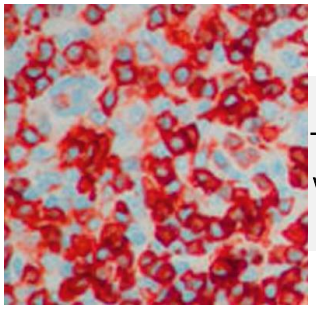


2015… 2018
T-Cell Lymphomas:
we are close to the
finalization

Standard treatment in front-line

Peripheral T-cell lymphomas-not otherwise specified

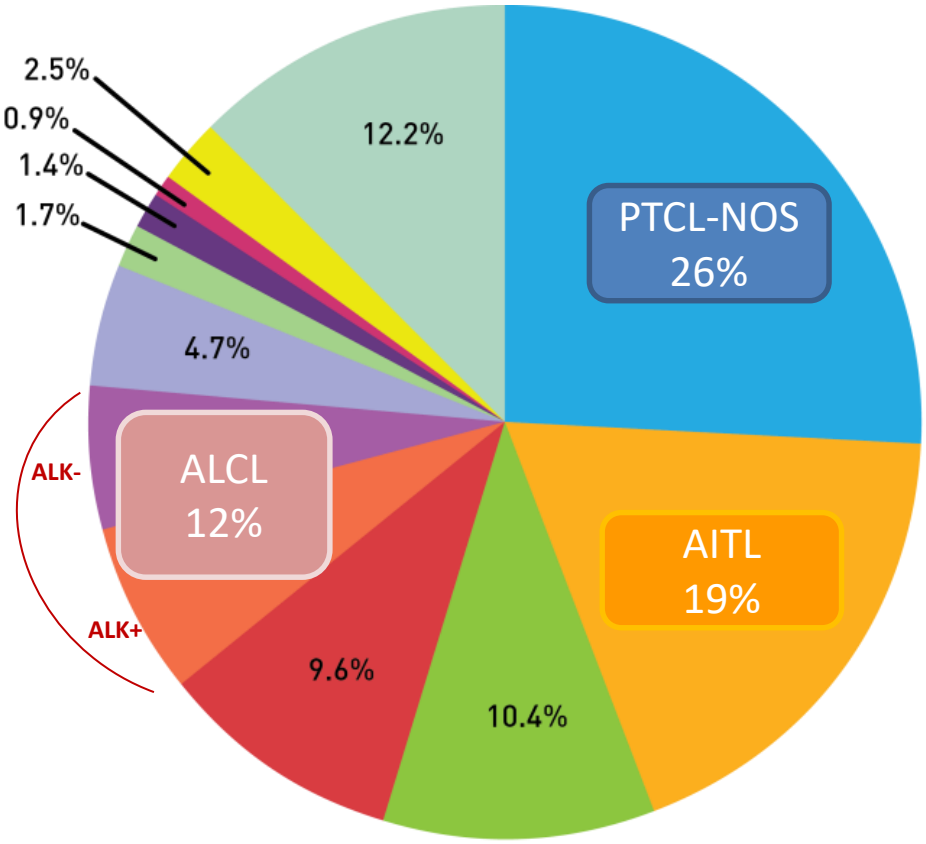
Francesco d'Amore, MD, PhD
Dept. of Hematology
Aarhus University Hospital
Aarhus, Denmark

7. Maj 2018
Bologna, Italy

Disclosures (last 2 yrs)

- Advisory boards: Nordic Nanovector, Servier Pharmaceuticals, Takeda/Millennium
- Speaker's honoraria: Takeda, Servier Pharmaceuticals
- Research support: Sanofi/Genzyme, Takeda, Roche, CTI Life Sciences, Servier Pharmaceuticals

PTCL subtypes according to the International T-cell Project



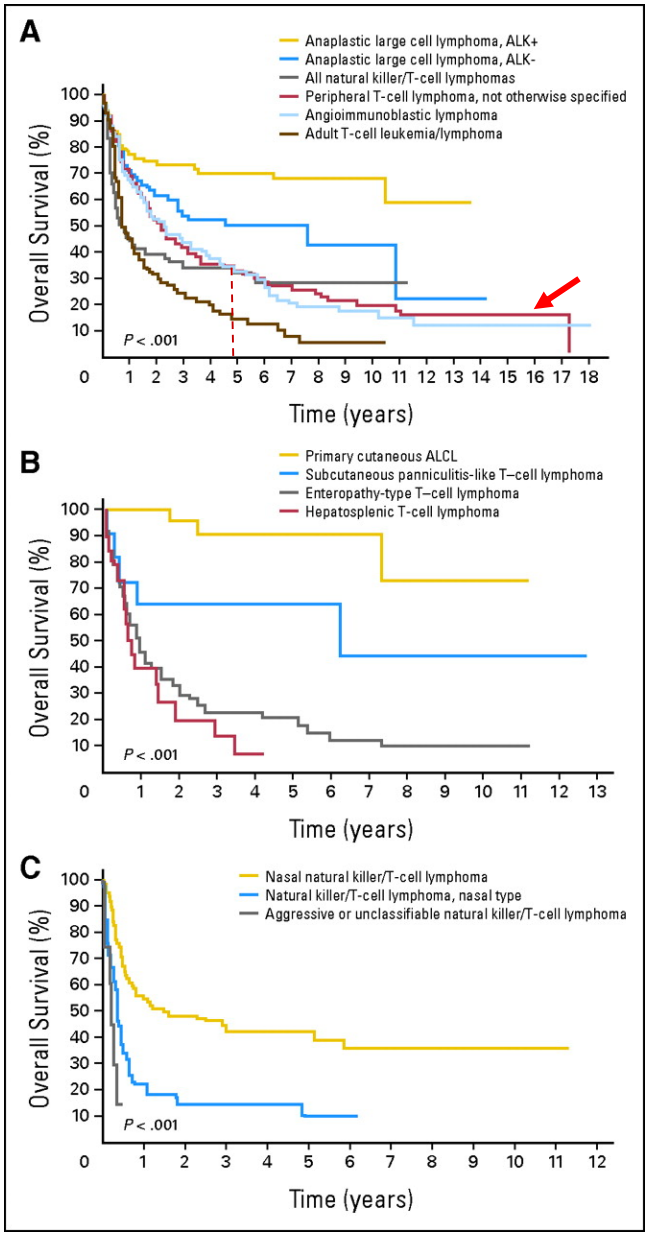
PTCL accounts for10-15% of all lymphomas[1]

