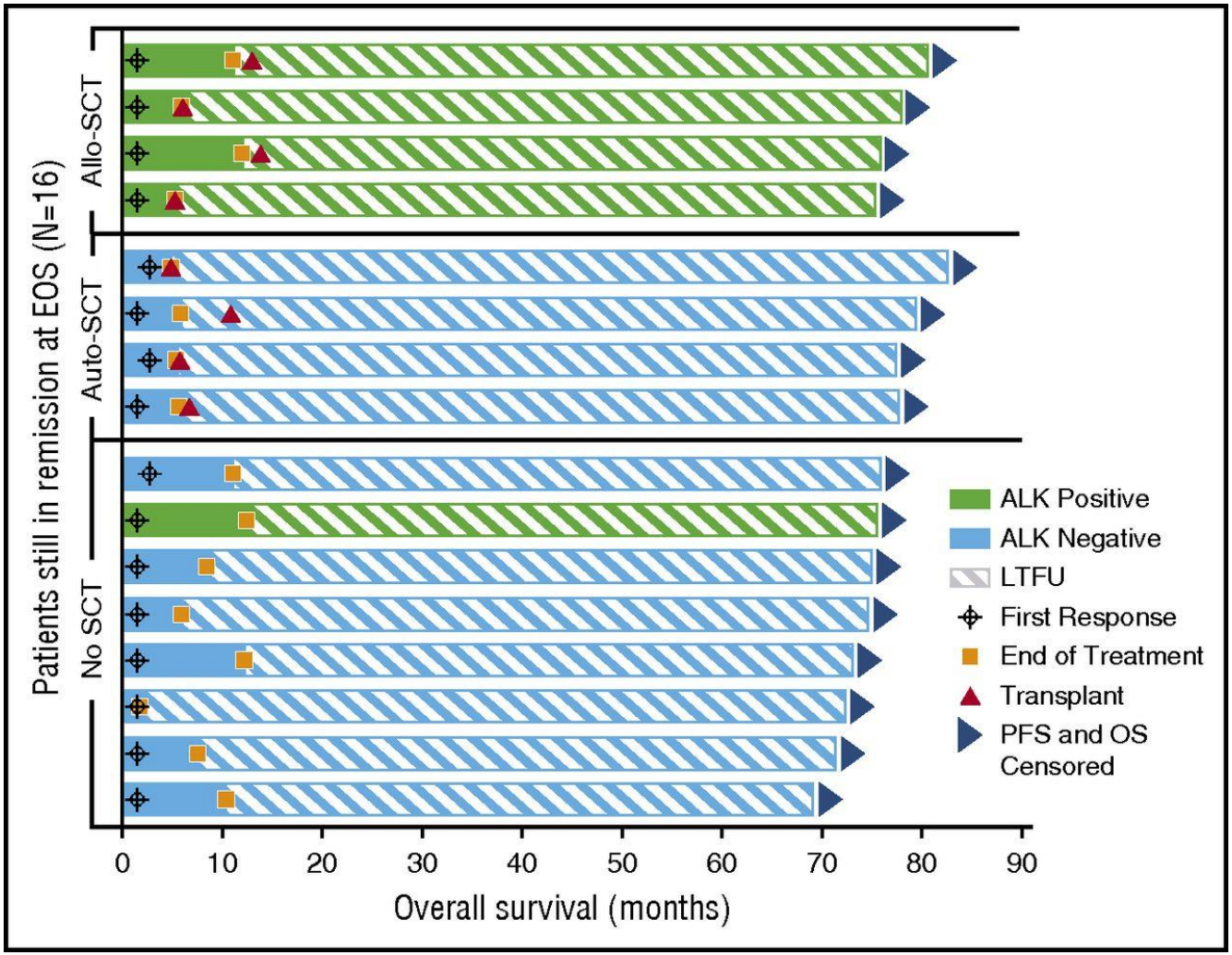
Klapper W. *Blood.* 2014;124:1385–6.

OS and PFS by SCT status.



Barbara Pro et al. Blood 2017;130:2709-2717

Patients who were in remission and in follow-up at study closure.

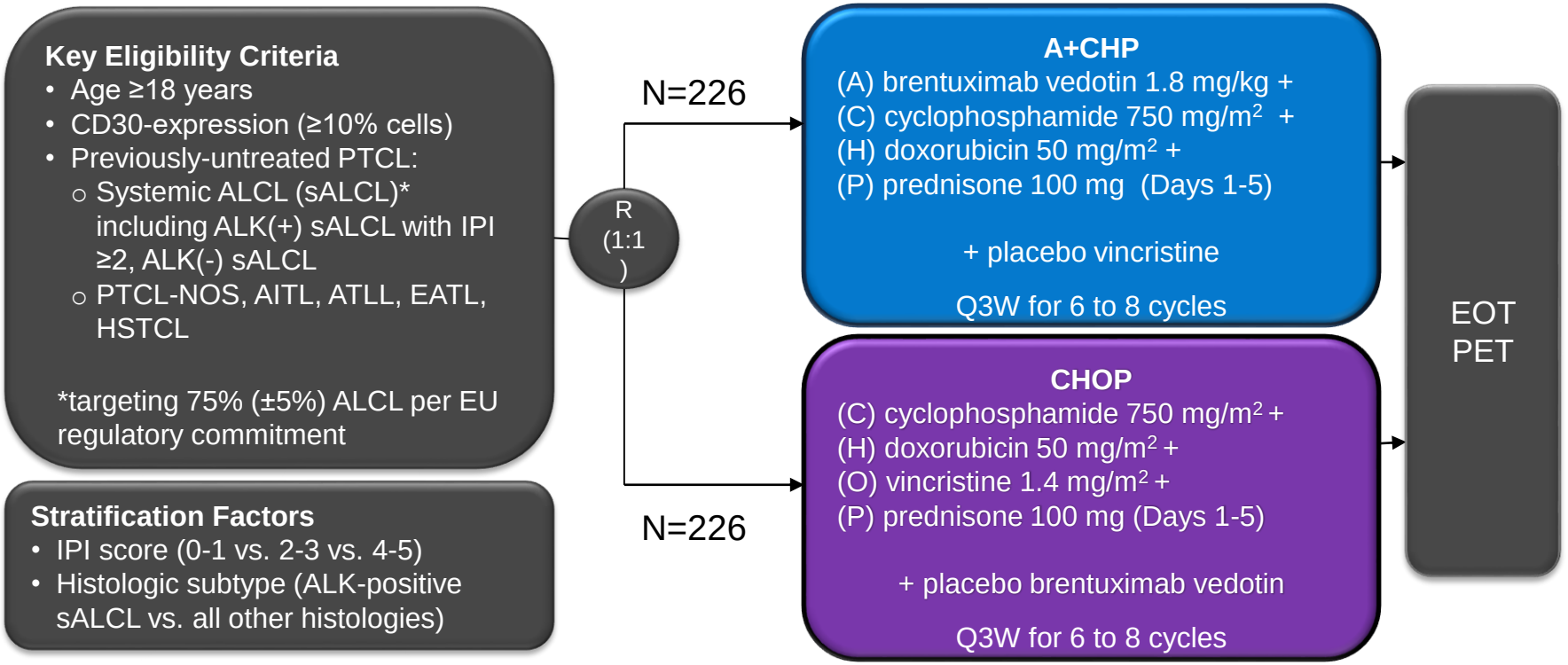


Barbara Pro et al. Blood 2017;130:2709-2717

The Phase 3 ECHELON-2 Trial: Results of a Randomized, Double-Blind, Active-Controlled Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Previously Untreated Subjects with CD30-Expressing Peripheral T-Cell Lymphomas (PTCL)

Steven Horwitz, Owen A O'Connor, Barbara Pro, Tim Illidge, Michelle Fanale, Ranjana Advani, Nancy L Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper

