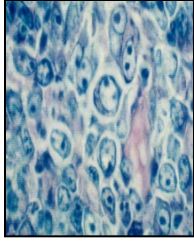
NORDIC LYMPHOMA GROUP

GERMAN HIGH-GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP



The ACT trial

for adult patients with treatment-naïve, systemic PTCL

Francesco d' Amore, MD PhD

Aarhus University Hospital

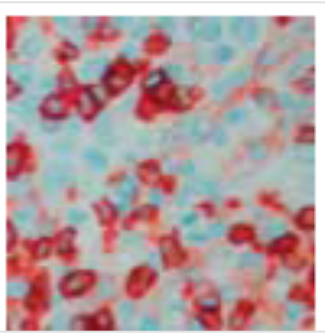
Denmark

2012...2015.

T-Cell Lymphomas:

We are illuminating

the darkest of tunnels



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*A*LEMTUZUMAB AND *C*HOP IN *T*-CELL LYMPHOMA

THE ACT-1 and ACT-2 TRIALS

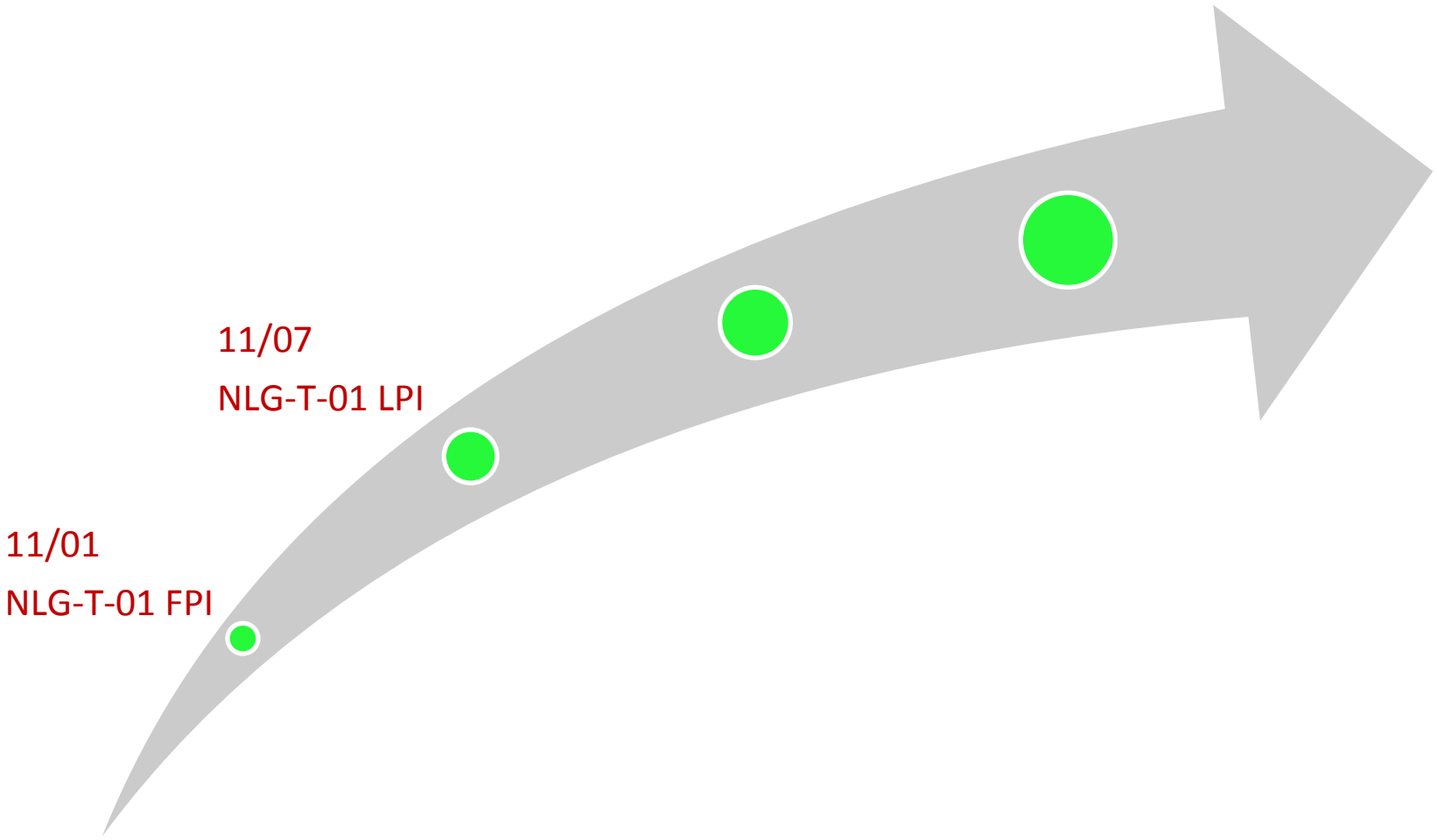
ACT-1 (younger patients)

A randomized phase III study to evaluate the efficacy of chemoimmunotherapy with the monoclonal antibody Campath-1H (Alemtuzumab) given in combination with 2-weekly CHOP versus 2-weekly CHOP alone and consolidated by autologous stem cell transplant, in young patients with previously untreated systemic peripheral T-cell lymphomas

ACT-2 (elderly patients)

A randomized phase III study to evaluate the efficacy of chemoimmunotherapy with the monoclonal antibody Campath-1H (Alemtuzumab) given in combination with 2-weekly CHOP versus 2-weekly CHOP alone in elderly patients with previously untreated systemic peripheral T-cell lymphomas

NLG-T-01 and ACT trial – Time line up to FPI



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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

Excluded:

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

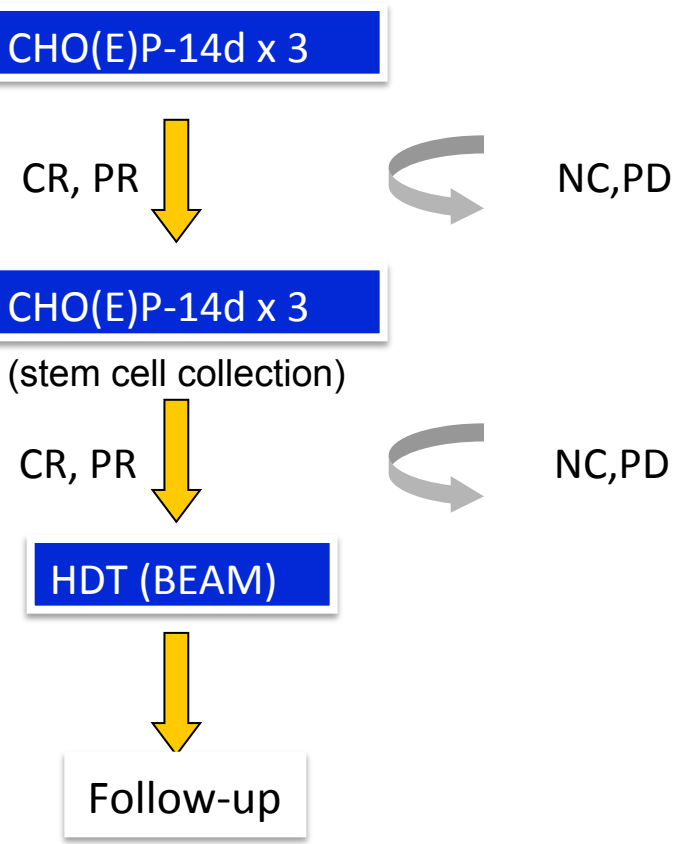
CHO(E)P :

18-60 yrs: CHOEP-14 (n=118)

61-67 yrs: CHOP-14 (n=42)