- Peripheral T-cell lymphoma-NOS
- Angioimmunoblastic lymphoma
- Natural killer/T-cell lymphoma
- Adult T-cell leukaemia/lymphoma
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative
- Enteropathy-type T-cell lymphoma
- Primary cutaneous anaplastic large cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Unclassifiable peripheral T-cell lymphoma
- Other disorders

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

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

Overall survival of patients with different subtypes of PTCL



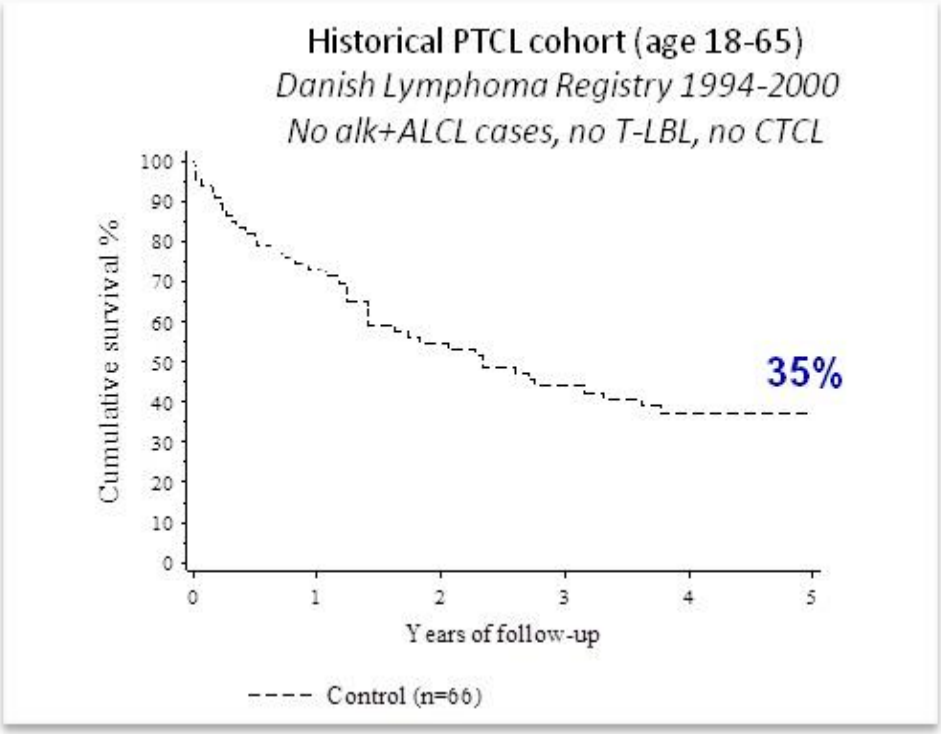
PTCL, peripheral T-cell lymphoma; ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma

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

‘Standard’ approach for PTCL-NOS outside clinical trials

Outcome with conventional CHOP

Danish registry data



Meta-analysis of conventional chemotherapy without ASCT

(Emory University, Atlanta, US)

31 clinical trials: tot 2815 pts (period:1990-2010)

*Overall (all subtypes): **5 yr OS*** **38.5%**

Subtype	5-Year OS
Nasal-type NK/T-cell	48%
AITL	36.5%
PTCL, NOS	34%
Enteropathy-type	21%
Panniculitis-like	~50%
Hepatosplenic	0–10%
ALCL (alk pos+neg)	**56.5%**

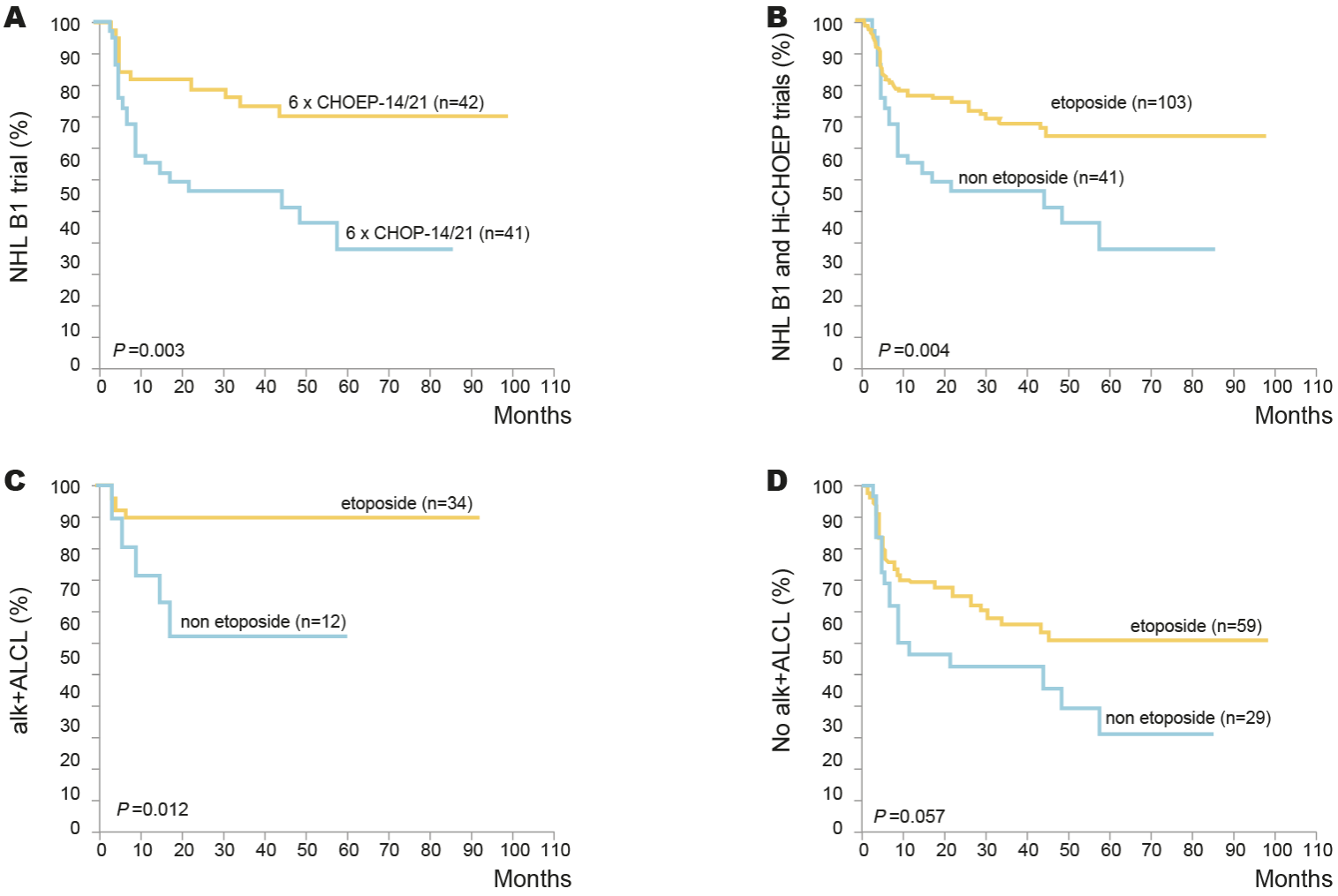
CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; PTCL, peripheral T-cell lymphoma; ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; CTCL, cutaneous TCL; ASCT, autologous stem cell transplantation; pts, patients; yr, years; OS, overall survival; NK, natural killer; AITL, angioimmunoblastic TCL; NOS, not otherwise specified; pos, positive, neg, negative