American Society of Hematology Annual Meeting; San Diego, California, December 1-4, 2018, Abstract #997



AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase ATLL, adult T-cell leukaemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; GCSF, granulocyte-colony stimulating factor; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index

Per investigator discretion:
GCSF primary prophylaxis, consolidative RT and SCT

Endpoints and Analysis Populations

Endpoints

Type 1 error control for primary and all key secondary endpoints

- **Primary Endpoint***
  - Progression-Free Survival (PFS) per blinded independent review of PFS
    - ASCT or RT consolidation **not** an event if preplanned by investigator
- **Secondary Endpoints**
  - Overall survival (OS)
  - PFS per BICR in sALCL subjects
  - Complete remission (CR) rate
  - Objective remission rate (ORR)
  - Safety

Analysis Populations

- **Efficacy**
  - Intention-to-treat (ITT)
- **Safety**
  - All subjects who received any amount of brentuximab vedotin or any component of CHOP

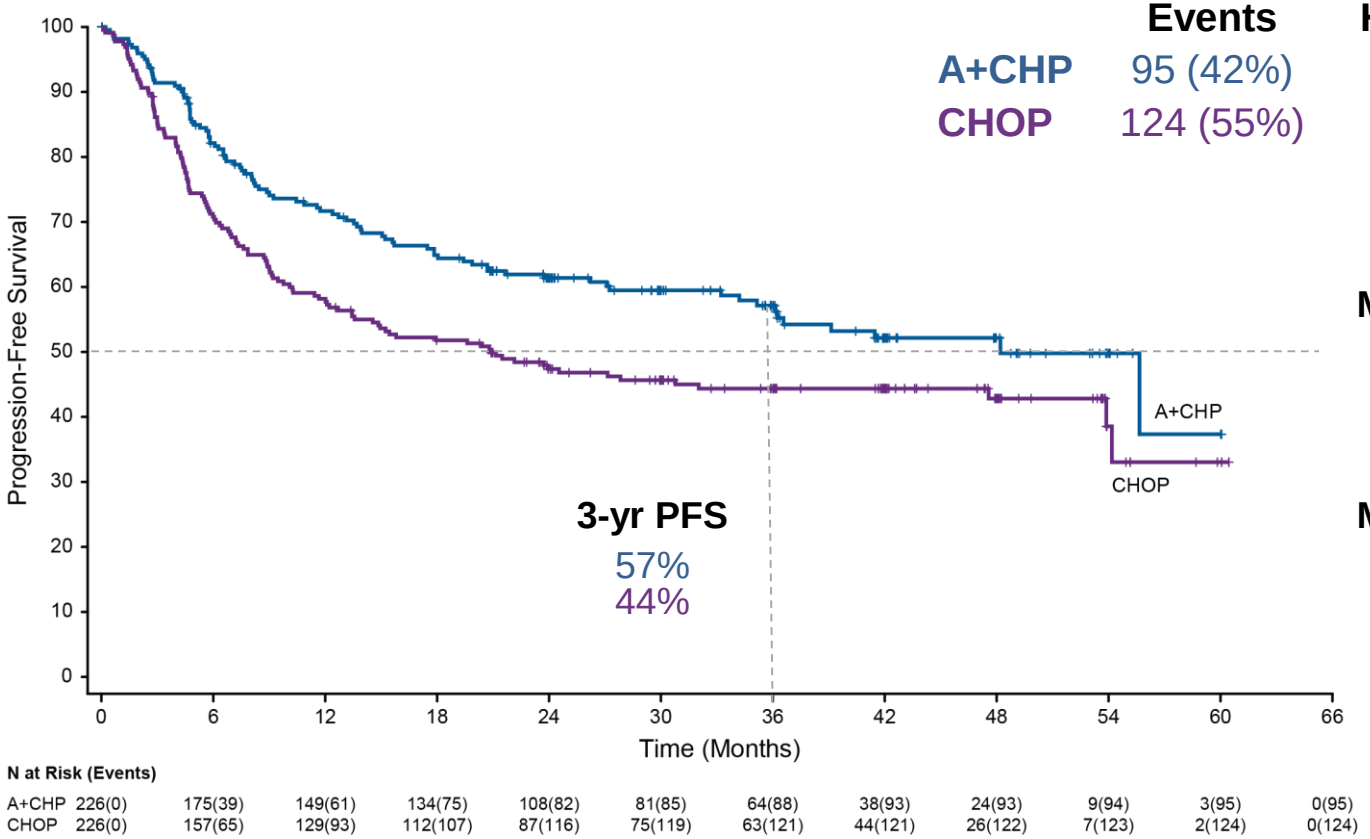
* PFS events = PD, death, or subsequent systemic therapy to treat **residual** or progressive disease

* Lymphoma response criteria Cheson 2007

Summary of Treatment

	A+CHP (N=226)	CHOP (N=226)
Exposure to study drug, n	223	226
Number of subjects treated by cycle, n (%)		
6 cycles	156 (70)	140 (62)
8 cycles	40 (18)	44 (19)
Median relative dose intensity (brentuximab vedotin or vincristine), %	99	99
Subsequent therapy, n	226	226
Systemic therapy for residual or progressive disease, n (%)	59 (26)	94 (42)
Palliative radiation, n (%)	10 (4)	8(4)

Progression-free Survival



	Events	HR (95% CI)	*P*
A+CHP	95 (42%)	0.71 (0.54, 0.93)	0.011
CHOP	124 (55%)		

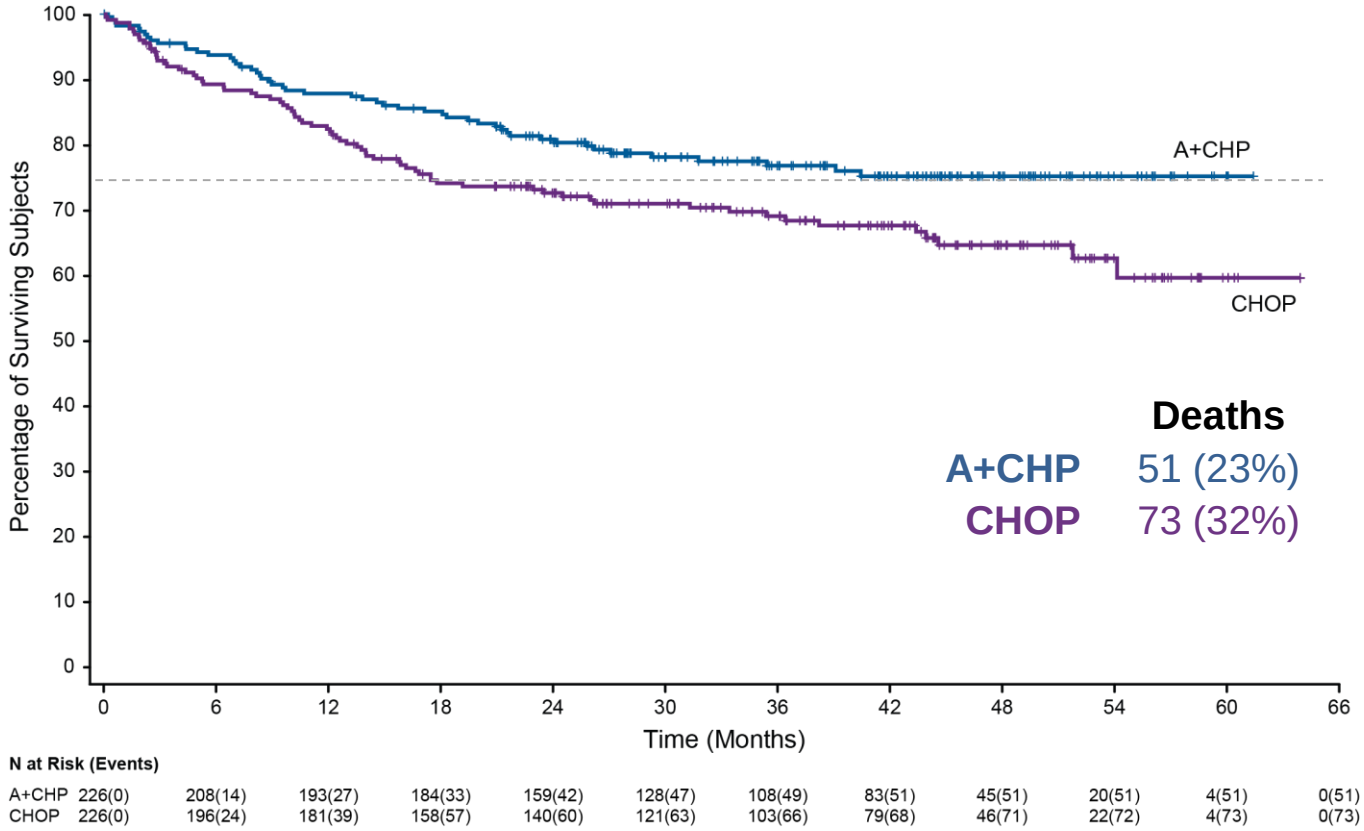
Median PFS (95% CI)