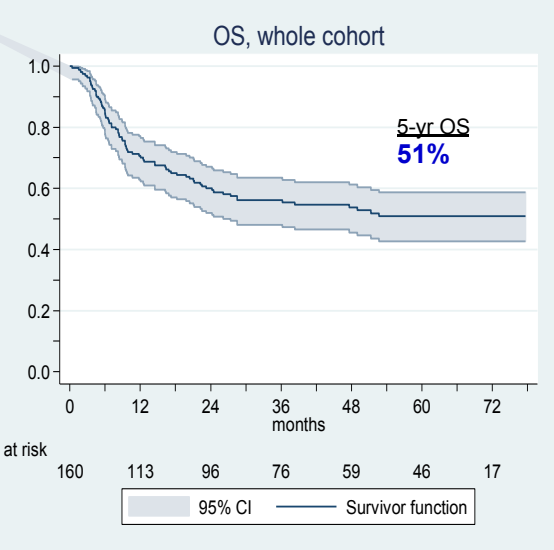
N evaluable pts: 160

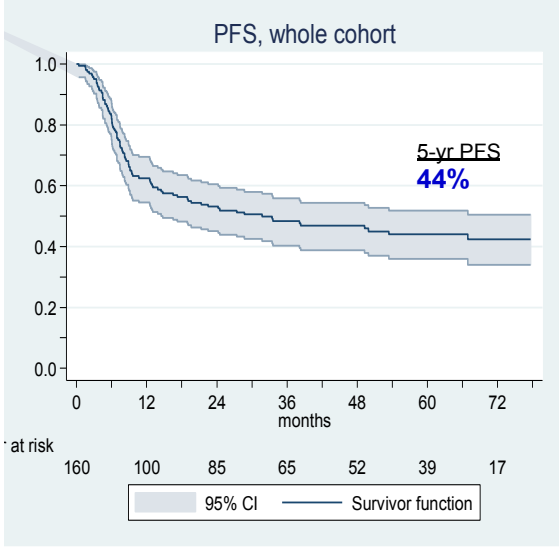
60 mo median follow-up



NLG-T-01: OS and PFS

Median follow-up: 5 yrs (range 2-8 yrs)





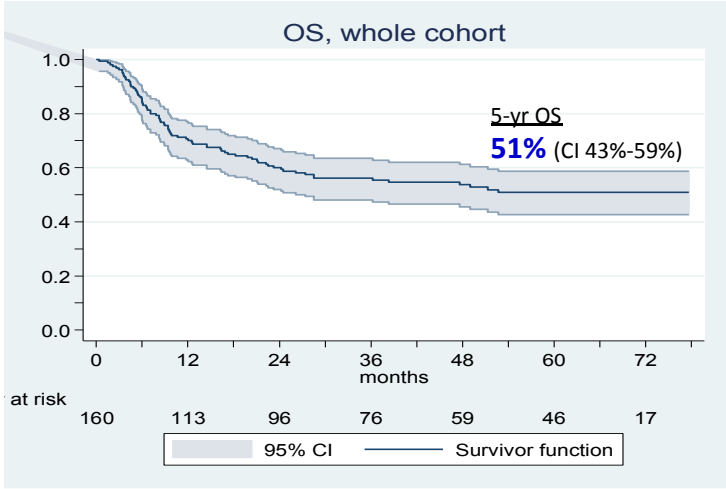
Median age: 57 yrs

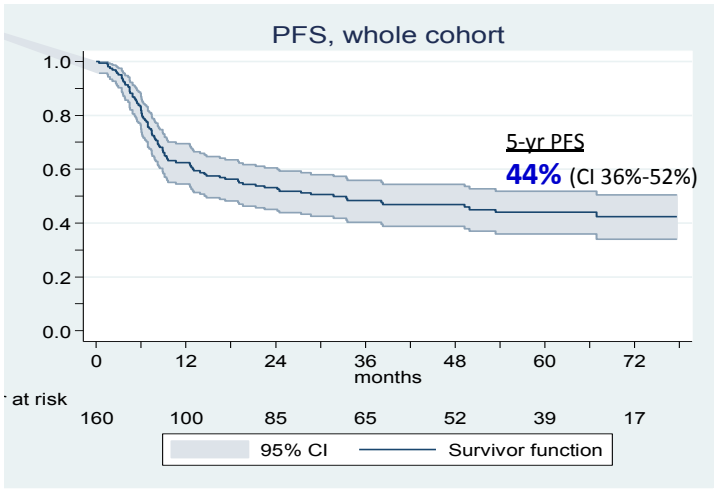
Dose-dense induction followed by HDT/ASCT:

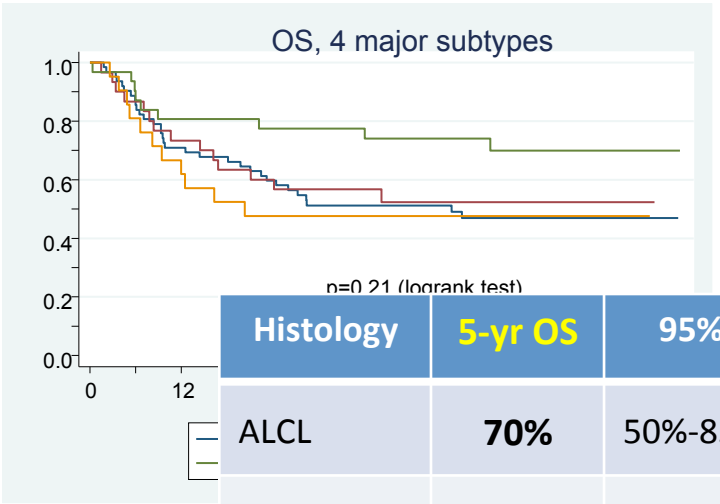
- ✓ is well tolerated (4% TRM)
- ✓ leads to long-term PFS in 44% of pts
- ✓ best in alk-neg ALCL (5y PFS:61%; OS:70%)
- ✓ useful reference for future studies

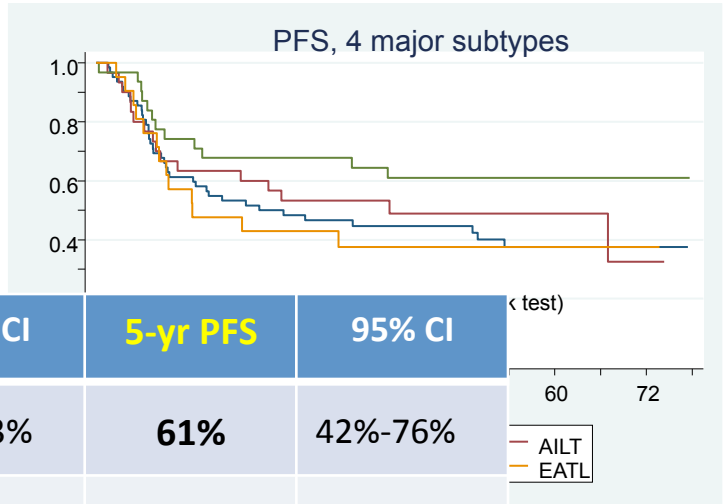
d'Amore et al, JCO 2012

NLG-T-01: Overall and subtype-specific outcome (N=160)







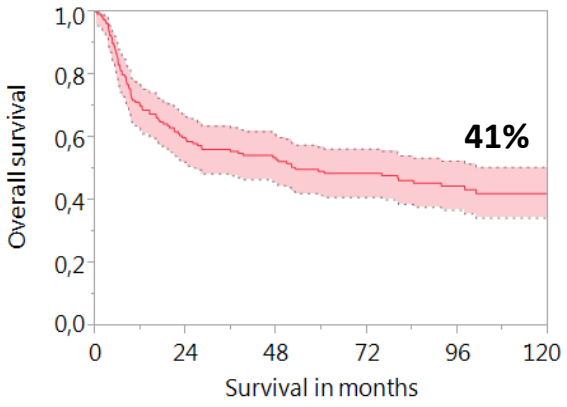


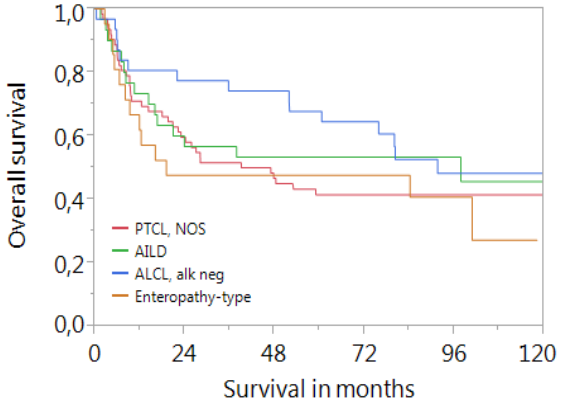
Histology	5-yr OS	95% CI	5-yr PFS	95% CI
ALCL	**70%**	50%-83%	**61%**	42%-76%
AILT	**52%**	33%-69%	**49 %**	30%-65%
EATL	**48%**	26%-67%	**38 %**	18%-57%
PTCL-NOS	**47%**	34%-59%	**38 %**	25%-50%

d'Amore et al, JCO 2012

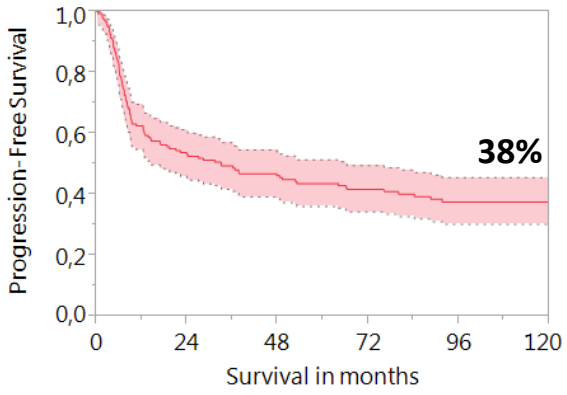
NLG-T-01 - Long-term follow-up (10yrs med; range:7-13 yrs)