Abouyabi S, et al. ISNR Hematology 2011;2011:623924. doi: 10.5402/2011/623924

The addition of etoposide to CHOP

The German experience in aggressive lymphomas: retrospective PTCL subset analysis

Event-free survival



Schmitz et al. 2010 Nov 4;116(18):3418-25

Population-based data from the Swedish lymphoma registry

CLINICAL TRIALS AND OBSERVATIONS

Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry

Fredrik Ellin,[1,2] Jenny Landström,[2] Mats Jerkeman,[3] and Thomas Relander[3]

BLOOD, 4 SEPTEMBER 2014 • VOLUME 124, NUMBER 10

N=755 pts with non-leukemic, non-cutaneous PTCL

Key Points

- The addition of etoposide to CHOP was associated with favorable PFS in patients ≤60 years with PTCL.

HR, 0.49; p 0.008

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; PFS, progression free survival; PTCL, peripheral T-cell lymphoma; pts, patients; HR, hazard ratio

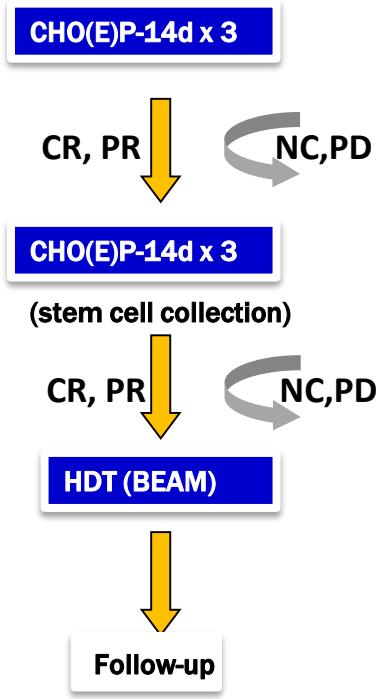
Ellin F, et al. Blood 2014;124:570-7

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

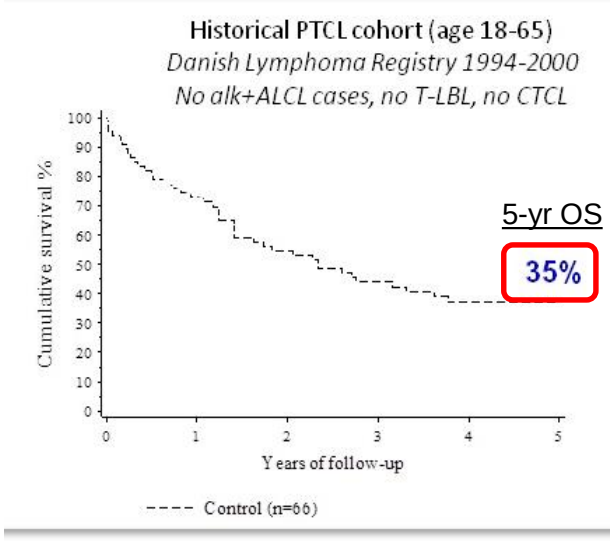


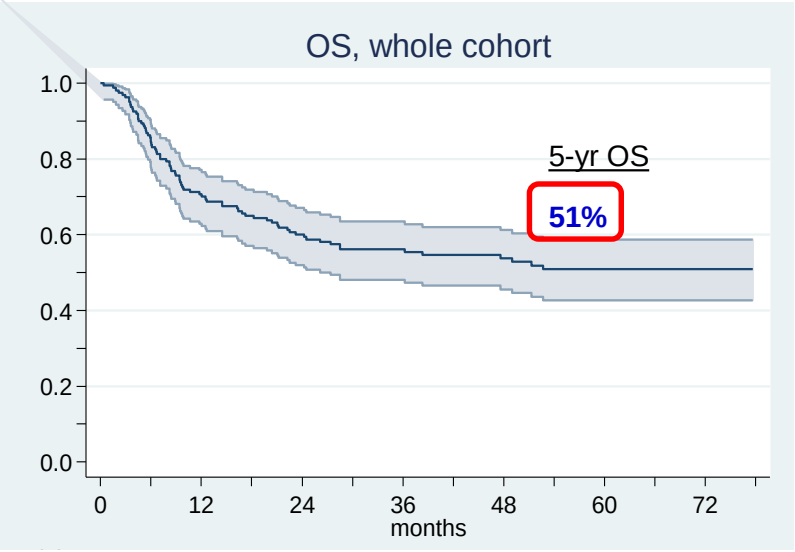
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