48.2 mo (35.2, NE)
20.8 mo (12.7, 47.6)

Median Follow-up

36.2 months

Overall Survival



75th Percentile

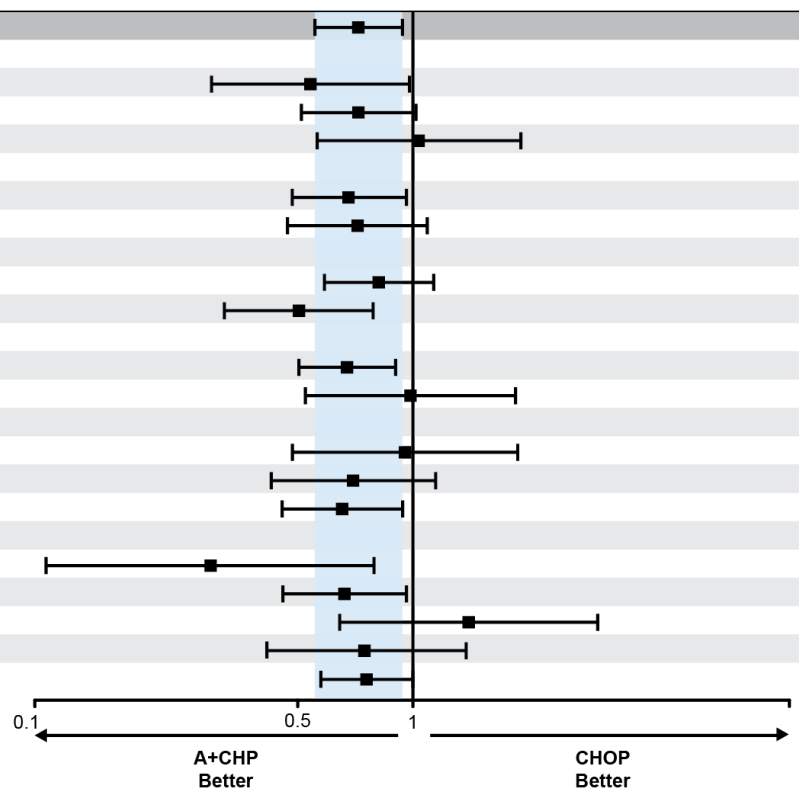
Not reached
17.5 mo

	Deaths	HR (95% CI)	*P*
A+CHP	51 (23%)	0.66 (0.46, 0.95)	0.0244
CHOP	73 (32%)		