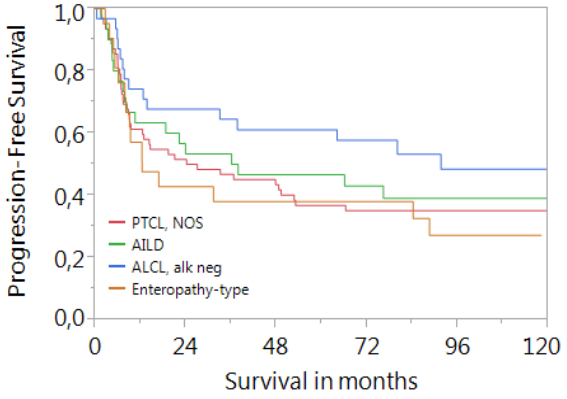
OS



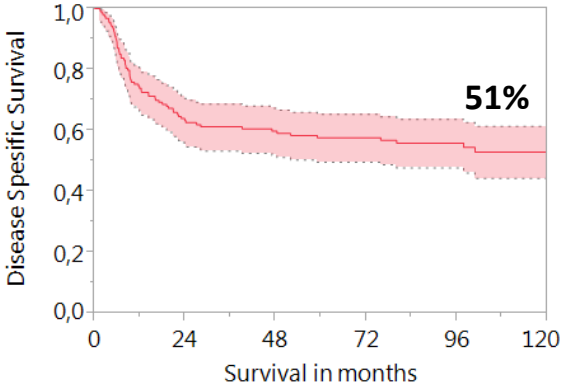


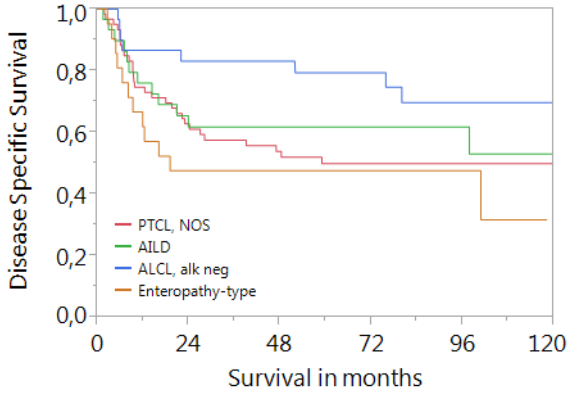
PFS





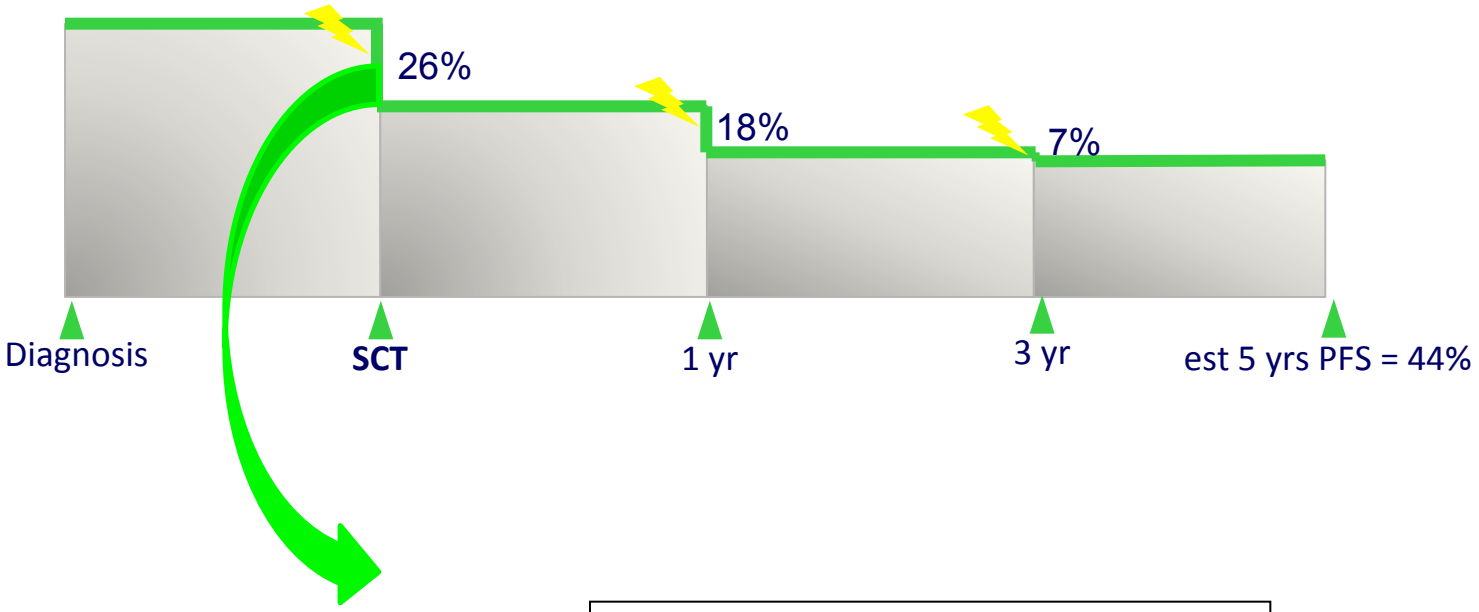
DSS





1st line treatment of transplant-eligible PTCL

Patterns of treatment failure



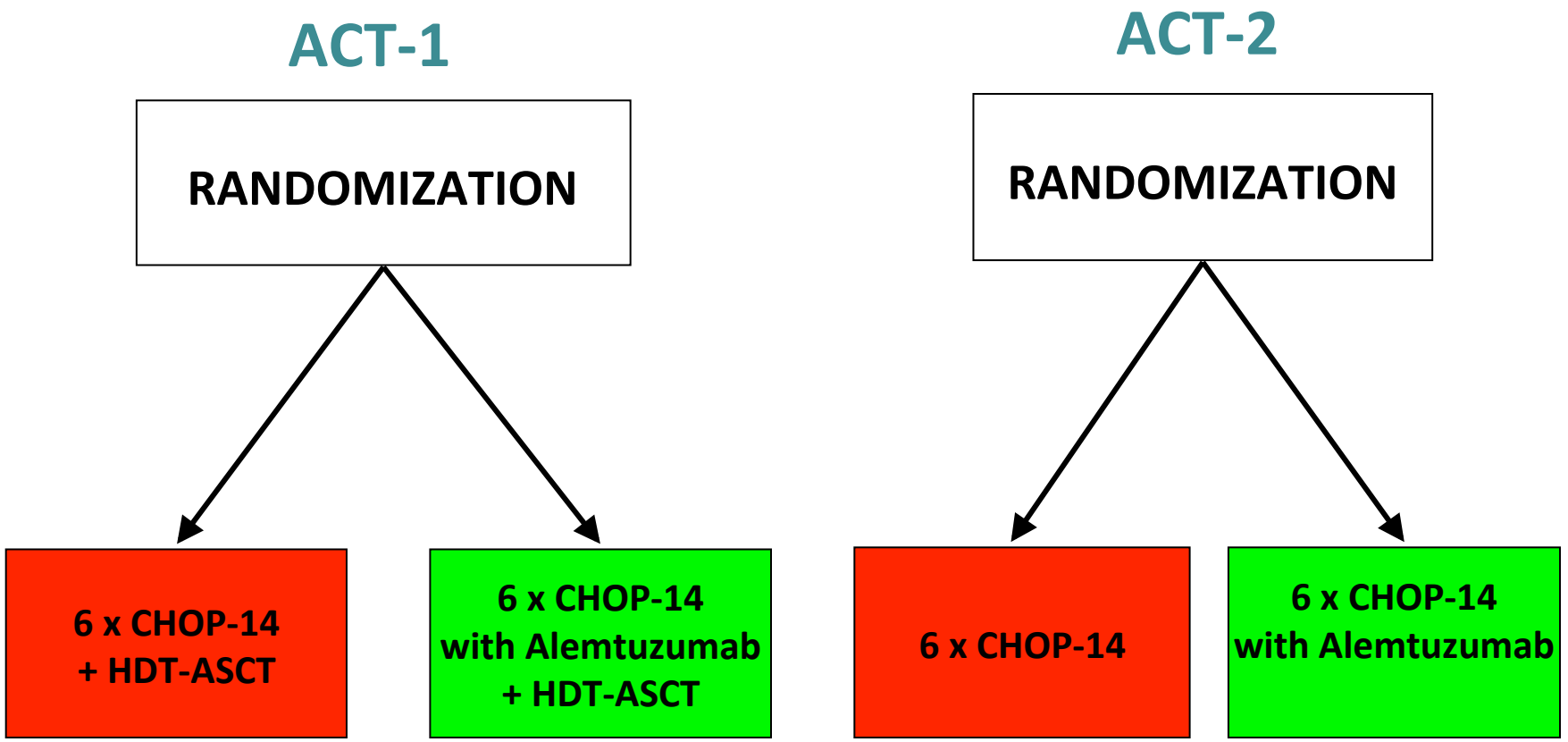
Improve induction ►►

Dose-dense induction *+ alemtuzumab*