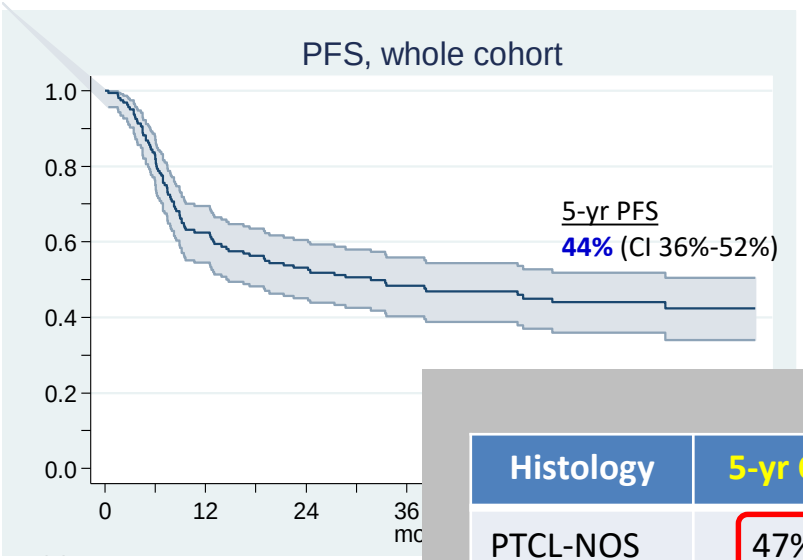


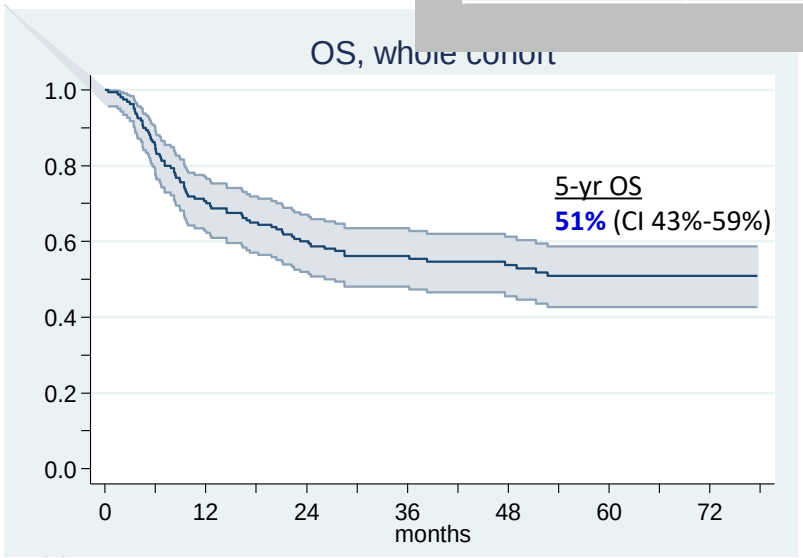


NLG-T-01 – CHOEP q2w x 6 + ASCT

5- and 10 yr median follow-up

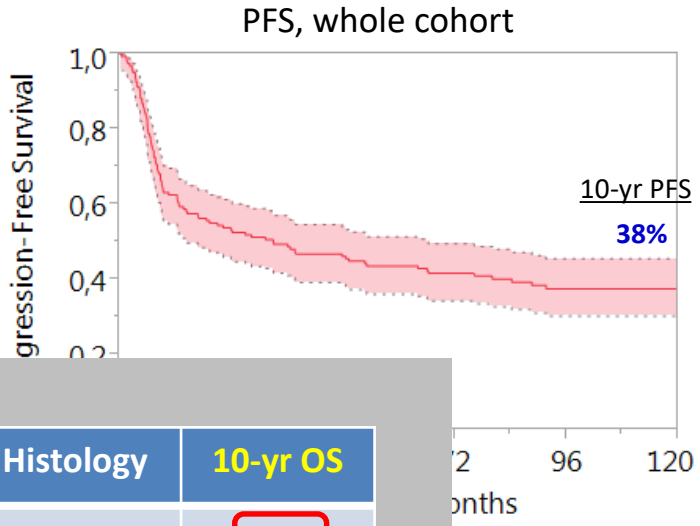
5 yr med foll up



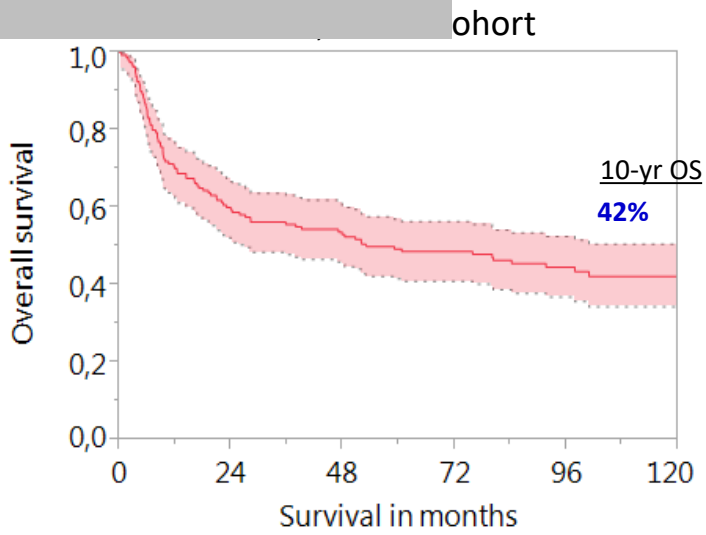


Histology	5-yr OS
PTCL-NOS	47%

10 yr med foll up



Histology	10-yr OS
PTCL-NOS	42%



d'Amore F, et al. J Clin Oncol 2012;30:3093-9

d'Amore F, et al. ICML 2015;abstract 74

A 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)

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.