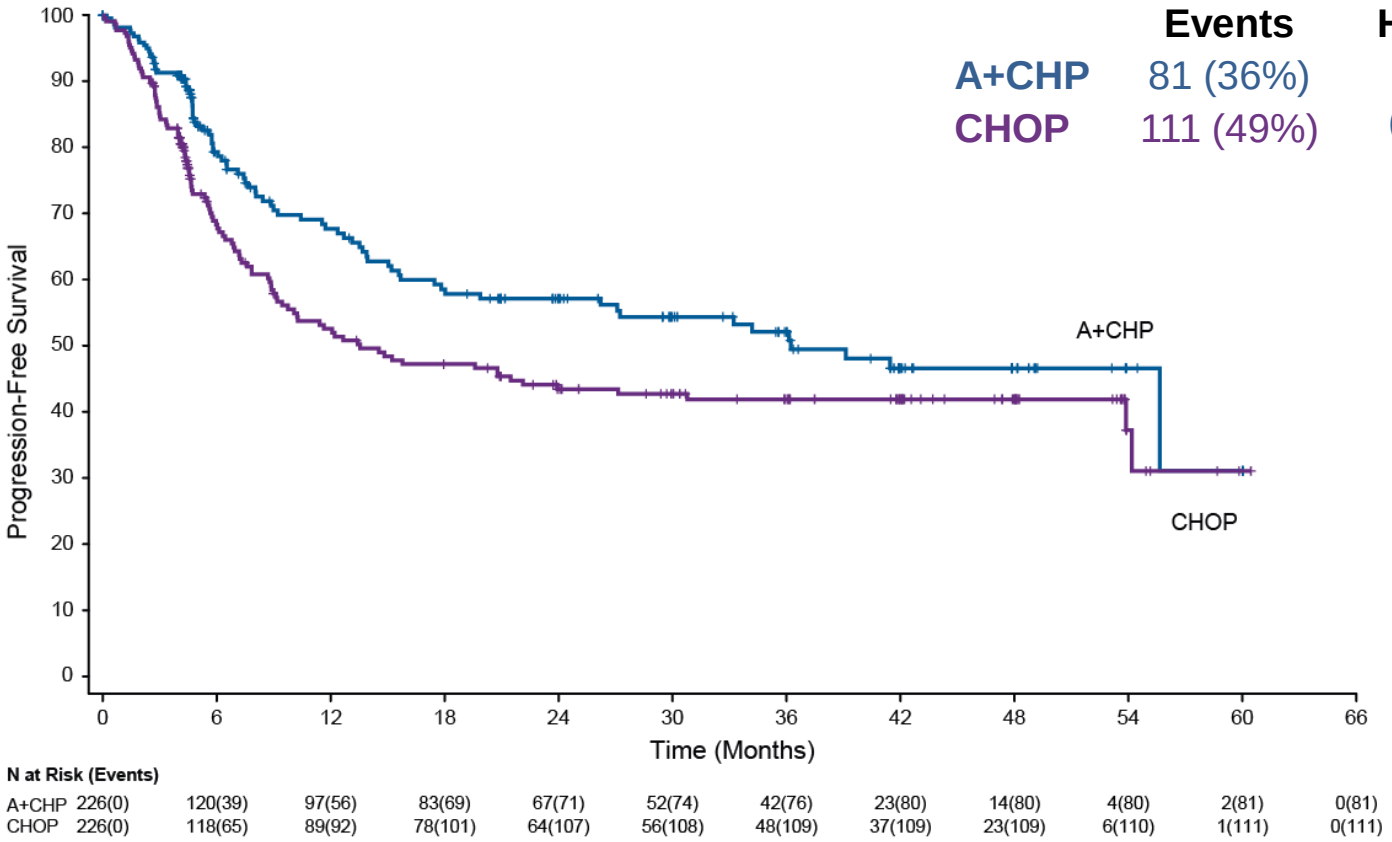
Median Follow-up
42.1 months

Prespecified Subset Analyses: PFS

ITT Subgroups	Event/N A+CHP	Event/N CHOP	Hazard Ratio (95% CI)
Overall	95/226	124/226	0.71 (0.54, 0.93)
IPI Score			
0–1	18/52	27/48	0.53 (0.29, 0.97)
2–3	56/141	77/145	0.71 (0.50, 1.00)
4–5	21/33	20/33	1.03 (0.55, 1.92)
Age			
<65 years	54/157	75/156	0.67 (0.47, 0.95)
≥65 years	41/69	49/70	0.70 (0.46, 1.08)
Gender			
Male	59/133	80/151	0.80 (0.57, 1.13)
Female	36/93	44/75	0.49 (0.31, 0.78)
Baseline ECOG Status			
0/1	76/174	105/179	0.66 (0.49, 0.89)
2	19/51	19/47	0.98 (0.51, 1.87)
Disease Stage			
I/II	15/42	19/46	0.95 (0.48, 1.88)
III	29/57	35/67	0.69 (0.42, 1.14)
IV	51/127	70/113	0.64 (0.45, 0.93)
Disease Indication			
ALK-positive sALCL	5/49	16/49	0.29 (0.11, 0.79)
ALK-negative sALCL	50/113	60/105	0.65 (0.44, 0.95)
AITL	18/30	13/24	1.40 (0.64, 3.07)
PTCL-NOS	19/29	31/43	0.75 (0.41, 1.37)
PFS (PD, Death)	84/226	103/226	0.75 (0.56, 1.00)

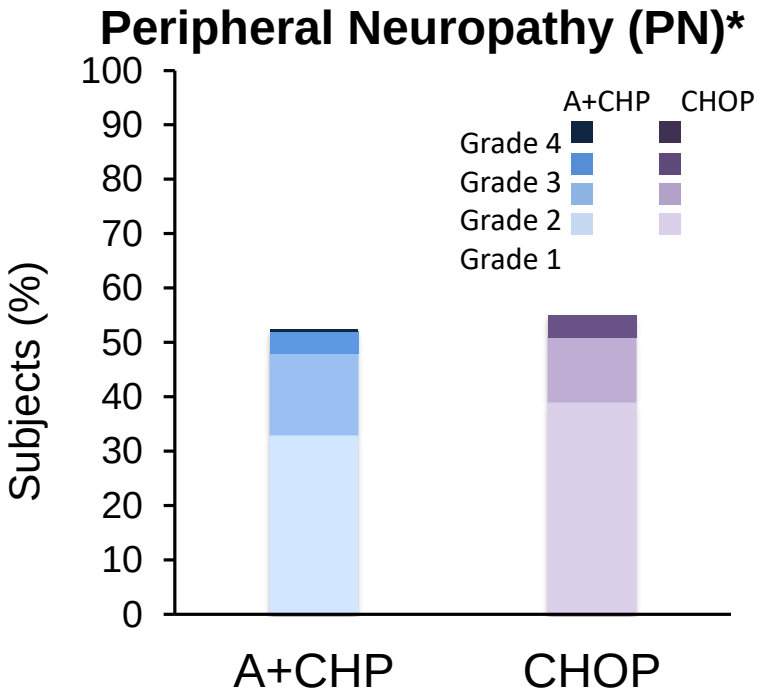


PFS: censored at time of consolidative ASCT or RT



	Events	HR (95% CI)	*P*
A+CHP	81 (36%)	0.71 (0.53, 0.94)	0.017
CHOP	111 (49%)		

Treatment-Emergent Peripheral Neuropathy



Subjects, n (%)	A+CHP (N=223)	CHOP (N=226)
Treatment-emergent PN, n	117	124
Resolution† of all PN events	58 (50)	79 (64)
Ongoing PN at last follow-up	61 (52)	45 (36)
Grade 1	44 (72)	32 (71)
Grade 2	15 (25)	12 (27)
Grade 3	2 (1)	1 (1)

†Resolution was defined as resolved/recovered with or without sequelae; or return to baseline or lower severity as of the latest assessment for pre-existing events

*Includes the preferred terms of peripheral sensory neuropathy, paraesthesia, peripheral motor neuropathy, muscular weakness, peripheral sensorimotor neuropathy, hypoaesthesia, dysaesthesia, areflexia, burning sensation, peroneal nerve palsy, polyneuropathy, autonomic neuropathy, gait disturbance, muscle atrophy, and neuralgia.

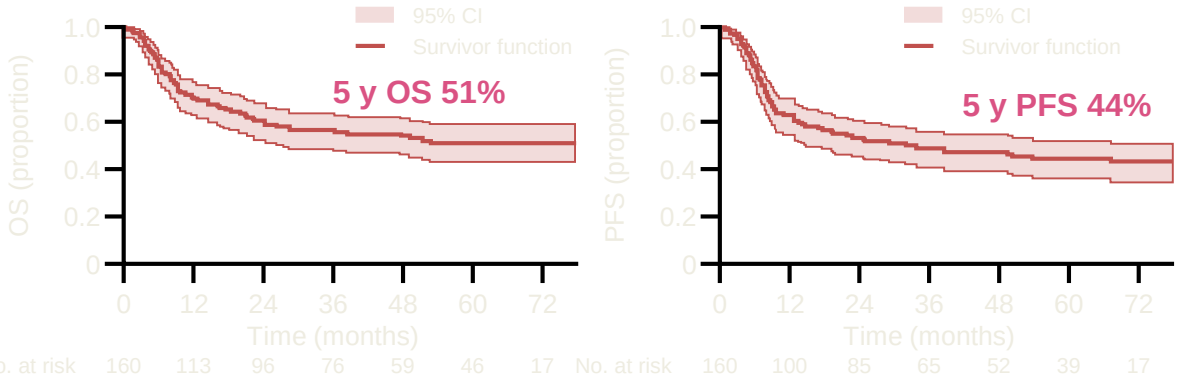
Summary and Conclusions

- ECHELON-2 first prospective trial in PTCL to show OS benefit over CHOP
- A+CHP provided clinically meaningful improvement in PFS and OS versus CHOP
  - 29% reduction in the risk of a progression event
    - 3-yr PFS: A+CHP 57% versus CHOP 44%
  - 34% reduction in the risk of death
- A+CHP has a comparable safety profile to CHOP
- FDA approved brentuximab vedotin in combination with CHP for adults with previously-untreated sALCL **or other** CD30-expressing PTCL, including AITL and PTCL-NOS in November, 2018

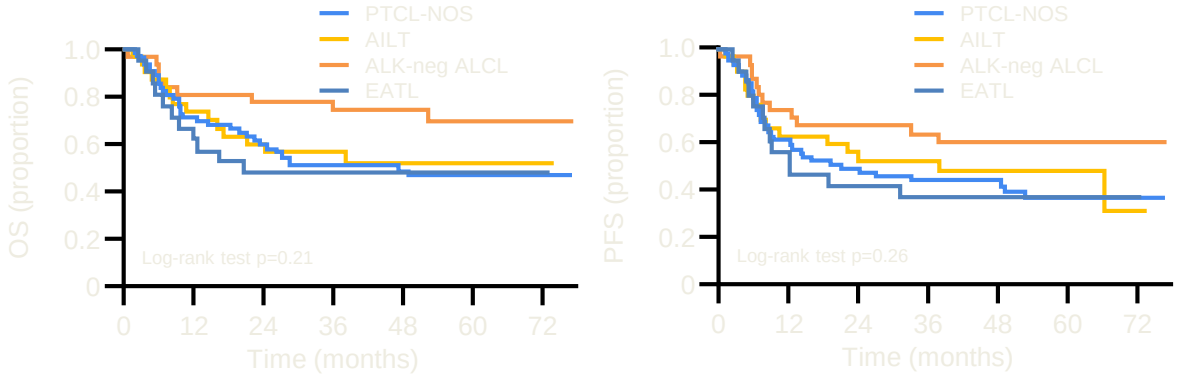

Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial

Steven Horwitz, Owen A O'Connor*, Barbara Pro*, Tim Illidge*, Michelle Fanale, Ranjana Advani, Nancy L Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper*, for the ECHELON-2 Study Group†