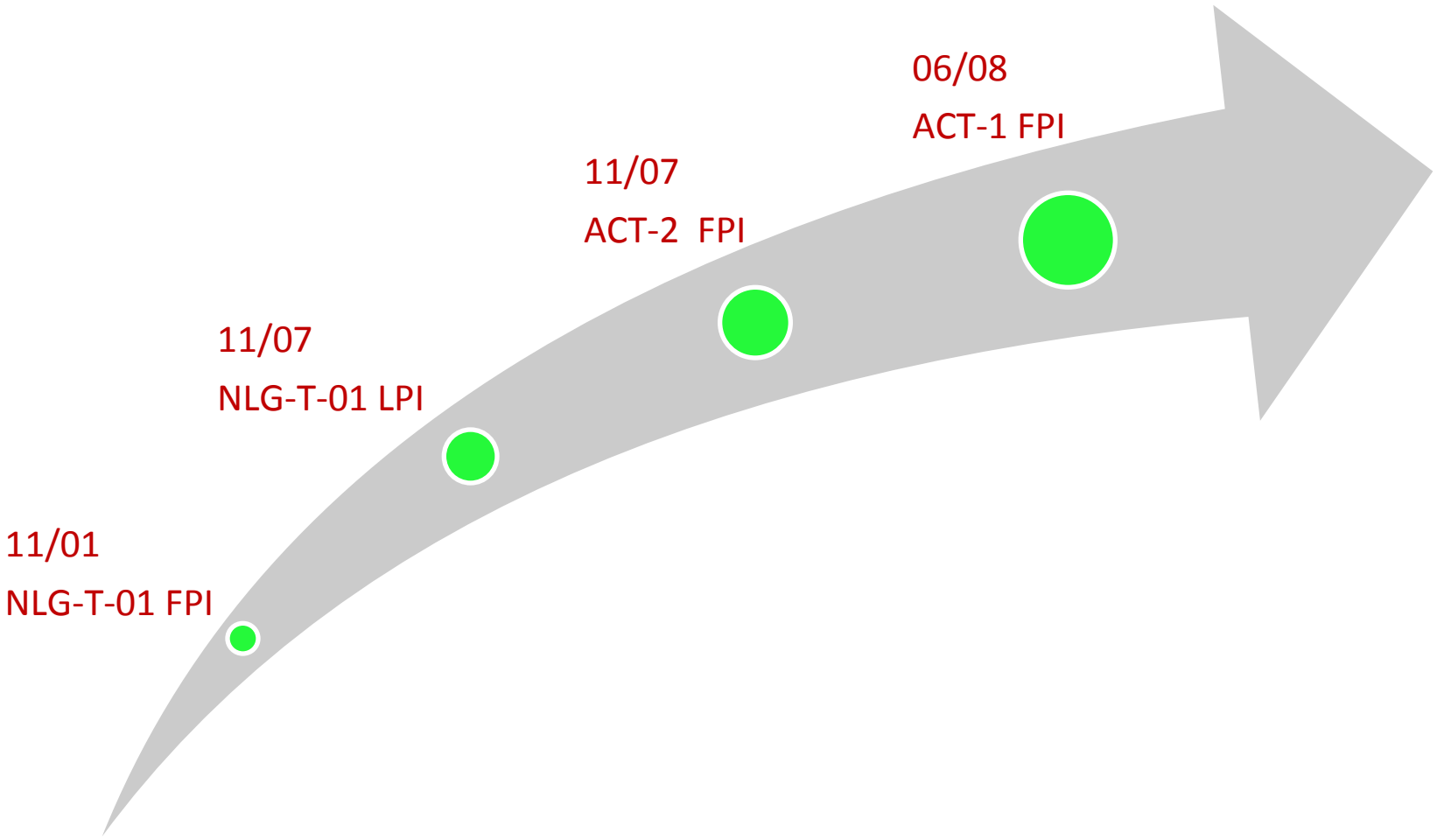
ACT trial

ACT study

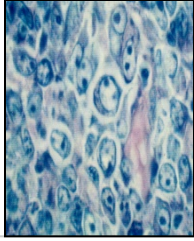
Trial design



NLG-T-01 and ACT trial – Time line up to FPI



Why alemtuzumab?

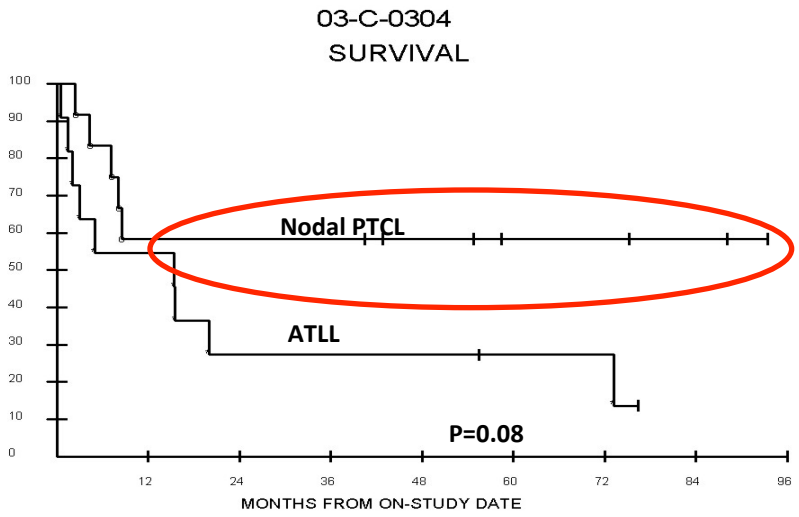


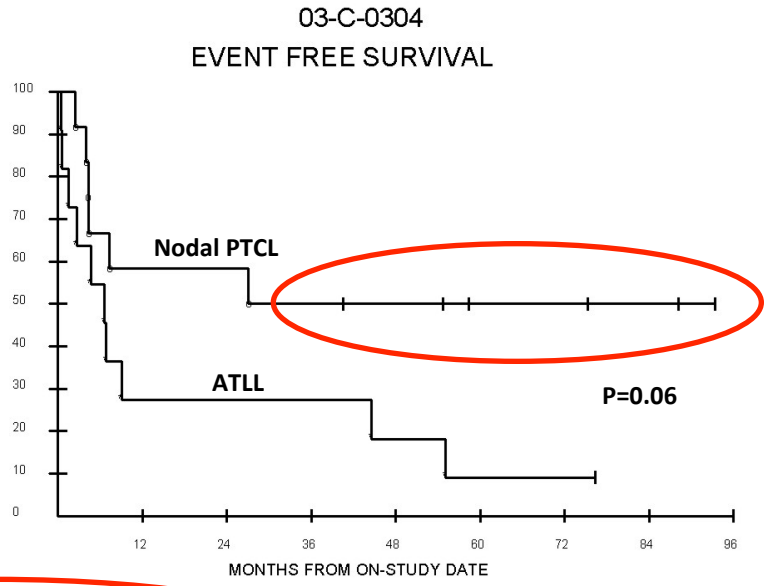
At the time of planning (2005-2007)
the most mature phase II experience
in combination with chemotherapy