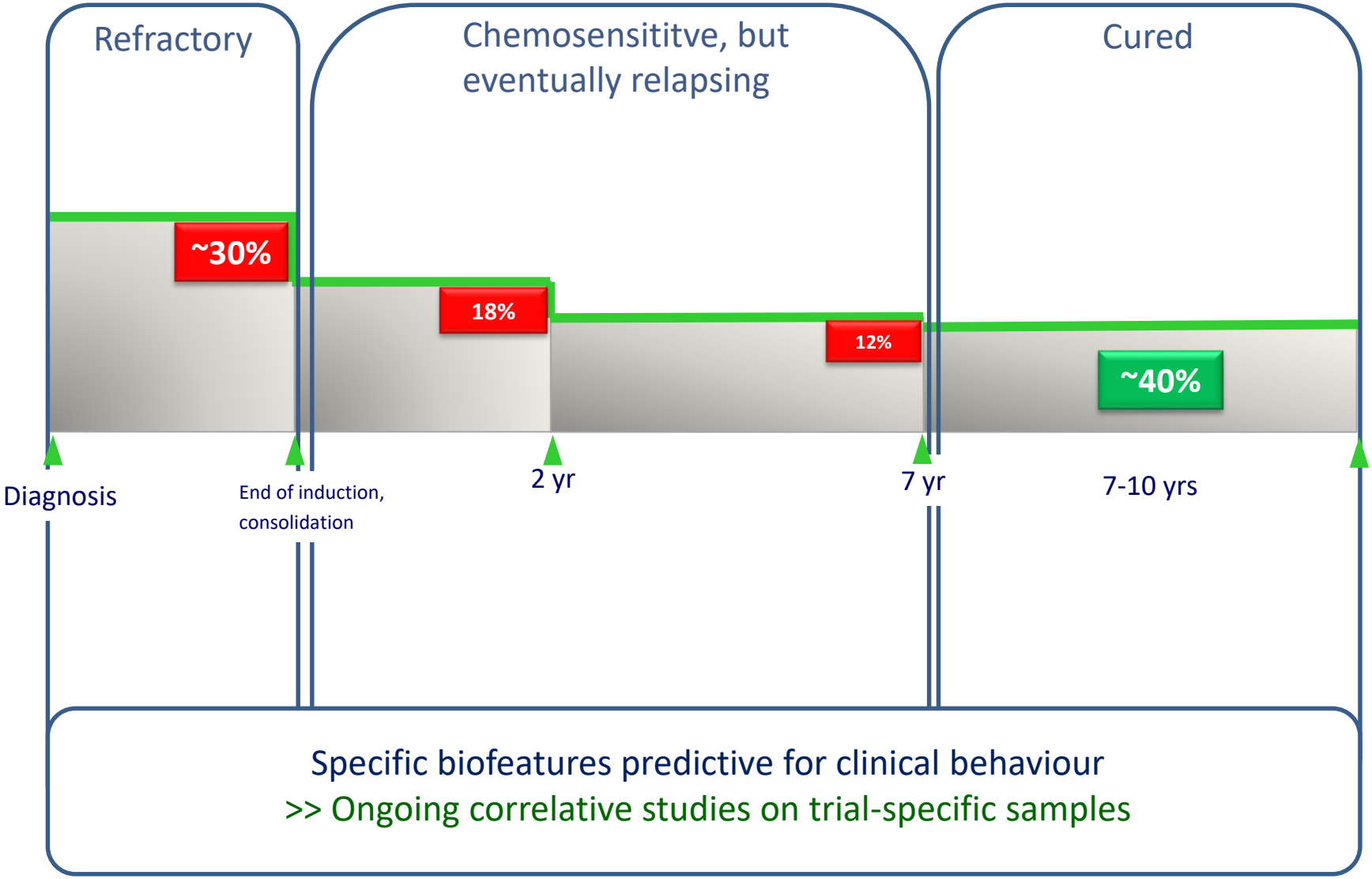
AATT, autologous allogeneic, transplantation trial; auto, autologous; allo, allogeneic; tot, total; ORR, overall response rate; y, year; EFS, event free survival; OS, overall survival; SCT, stem cell transplantation; GvL, graft verses lymphoma; TRM, treatment related mortality; pts, patients; DSBM, Data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

Schmitz N, et al. ICML 2015;abstract 33

NORDIC LYMPHOMA GROUP

1st line treatment of PTCL

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

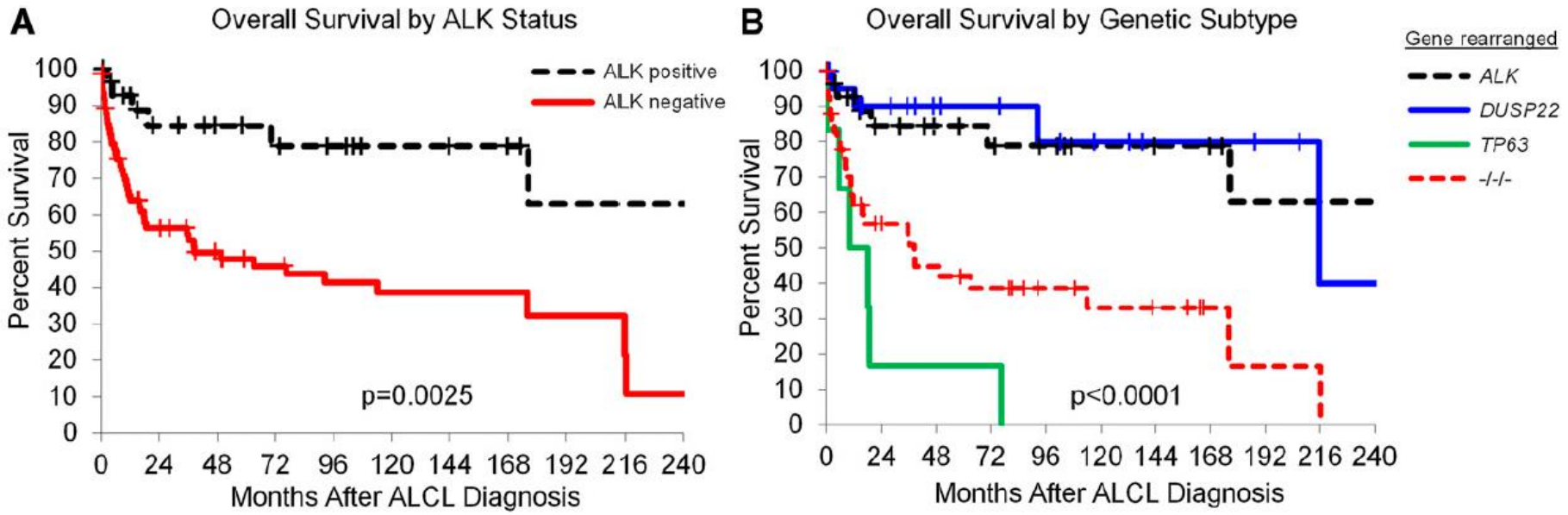


PTCL, peripheral T-cell lymphoma; yr, years

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

ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

Edgardo R. Parrilla Castellar,[1] Elaine S. Jaffe,[2] Jonathan W. Said,[3] Steven H. Swerdlow,[4] Rhett P. Ketterling,[1] Ryan A. Knudson,[1] Jagmohan S. Sidhu,[5] Eric D. Hsi,[6] Shridevi Karikehalli,[7] Liuyan Jiang,[8] George Vasmatzis,[9] Sarah E. Gibson,[4] Sarah Ondrejka,[6] Alina Nicolae,[2] Karen L. Grogg,[1] Cristine Allmer,[10] Kay M. Ristow,[11] Wyndham H. Wilson,[12] William R. Macon,[1] Mark E. Law,[1] James R. Cerhan,[10] Thomas M. Habermann,[11] Stephen M. Ansell,[11] Ahmet Dogan,[1] Matthew J. Maurer,[10] and Andrew L. Feldman[1]