Upfront transplant in PTCL



All patients[1]



5 y OS by subtype[1]

ALK-neg	70%
AITL	52%
NOS	47%
EATL	48%

5 y PFS by subtype[1]

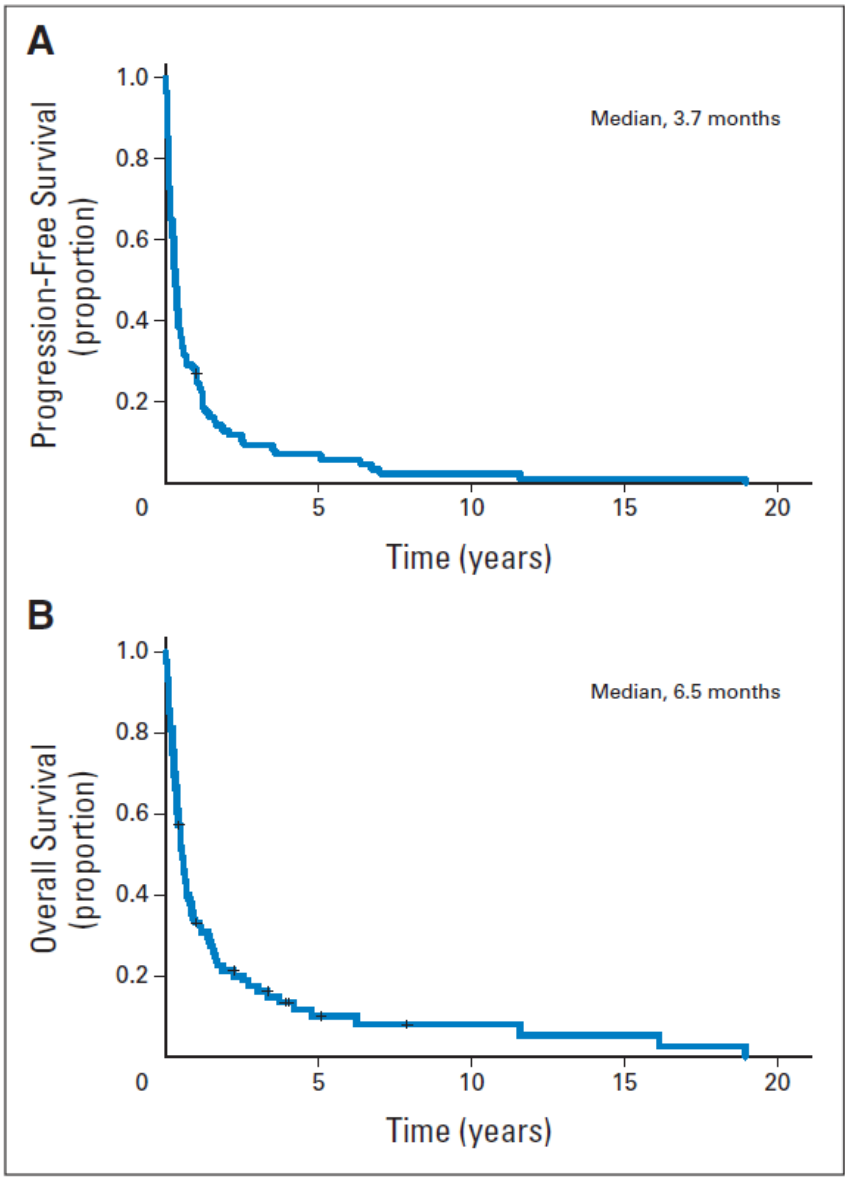
ALK-neg	61%
AITL	49%
NOS	38%
EATL	38%

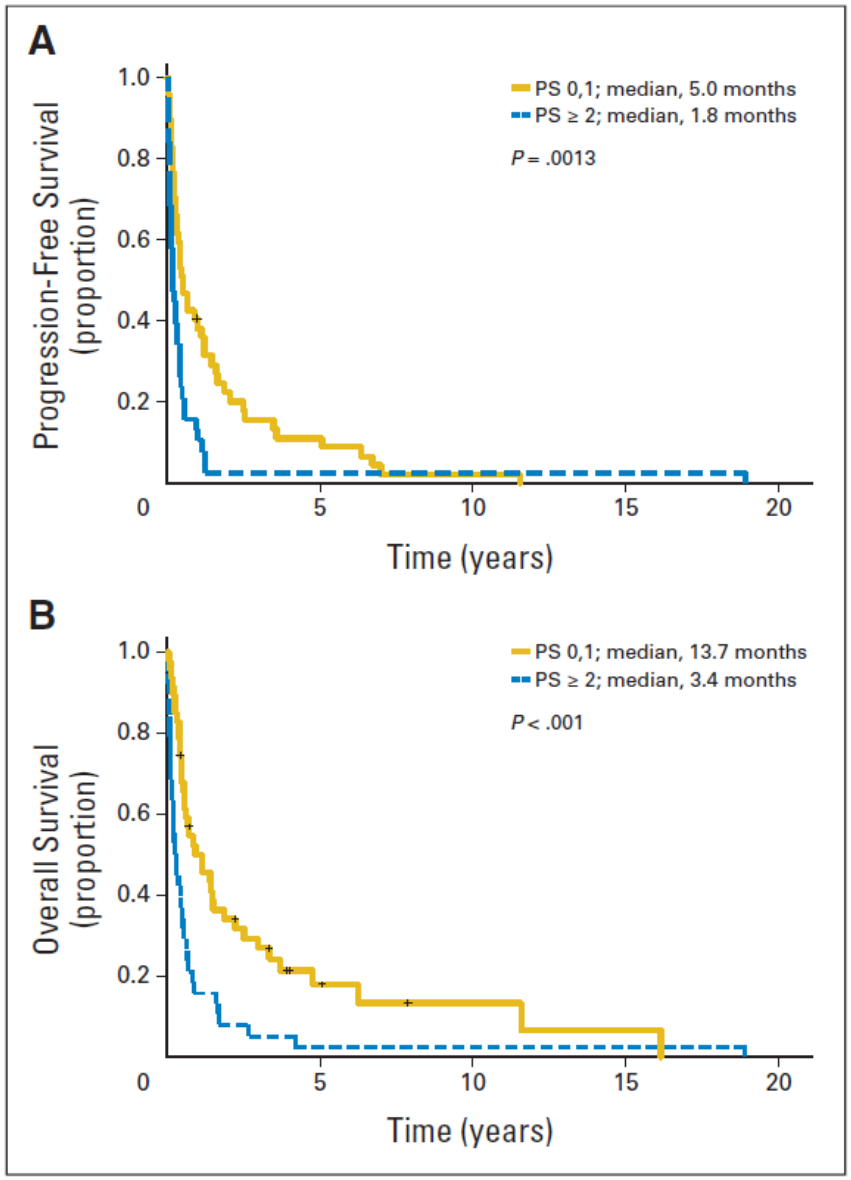
Updated analysis with 10 y median follow-up:[2]
ALK-neg ALCL 10 y: OS 48%; PFS 48%; DSS 67%

DSS, disease-specific survival

1. D'Amore F, et al. *J Clin Oncol* 2012;30:3093–9.
2. D'Amore F, et al. *Hematol Oncol* 2015;33:abstract 074.

long-term outcome of pts. with r/r PTCL and conventional chemotherapy, excluding SCT