	Phase II					Phase III
	Weidmann (D)	Gallamini (I)	Grant (USA)	Kluin-Nelemans (NL)	Trümper (D)	ACT-1/2 (Int trial)
PTCL Cohort	excl: alk +ALCL	excl. alk +ALCL	CD52-pos, ATLL	excl: ALCL, HSL, EATL	excl. alk+ALCL	excl. alk + ALCL
Regimen	FCD	CHOP-28 x8	da-EPOCH	CHOP-14 x8	CHO(E)P-14 x6	CHOP-14 x6
ALZ timing	Induction	Induction	Induction	Induction	Consolidation	Induction
ALZ Cum dose mg	292	180-300	180-540	673	180	360
ALZ route	i.v.	s.c.	i.v.	s.c.	i.v.	s.c.
Ref	L&L 2010	Blood 2007	ASCO 2012	Ann Oncol 2011	ASCO 2009	ASH 2012 (Interim)

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

Grant C et al ASCO 2012, Abstr.8051





45 mo median follow-up

Prior dose-finding Phase I study (Janik et al, ASH 2007)
▸▸ 30 mg pr course of daEPOCH

CD52 expression required for protocol entry

CD52 expression

	Jiang BJH 2009	Geissinger L& L 2009
PTCL-NOS	93%	90 %
AILT	100%	90%
ALCL	---	0%
HS	100%	
T/NK	25%	

Courtesy of dr. Cliona Grant (adapted)

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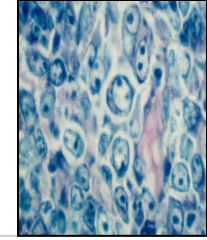
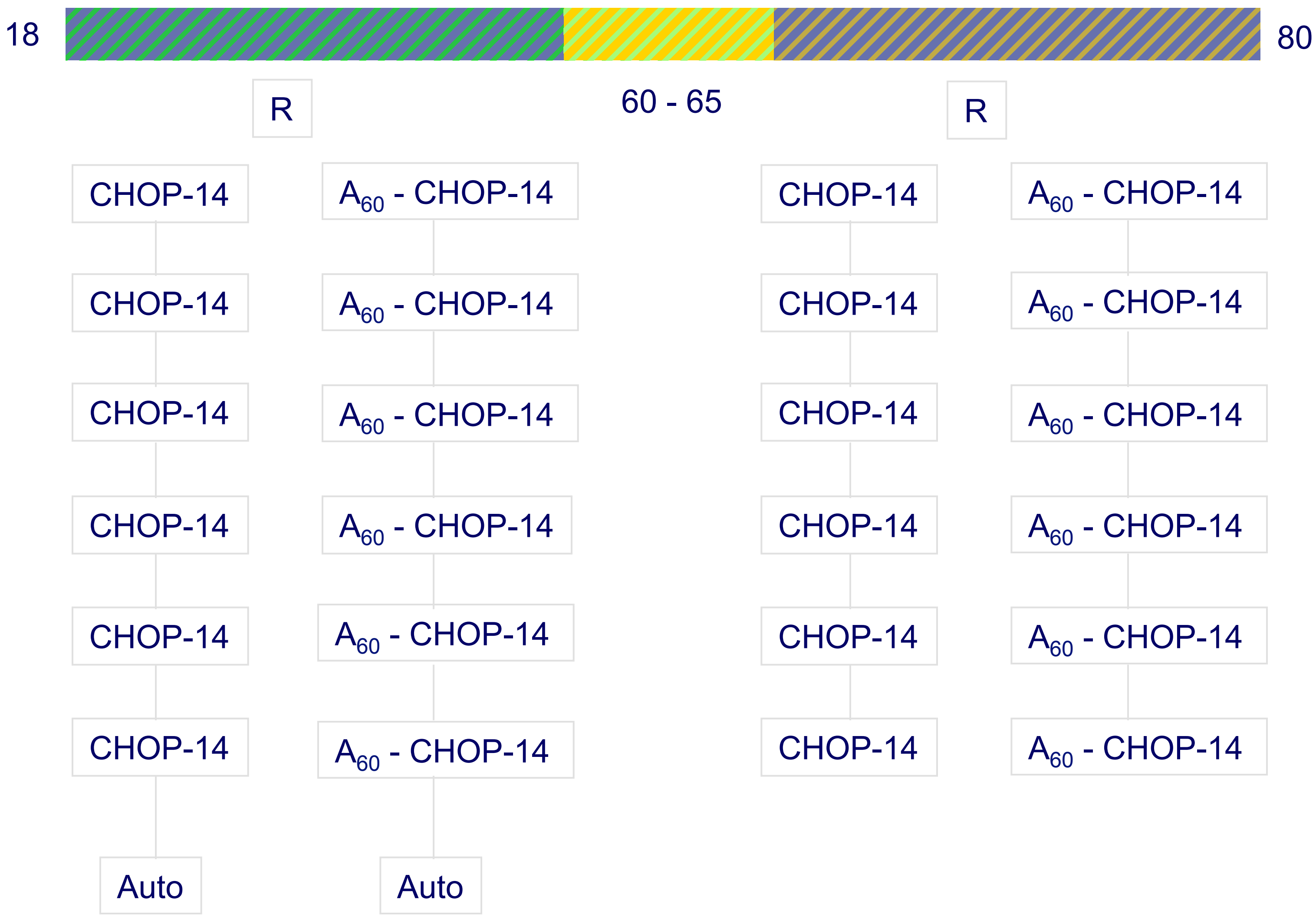


The ACT trial

Original schedule



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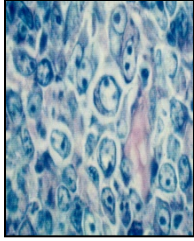


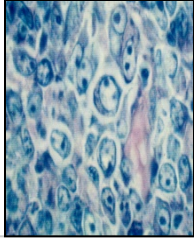
Dose and age amendment

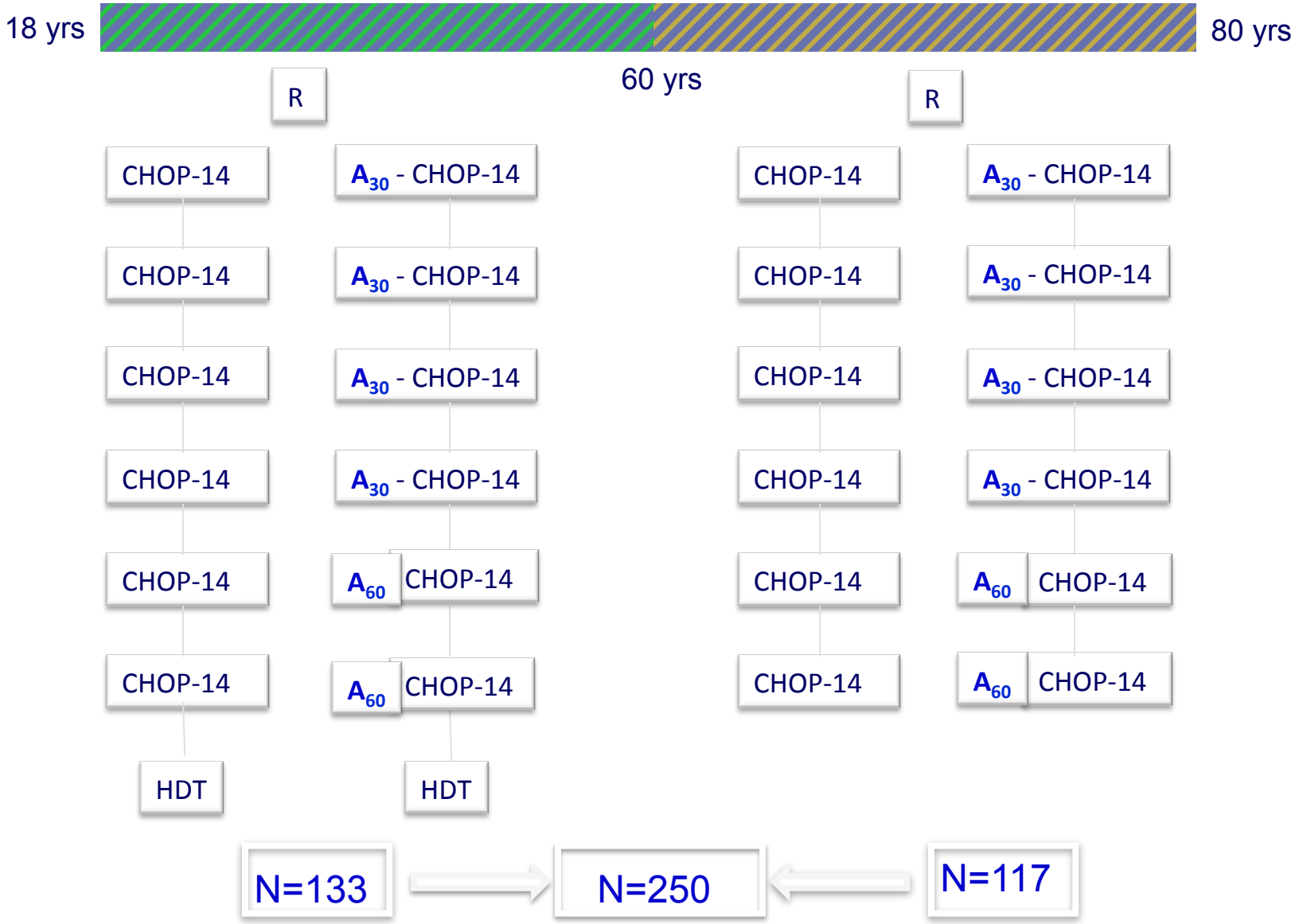
Due to 2 cases of aspergillosis in pts aged >60yrs