Parrilla Castellar et al, *Blood*, 2014

blood

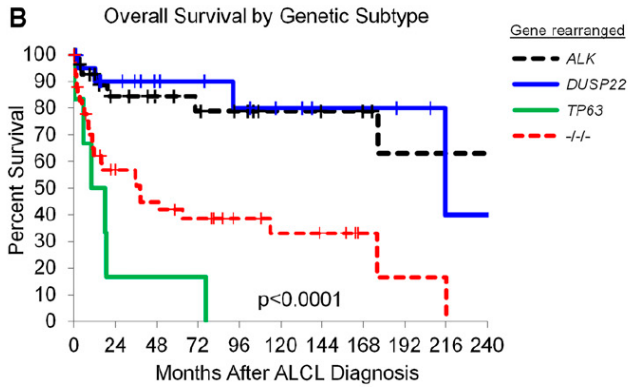
DUSP22 and *TP63* rearrangements predict outcome of ALK-negative anaplastic large cell lymphoma: a Danish cohort study

Martin Bjerregård Pedersen,[1] Stephen Jacques Hamilton-Dutoit,[2] Knud Bendix,[2] Rhett P. Ketterling,[3] Patrick P. Bedroske,[3] Ivy M. Luoma,[3] Christopher A. Sattler,[3] Rebecca L. Boddicker,[3] N. Nora Bennani,[4] Peter Nørgaard,[5] Michael Boe Møller,[6] Torben Steiniche,[2] Francesco d'Amore,[1,*] and Andrew L. Feldman[3,*] (*Contributed equally)

[1]Department of Hematology and [2]Institute of Pathology, Aarhus University Hospital, Aarhus, Denmark; [3]Department of Laboratory Medicine and Pathology and [4]Division of Hematology, Mayo Clinic, Rochester, MN; [5]Department of Pathology, Herlev Hospital, Herlev, Denmark; and [6]Department of Pathology, Odense University Hospital, Odense, Denmark

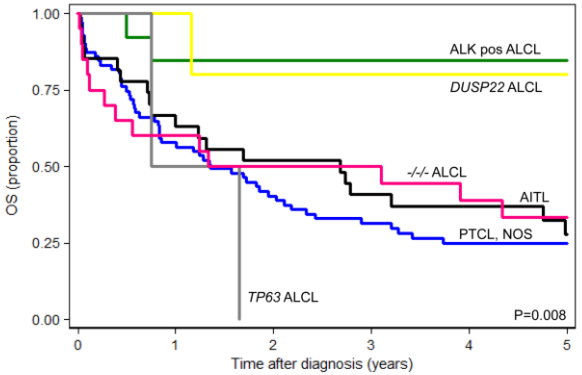
BLOOD, 27 JULY 2017 • VOLUME 130, NUMBER 4

- 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

- 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

PTCL-NOS patient

with co-occurrence of DUSP22+ and TP63+

- 1 pt. PTCL-NOS with rearrangements of both *DUSP22* and *TP63* had a poor clinical outcome.
- no co-occurrence of *DUSP22* and *TP63* rearrangements in systemic ALCL
- confirmed the absence of *DUSP22* and *TP63* rearrangements in ALK+ ALCL and AITL.