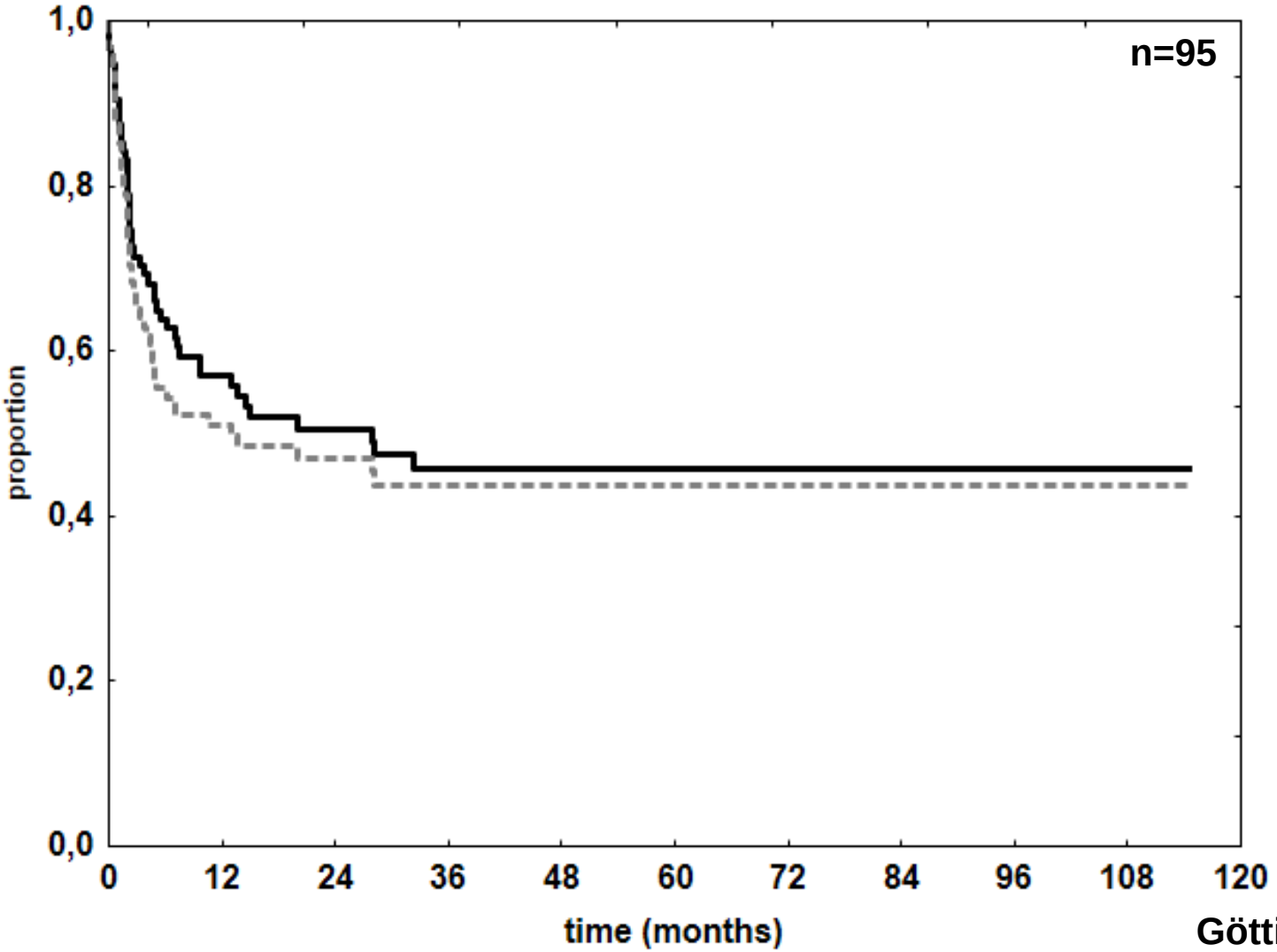




n=153; populational based (British Columbia Cancer Agency Lymphoid Cancer) 1976-2010
recipients of stem cell transplantation excluded

Mak et al. J Clin Oncol 2013; 31:1970-1976

allogeneic stem cell transplantation for r/r PTCL
Wulf et al., BMT 2018, in press

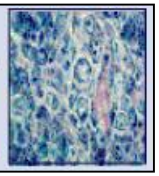


Göttingen	51
Hamburg	36
Homburg	5
Marburg	3

DSHNHL 2006-1A

accrual stopped 08.2013 for futility

GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)
www.lymphome.de/en/Groups/DSHNHL

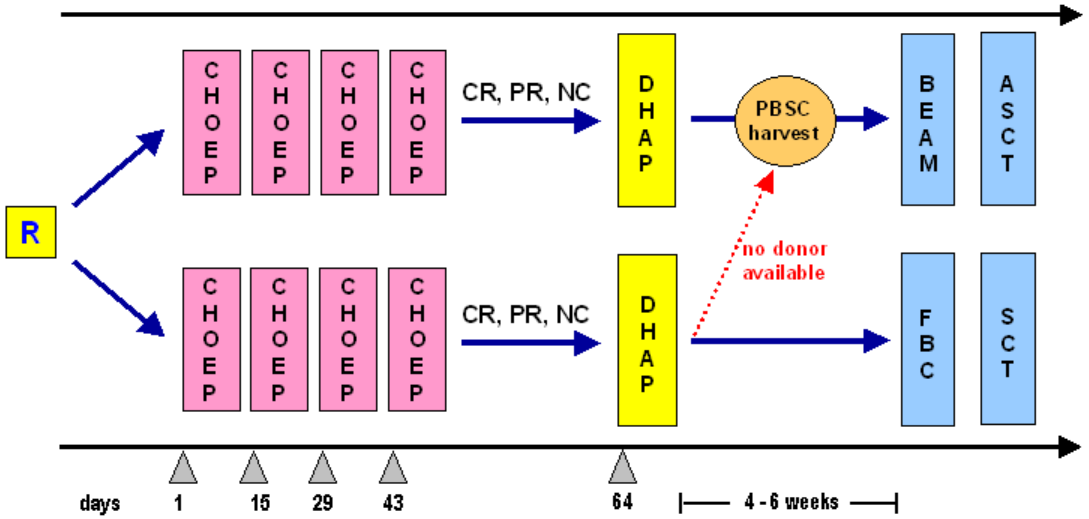


first-line treatment of mature (peripheral) T-cell lymphoma (PTCL) for patients ≤60 years

inclusion criteria

- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK negative
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis type T-cell lymphoma