- Dose reduction of Alemtuzumab from 360mg (60mg/course for 6 courses) to 120mg (30 mg/course for4 courses)
- Sharp age cut-off: 60 yrs

The ACT trial

AFTER the dose/age amendment

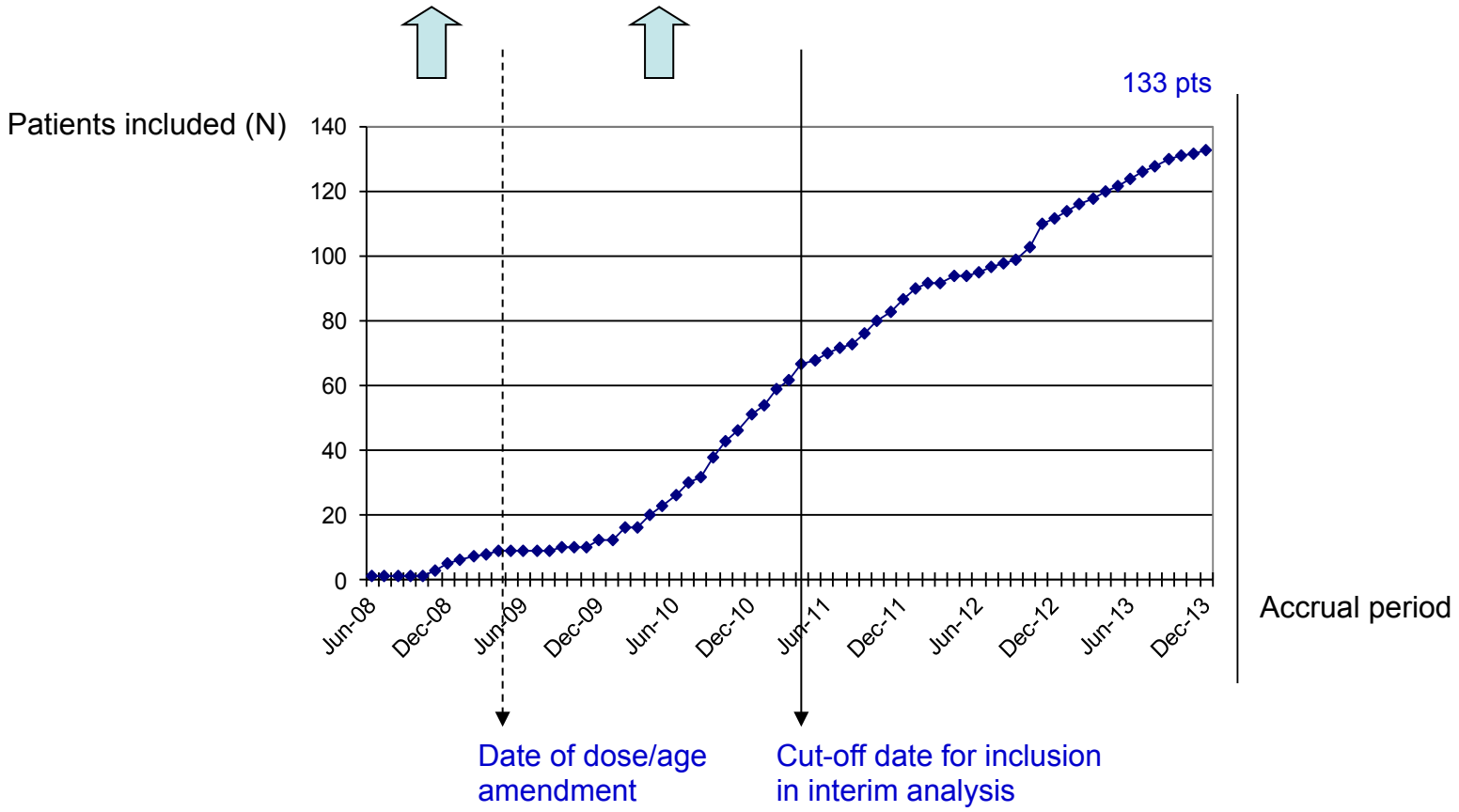




ACT-1

Interim analysis cohort

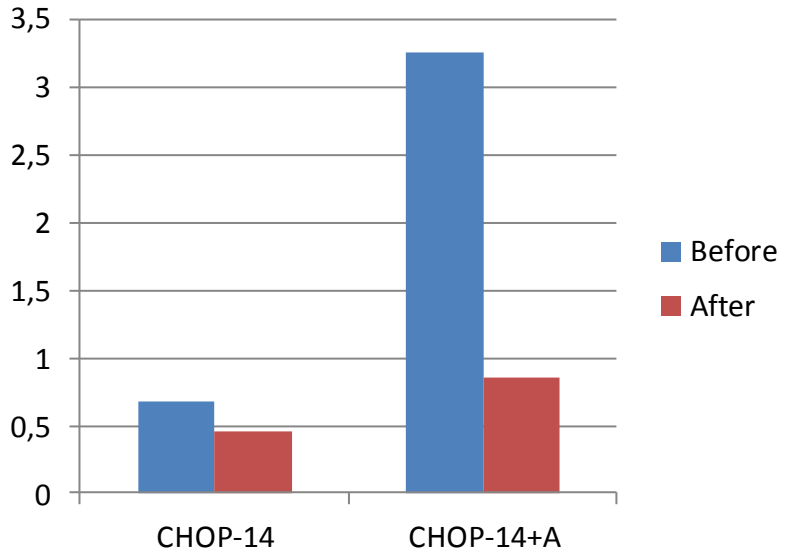
Cohort	Pre-amendment	Post-amendment	Total
N pts	9	59	68
N evaluable pts	7	56	63
A / B arm	3 / 4	28 / 28	31 / 32



ACT-1

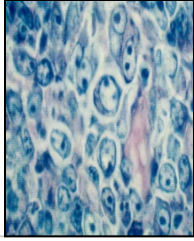
SAEs before and after the ALZ dose amendment

Treatment group	SAE per patient	
	Before amendment (n=7)	After amendment (n=56)
6x CHOP-14 (n=31)	2/ 3 (0.67)	13/ 28 (0.46)
6x CHOP-14 + A (n=32)	13/ 4 (3.25)	24/ 28 (0.86)
Total (n=63)	15/7 (2.43)	37/56 (0.66)

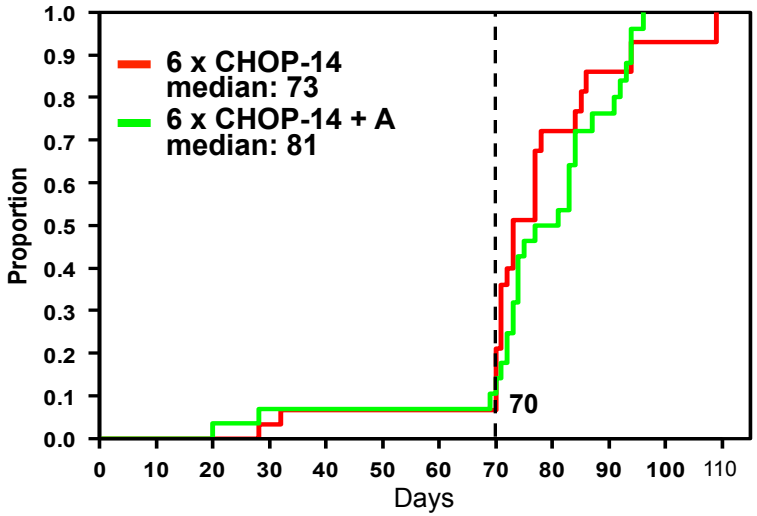


ACT-1

Feasibility



Schedule adherence



Haematological toxicity

CTC (grade ≥3)	% pts		
	6 x CHOP-14	6 x CHOP-14 + A	all
Leukocytopenia	24.0	69.0	48.1
Thrombocytopenia	20.0	12.0	15.6
Anemia	19.4	31.2	25.4