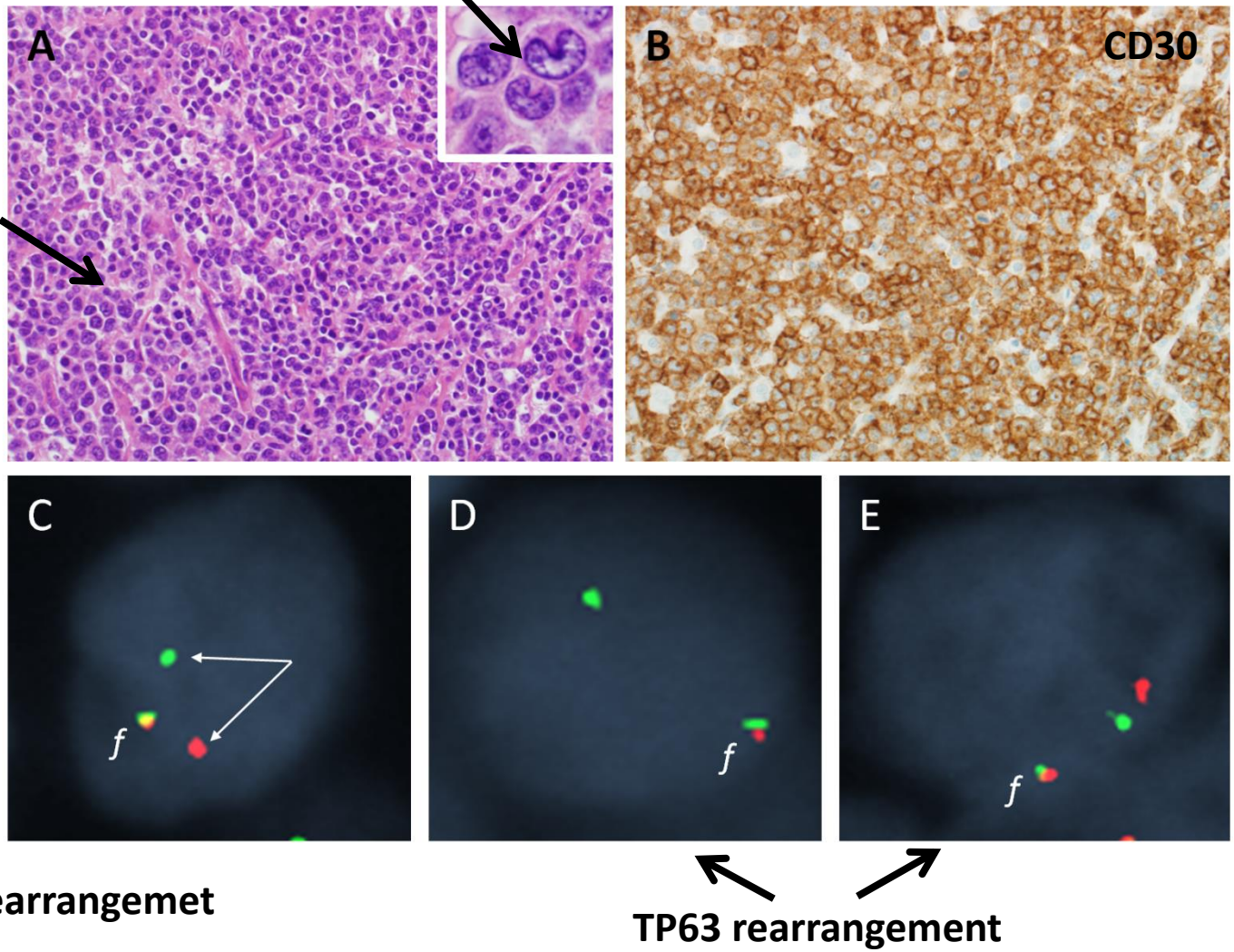
Pedersen et al, Blood, 2017

PTCL-NOS

co-occurrence of DUSP22+ and TP63+

Focal findings of larger cells with cytological features of “hallmark” cells

a diffuse infiltrate of mostly small to medium-sized cells



DUSP22 rearrangemet

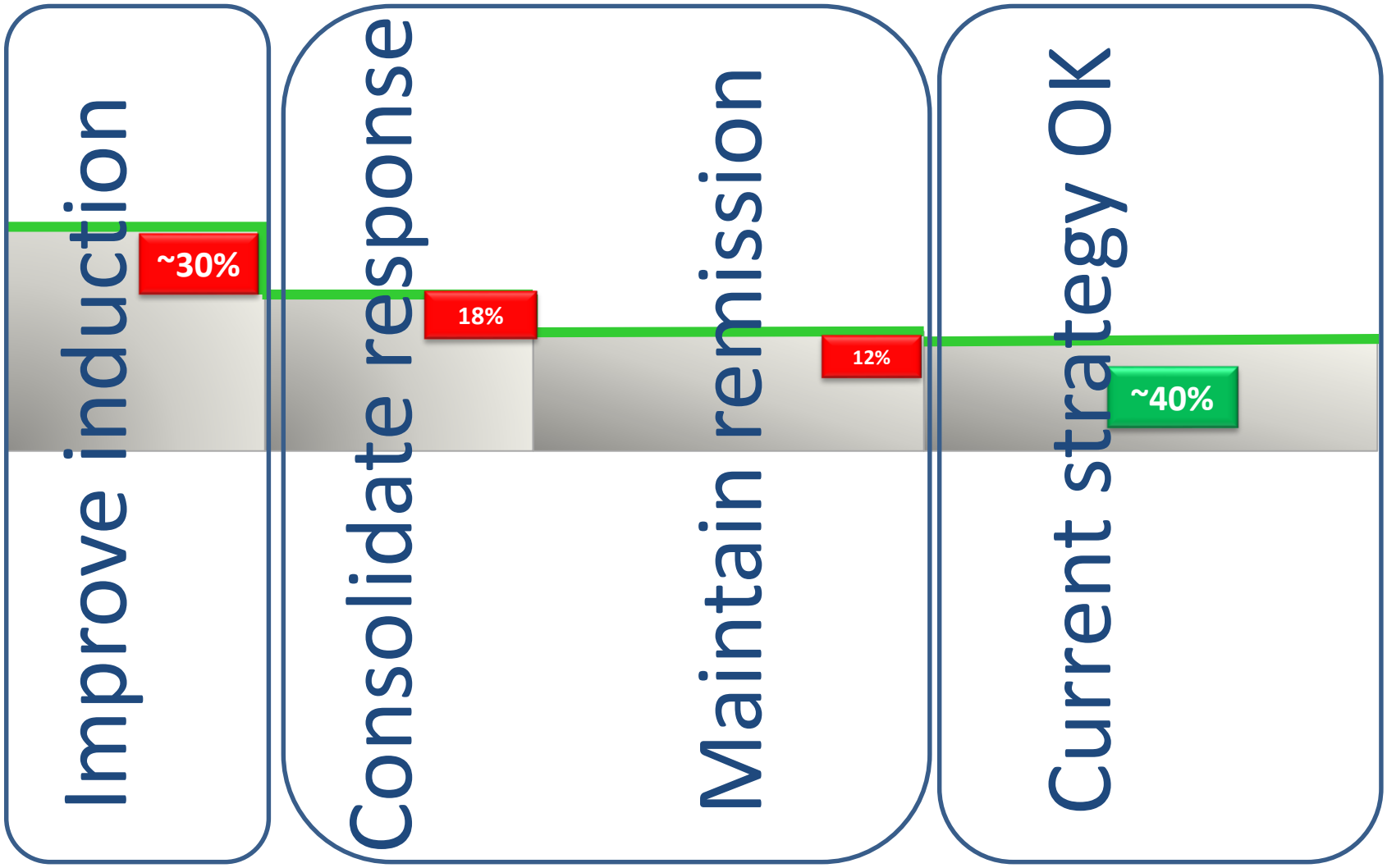
TP63 rearrangement

Conclusion

- Confirms the good outcome of DUSP22+ ALCLs regardless of HDT/ASCT.
- Suggests absence of *DUSP22* and *TP63* rearrangements in other PTCL subtypes than ALK- ALCL and (CD30+) PTCL-NOS (*i.e.* ALK+ ALCL, AITL, EATL, NKTCL)
- Supports the impression that non-DUSP22+ ALCL and PTCL-NOS have a better survival when consolidated with HDT/ASCT.
- The only long-term survival in a patient with TP63+ ALCL was observed after up-front HDT/ASCT consolidation.