- all stages and IPI except stage I with aaIPI 0



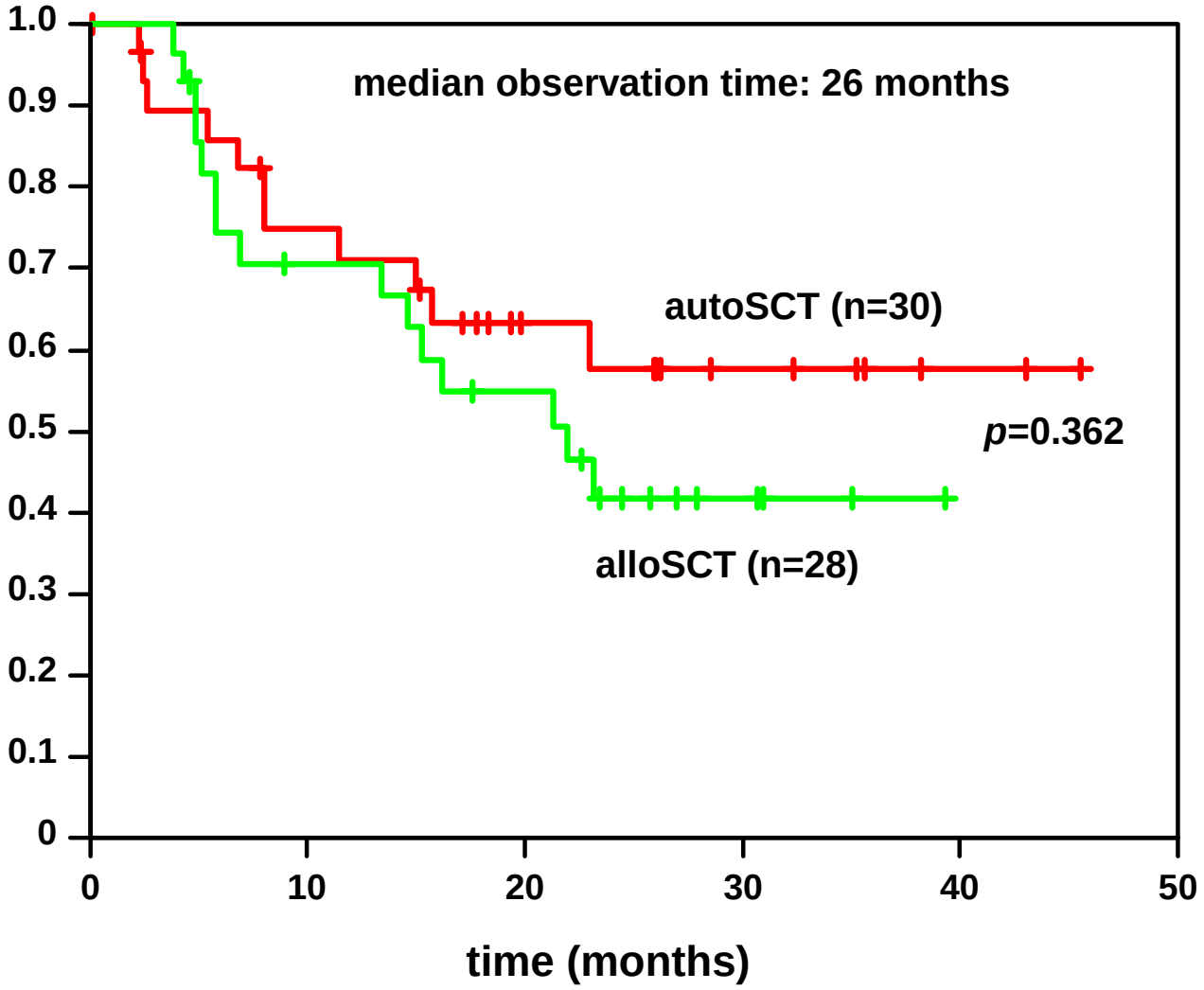
R = At diagnosis, patients are randomized to allogeneic or autologous transplantation (tx). Donor search (family or unrelated) will be initiated only in patients randomized to allogeneic transplantation. Patients randomized to allogeneic tx but without a donor will receive autologous tx. Peripheral blood stem cells are harvested after DHAP in patients who are to receive autologous tx (randomized or crossed over [dotted line ••• in the diagram] from the allogeneic transplant arm because no donor is available).

ASCT = autologous stem cell transplantation, SCT = allogeneic stem cell transplantation

Bundesministerium
für Bildung
und Forschung

DSHNHL: http://www.dshnhl.org/

AATT study: updated results of the interim analysis
OS according to treatment arm



Schmitz et al. ASCO 2015

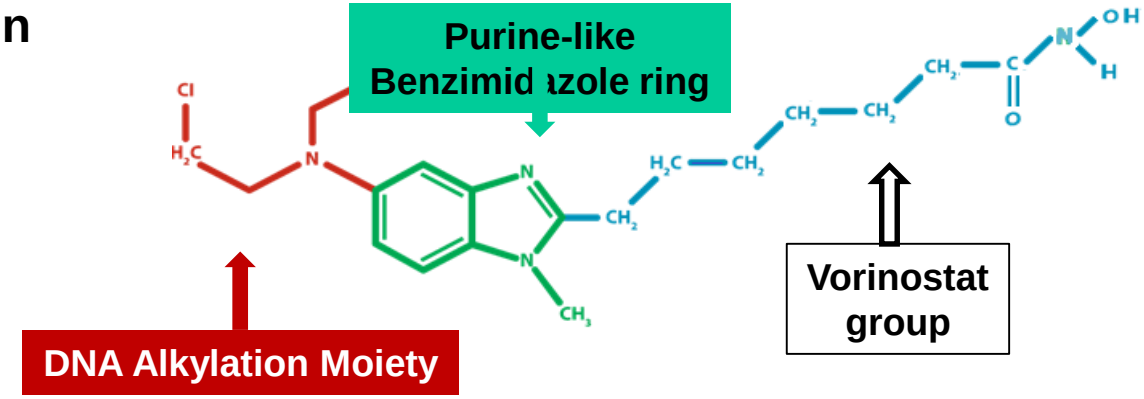
AATT study: cause of death after SCT

	autoSCT (n=30)	alloSCT (n=28)	Total (n=58)
Lymphoma	6	0	6
Salvage treatment	1	0	1
NRM	0	8*	8

* includes one patient with PTLD

Schmitz et al. ASCO 2015

Tinostamustin



EDO-S101

- is a functional **pan-HDAC inhibitor**
- is a functional **alkylating agent**
- causes cell cycle arrest
- reduces proteins of the DSB repair system
- increases pro-apoptotic BIM
- reduces anti-apoptotic proteins (XIAP, Mcl-1)
- triggers the classical pathway of apoptosis
- works synergistically with proteasome inhibitors

Phase IB/II, n=30

PFS-3 years

pTNHL – CAR T problems

Diese illustrative Abbildung wurde urheberrechtlichen Gründen entfernt.

- *Fratricide* (or soricide)
- NB: Less of a problem in CD19/20 directed B cell depletion

- *Specific antigens* (TAA) beyond idiotype

NCCN Guidelines version 2. 2019:

Peripheral T-cell lymphomas

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
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Discussion

SUGGESTED TREATMENT REGIMENS[a]

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    - **Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] (category 1)**
  - **Other recommended regimens**
    - **CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)**
    - **CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)**
    - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)**
- **Other histologies:[e,f]**
  - **Preferred regimens (in alphabetical order)**
    - **Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[d] for CD30+ histologies**
    - **CHOEP**
    - **CHOP**
    - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)**
  - **Other recommended regimens (in alphabetical order)**
    - **CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL][g]**
    - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)**

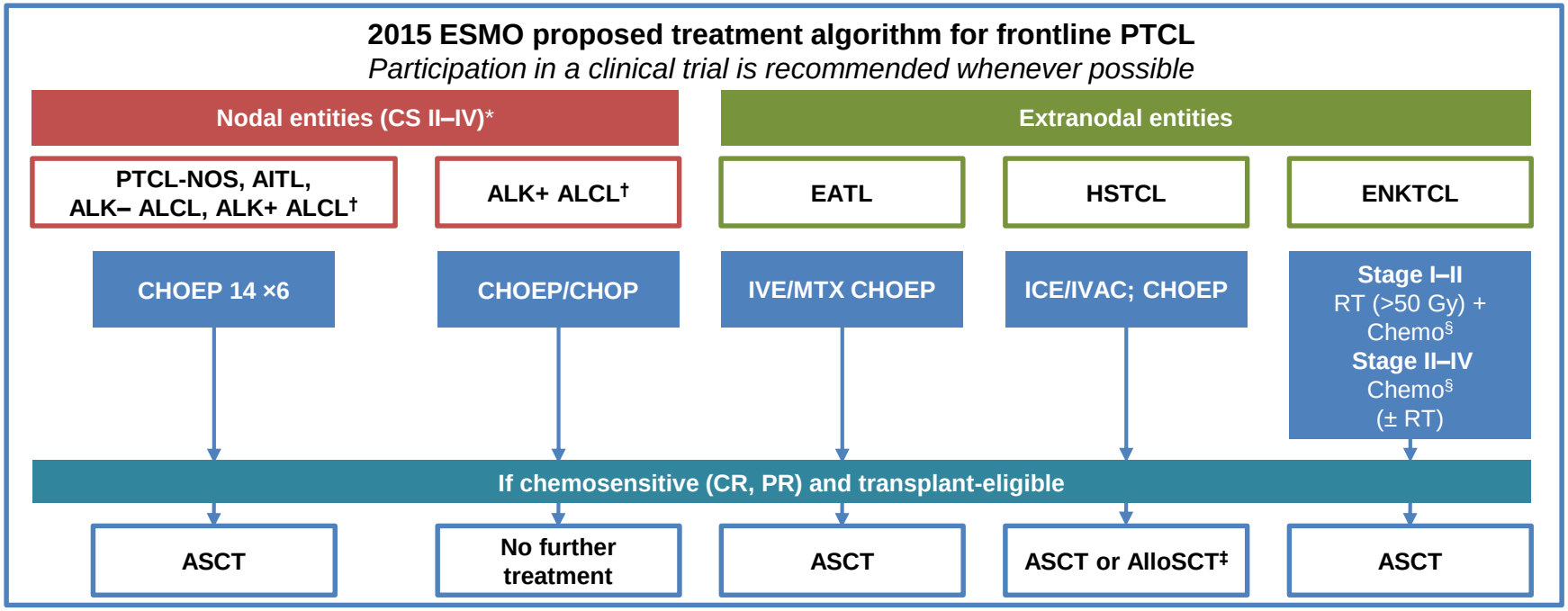
First-line Consolidation:

- **Consider consolidation with high-dose therapy and stem cell rescue.**

NCCN guidelines Version 2.2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed 16Jan2019

ESMO guidelines 2015:

Treatment algorithm for PTCL

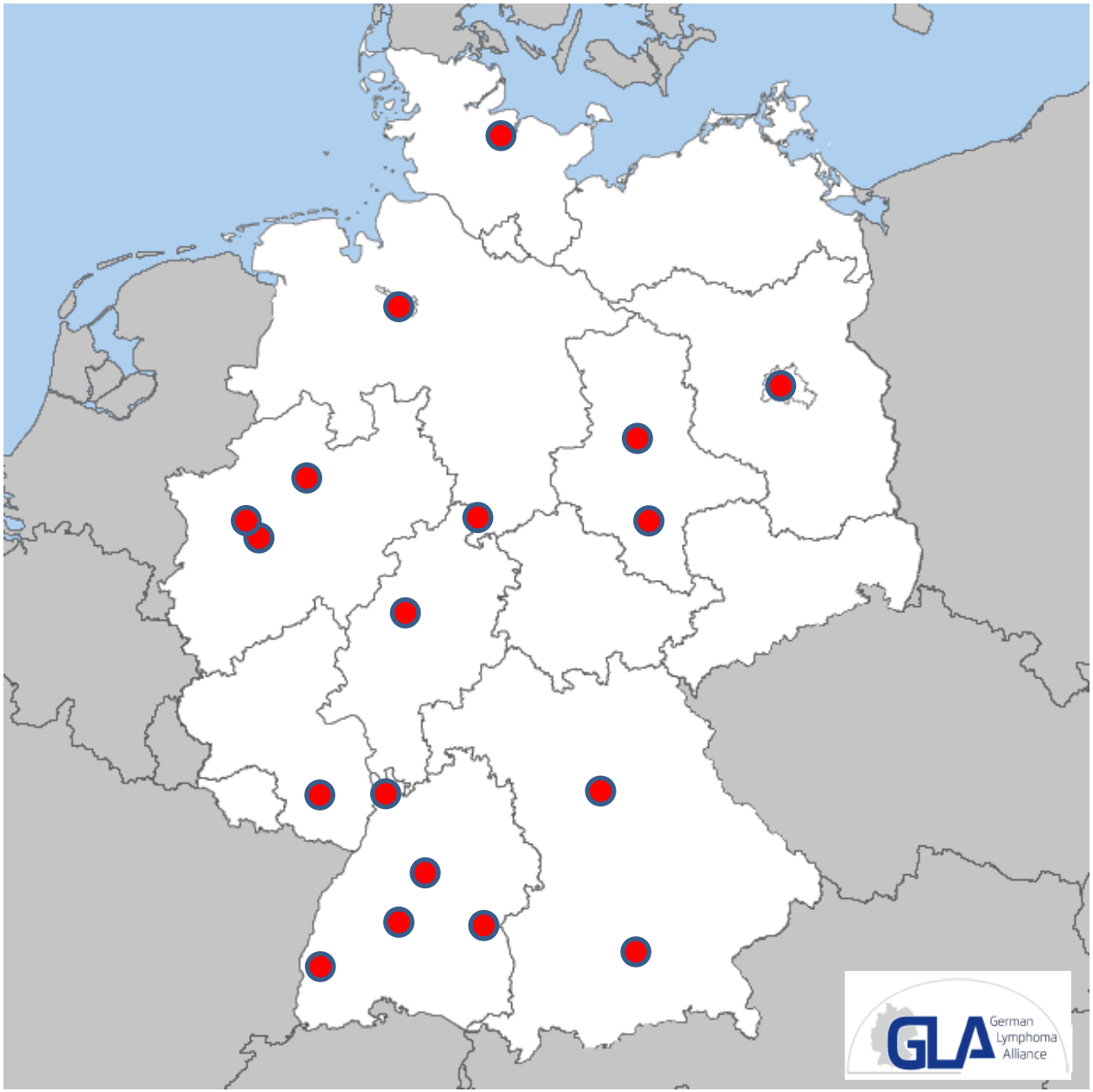


*Stage I: shortened chemotherapy schedule (e.g. 3 courses) followed by curatively intended radiotherapy. †ALK+ ALCL with a high-risk profile (e.g. IPI >2) should be considered for ASCT consolidation, while ASCT in low-risk profile patients is not recommended. ‡If donor available. §SMILE or AspaMetDex.

CS, clinical stage; ICE, ifosfamide + etoposide + carboplatin; IVAC, ifosfamide + cytarabine + etoposide; IVE/MTX, ifosfamide + vincristine + etoposide/methotrexate; RT, radiotherapy

D'Amore F, et al. *Ann Oncol* 2015;26:108–15.

Mitglieder AG T-NHL 11/2017



n=27, 18 Institutionen

Universitätsmedizin Göttingen, Klinik f. Hämatologie u. Med. Onkologie
Universitätsklinikum Giessen und Marburg GmbH, Marburg
Uniklinik Heidelberg, Med. Klinik V
Klinikum der Universität München, Med. Klinik III
Universitätsklinikum Tübingen, Institut f. Pathologie u. Neuropathologie
Uniklinik Münster, Med A
HELIOS- Klinikum Berlin-Buch GmbH, Hämatologie u. Onkologie
Westpfalz Klinikum Kaiserslautern, Innere I
Charité Berlin
Klinikum Magdeburg
Uniklinik Freiburg
Uniklinik Ulm
Robert-Bosch-Krankenhaus, Hämatologie u. Onkologie
Universität Schleswig-Holstein, Med. Klinik II, Kiel
Ev. Krankenhaus Essen-Werden
Petrus KKH Wuppertal
Uniklinik Münster, Med A
Uniklinik Heidelberg, Medizinische Klinik 5
Ev. Diakonie-Krankenhaus gemeinnützige GmbH, Med. II
Universitätsklinik Ulm
Robert-Bosch-Krankenhaus, Hämatologie u. Onkologie
Universitätsklinikum Halle/ Saale, Innere Med. IV
Klinikum der Universität München, Campus Großhadern
Klinikum Nürnberg, Paracelsus Medizinische Privatuniversität

Studientreffen der GLA e.V. –
ULM 2017, Göttingen 2018
Nächster Termin: Münster, November 2019
Leipzig, November 2020

AGs Aggressive B, T Zell Lymphome
Dank an alle Studienteilnehmer
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www.german-lymphoma-alliance.de

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2019 | 2020

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www.lymphome.de