Infections

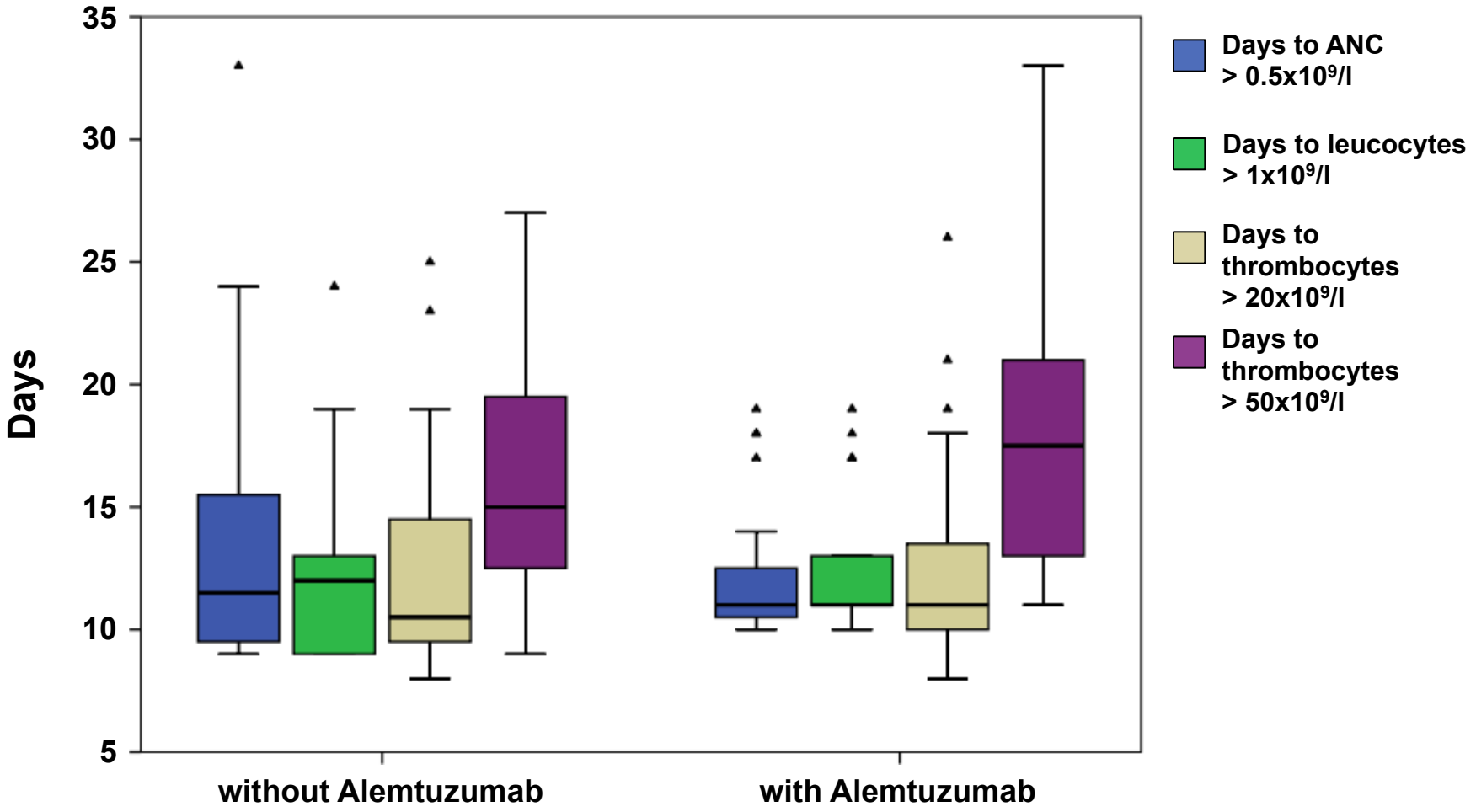
Infection type (grade ≥3)	6x CHOP-14	6x CHOP-14 + A
Bacterial	58.3%	38.1%
Fungal	16.7%	4.8%
Viral	25.0%	42.9%

SC harvest and recovery

Parameter	6x CHOP-14	6x CHOP-14 + A	p-value
	Median	Median	
N reinfused CD34+ cells (10^6)/ kg b.w.	4.0	3.6	0.2
Days to ANC >0.5x10^9/l	12	11	0.8
Days to PLTS >50x10^9/l	15	18	0.4

ACT-1 study

Hematopoietic Recovery



4 pat. with > 35 days (thrombocytes>50x10^9/l), 1 pat. with not recovered thrombocytes, 4 unknown values

NLG 03.05.12

ACT-1

Response rates and time-related end-points

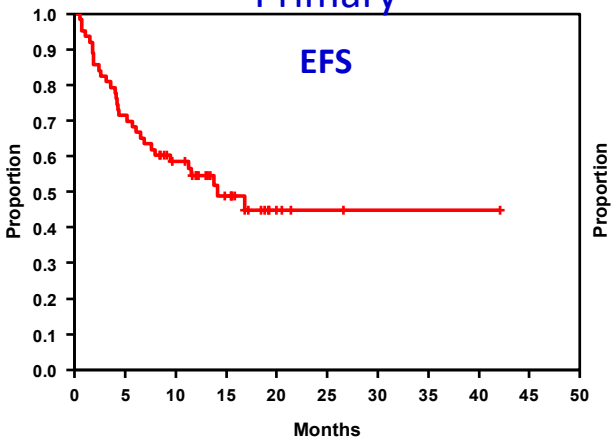
Results of the final analysis: July 2015

Response rates

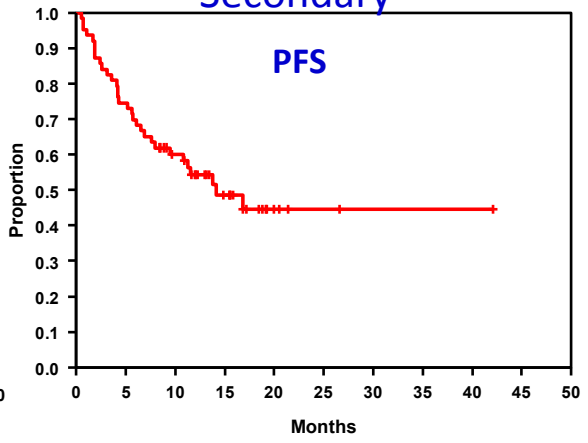
Response rates	N (%)
ORR	42 (67)
CR/CRu	38 (61)
PR	4 (6)
SD	3 (5)
PD	16 (25)
Not evaluable	2 (3)
Total	63 (100)

Time-related end-points (not arm-specific)

Primary



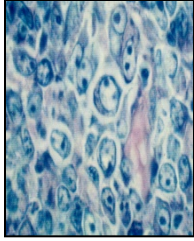
Secondary



End-point	1-yr (95% CI)
EFS	**55%** (42-67)
PFS	**54%** (42-67)
OS	**78%** (67-88)

d'Amore et al, ASH 2012 abs #57

2008 WHO classification of PTCL subtypes: **Comparison of NLG-T-01 and ACT**



NLG-T-01

Cutaneous	Extranodal	Nodal	Leukemic
MF	NK/TCL nasal type	PTCL-NOS	ATLL
Sézary syndrome	EATL	AITL	T-PLL
Primary cutaneous CD30+ T-cell disorders	HSTCL	ALCL(ALK−)	T-cell LGL leukaemia
Primary cutaneous ALCL	SPTCL	ALCL (ALK+)	
Primary cutaneous γδ TCL	Systemic EBV+ T-cell childhood LPD		
Primary cutaneous CD8+ aggressive epidermotropic	Hydroa vacciniforme-like		
Primary cutaneous CD4+ small/ medium			

ACT

Cutaneous	Extranodal	Nodal	Leukaemic
MF	NK/TCL nasal type	PTCL-NOS	ATLL
Sézary syndrome	EATL	AITL	T-PLL
Primary cutaneous CD30+ T-cell disorders	HSTCL	ALCL(ALK−)	T-cell LGL leukaemia
Primary cutaneous ALCL	SPTCL	ALCL (ALK+)	
Primary cutaneous γδ TCL	Systemic EBV+ T-cell childhood LPD		
Primary cutaneous CD8+ aggressive epidermotropic	Hydroa vacciniforme-like		
Primary cutaneous CD4+ small/ medium			

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

ACT-1 vs NLG-T-01

ORR and 1-year PFS/OS

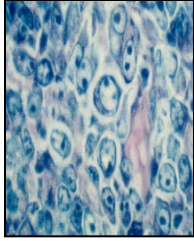
	ACT-1 (not arm-specific) **50% CHOP -14x6** **50% A-CHOP-14 x6** } **+ ASCT**	**NLG-T-01** (**without** ALCL) **CHOEP-14 x6 +ASCT**
ORR %	67	64
CR-CRu (%)	61	56
1-yr PFS (%)	54.4 (95% CI: 42;67)	57,5 (95% CI: 50; 65)
1-yr OS (%)	77.6 (95% CI: 67;88)	68,3 (95% CI: 61; 75)

The non arm-specific outcome of the ACT-1 trial is similar to the one of the NLG-T-01 trial for both ORR, CR and 1-yr PFS and OS

ACT-1 Interim Analysis

DSMB vote after evaluation of arm-specific results

Statement to investigators



- No indication to stop the trial due to futility, overt superiority or feasibility concerns.