1st line treatment of PTCL

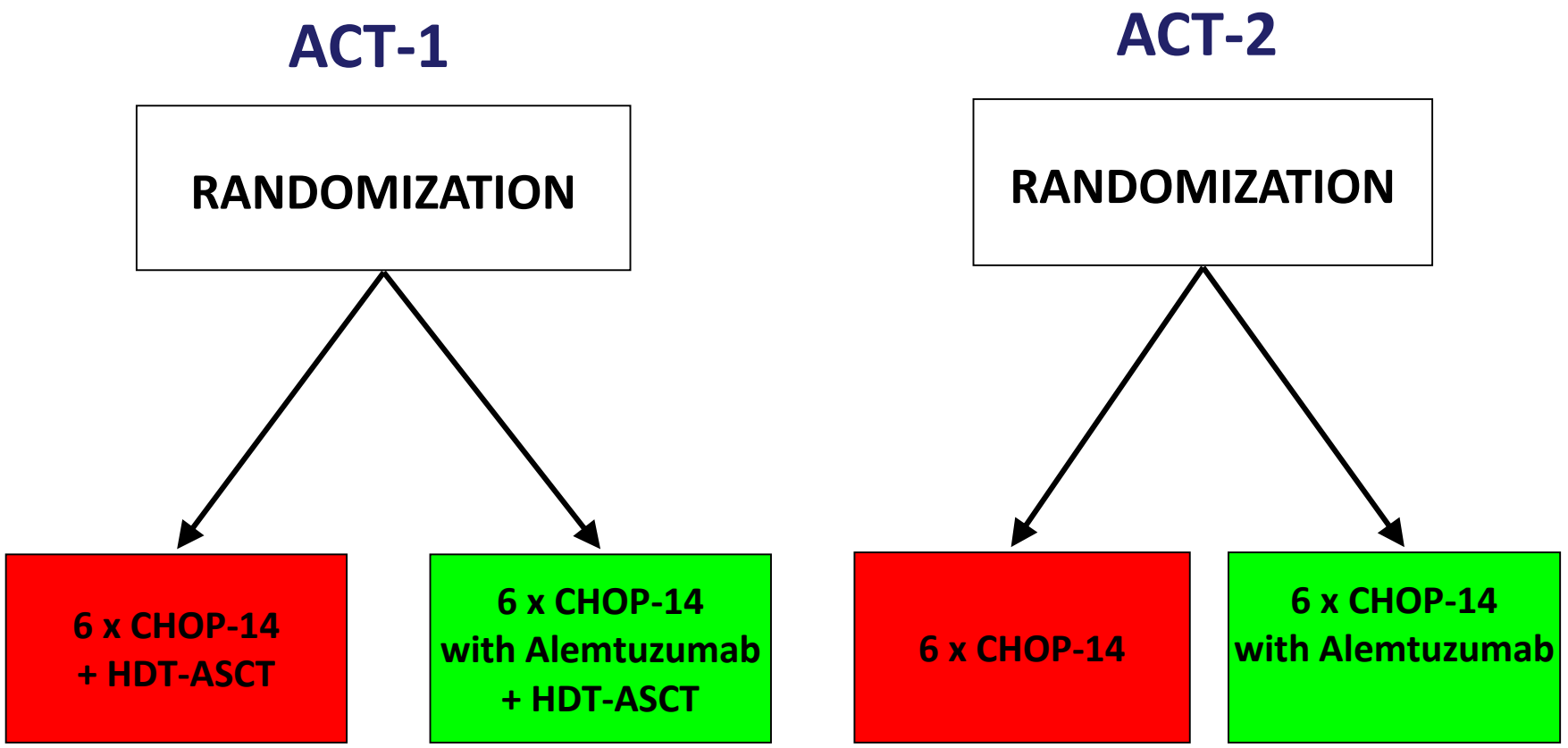
Possible interventional strategies



New trials

ACT trials

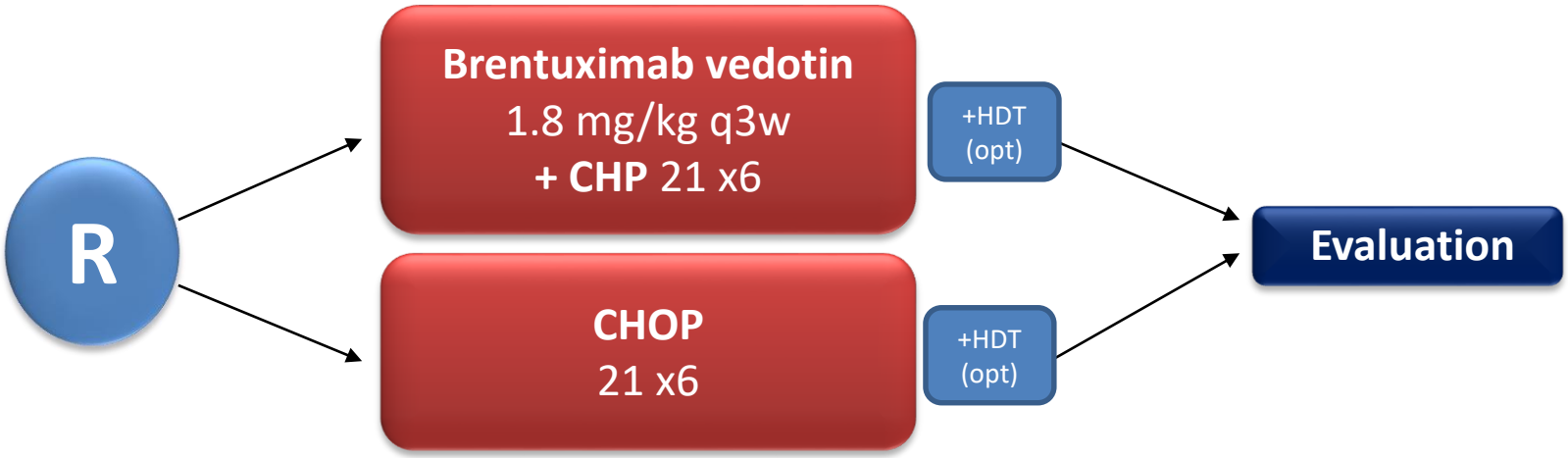
Trial design



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

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.

Romidepsin-CHOP vs CHOP

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

OXFORD

JNCI J Natl Cancer Inst (2017) 109(2): djw248

doi: 10.1093/jnci/djw248

Recommended High-Priority Clinical Trial Questions

Trial Structure Including Current Standards of Care

REVIEW

T-Cell Lymphoma: Recent Advances in Characterization and New Opportunities for Treatment

Carla Casulo, Owen O'Connor, Andrei Shustov, Michelle Fanale, Jonathan W. Friedberg, John P. Leonard, Brad S. Kahl, Richard F. Little, Lauren Pinter-Brown, Ranjani Advani, Steven Horwitz

Table 1. Current landscape of key ongoing and recently completed phase 3 trials*

Clinical study	Setting	Therapies being studied	Results
ACT 1 (NCT00646854)	Newly diagnosed, frontline	Alemtuzumab + CHOP vs CHOP (CHOP given every 2 wks)	Primary end point: event-free survival; recruitment complete
ECHELON 2 (NCT01777152)	Newly diagnosed, frontline	Brentuximab + CHP vs CHOP	Primary end point: progression-free survival; recruitment ongoing
Ro-CHOP (NCT01796002)	Newly diagnosed, frontline	Romidepsin + CHOP vs CHOP	Primary end point: progression-free survival; recruitment ongoing
Lumiere (NCT01482962)	Relapsed and refractory	Alisertib vs pralatrexate vs romidepsin vs gemcitabine	Overall response rate: alisertib 33%, pralatrexate 40% (95% CI −0.34 to 1.23); pralatrexate 40%; romidepsin 59%; gemcitabine 35%; median PFS in months: 3.7, 3.4, 8, and 1.9, respectively