- Results should not yet be unblinded to physicians or patients.

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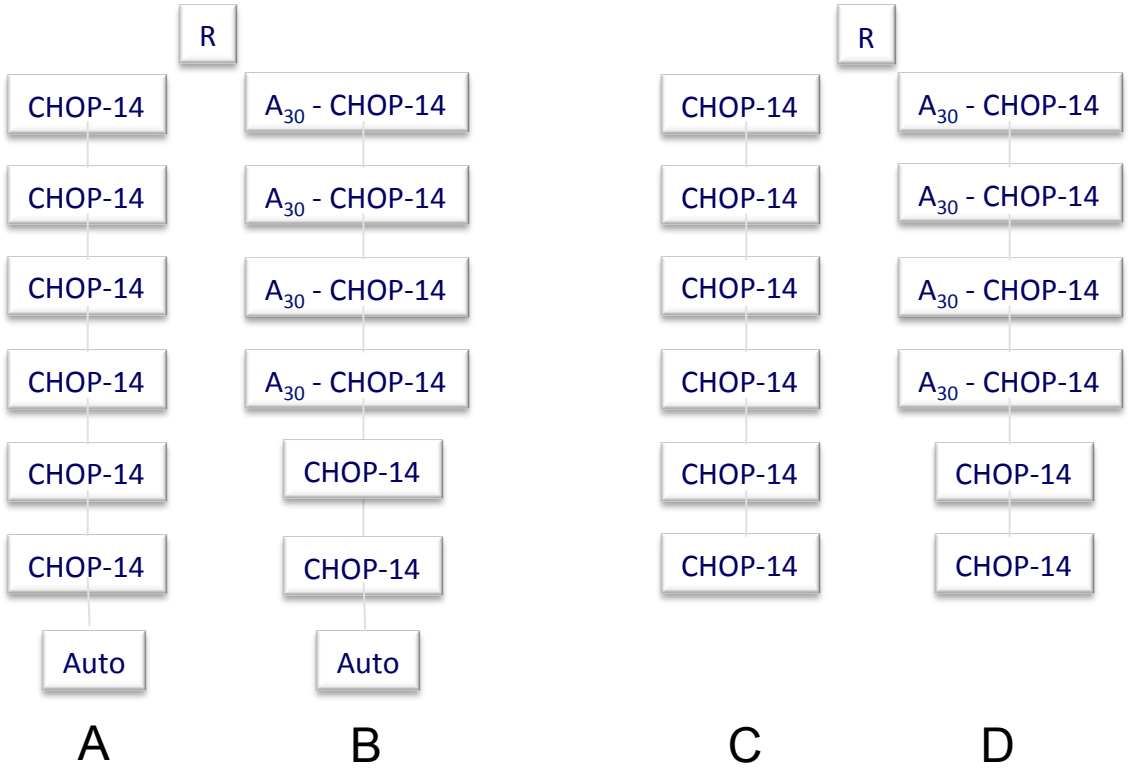
The ACT trial

Final analysis

GERMAN HIGH-GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP



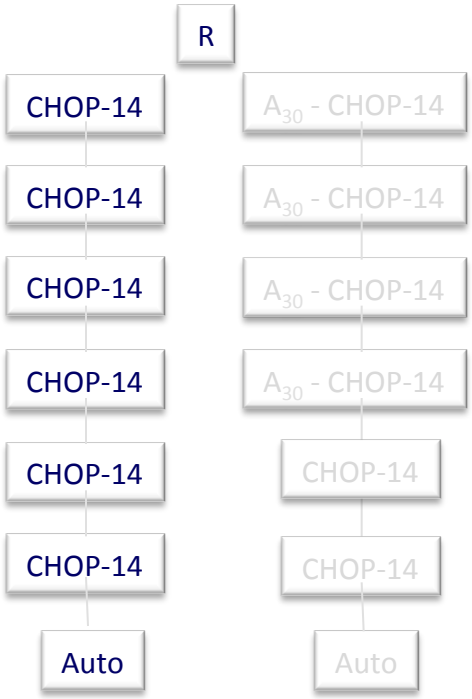
Analysis	Cohort	Parameter	CD52	Biology	PET
A vs B	ACT-1	EFS, PFS, OS	End-points according to CD52 status	Correlative biological studies	Correlative imaging studies
C vs D	ACT-2	EFS, PFS, OS			
A+C vs B+D	ACT-1+2	ORR			

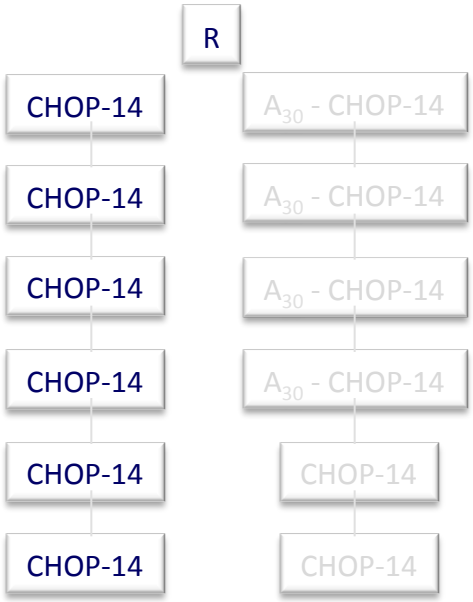
NORDIC LYMPHOMA GROUP

The ACT trial

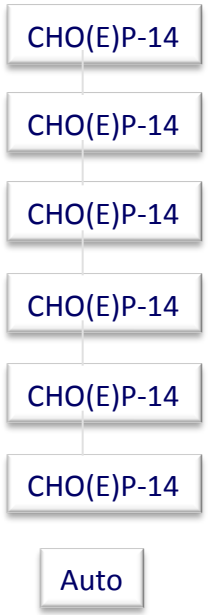
Joined NLG-T-01/ACT analysis with regard to ASCT

GERMAN HIGH-GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP





NLG-T-01 (>60yrs)



"Meta-analysis"	Cohort	Est. N
NLG-T-01	61-67 yrs (CHOP + HDT)	60-70
Std ACT-1	50-60 yrs (CHOP + HDT)	
Std ACT-2	61-70 yrs (CHOP)	60-70

PTCL restricted prospective trials with > 100 pts

Study	Design	Cohort size	Accrual status	Ref.
1st line treatment				
ACT	phase 3	250	Closed	ASH 2012
NLG-T-01	phase 2	160	Closed	JCO 2012
Relapsed/refractory				
NCI/Rmdps	phase 2	130	Closed	JCO 2012
PROPEL	phase 2	109	Closed	JCO 2011

ORRs of selected compounds given as **monotherapy** in systemic PTCL

+1st line phase III trials

Ref	Compound	ORR	Clin setting	Phase III trials 1st line
Enblad et al, Blood 2004	Alemtuzumab (CD52)	36%	Rel/ref	ACT-1 and -2
O'Mahony et al, CCR 2009	Siplizumab (CD2)	31%	Rel/ref	
O'Connor et al, ASCO 2013	Belinostat	26%	Rel/ref	BEL-CHOP
d'Amore et al, BJH 2010	Zanolimumab (CD4)	26%	Rel/ref	
O'Connor et al, JCO 2011	Pralatrexate	39%	Rel/ref	CHOP>>PRL vs obs
Coiffier et al, JCO 2012	Romidepsin	25%	Rel/ref	Ro-CHOP
Foss F et al, ASCO 2010	Denileukin Diftitox	40%	Rel/ref	
Pro et al, JCO 2012	Brentuximab vedotin (CD30)	86%	Rel/ref	CH[O]P+/-BV