Clinical trial results:
A randomised Phase III trial to evaluate the efficacy of chemoimmunotherapy with the monoclonal antibody Campath-1H (Alemtuzumab) given in combination with 2-weekly CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) versus 2-weekly CHOP alone in elderly patients with previously untreated systemic T- cell Lymphoma Short Title: A-CHOP-14 (elderly)

Summary

EudraCT number	2007-000821-23
Trial protocol	DE DK AT NL FR BE SE
Global end of trial date	31 March 2016
Results information	
Result version number	v1 (current)
This version publication date	30 November 2020
First version publication date	30 November 2020
Summary attachment (see zip file)	a Statement about non-SAEs (2007-000821-23, DSHNHL2006-1B_ACT-2_Statement_Final.pdf)

Trial information

Trial identification	
Sponsor protocol code	DSHNHL2006-1B/ACT-2
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Universitätsmedizin der Georg-August-Universität Göttingen
Sponsor organisation address	Robert-Koch-Straße 40, Göttingen, Germany, 37075
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Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2016
Global end of trial reached?	Yes
Global end of trial date	31 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Improvement of the efficacy of chemotherapy with CHOP-14 by the additional use of the CD52 monoclonal antibody alemtuzumab measured on the basis of Event-free Survival

Protection of trial subjects:

Before launching the trial, it was mentioned in the protocol that patients aged 71 - 80 years will be treated in a separate stratum because the tolerability of chemotherapy is poorer in patients of advanced age. Special safety criteria will apply to patients >70 years of age which will include an extensive toxicity analysis during the interim restaging.
In case of a clinically symptomatic CMV disease, both alemtuzumab and CHOP-therapy are stopped and an intravenous therapy with ganciclovir (10 mg/kg BW) initiated. The diagnosis of CMV-disease has to be made on clinical grounds, based on typical organ involvement (pneumonia, retinitis, enterocolitis) and detection of the virus in the blood (pp65, PCR) or in a biopsy of the organ involved.
Neutropenia is a common side-effect of ganciclovir and valganciclovir. Monitoring of neutrophil counts is an effective and sensitive safety parameter during treatment. Likewise, regular monitoring of creatinine clearance for dose adaptation of ganciclovir or valganciclovir in case of renal insufficiency is essential.
In cases of asymptomatic EBV reactivation detected by quantitative PCR, alemtuzumab is stopped. When peripheral blood leukocytes are above the threshold of 2.500/µl, CHOP chemotherapy should be applied without delay. Alemtuzumab treatment should be restarted as soon as EBV-monitoring is negative again, and the alemtuzumab doses omitted should be added to the treatment schedule in two-week intervals at the end of therapy to ensure the full cumulative alemtuzumab dose to be applied. In cases of symptomatic EBV disease, immunochemotherapy should be stopped, and the trial office be consulted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 October 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 23

Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 53
Worldwide total number of subjects	116
EEA total number of subjects	116

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	116
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruitment was planned for a period of 4 years. Based on the experience of significant patient accrual delay in the first year due to center activation, the recruitment was extended to 6 years in amendment 2 (26.04.2010). There was temporary trial hold in recruitment (waiting for the safety analysis results): 08.04.2010 - 02.06.2010

Pre-assignment

Screening details:

It was planned in the protocol to recruit 274 patients between 61 - 80 years old.
116 patients from 52 hospitals were eligible to paticipate in the study. 58 patients in each group. 40 patients from the Standard arm were recruited after the protocol amendment (28.04.2010), while 37 patients from the Experimental arm recruited after that amendment.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	standard arm

Arm description:

After the prephase treatment completion; patients recieve six cycles of chemotherapy (CT) (CHOP-14): cyclophosphamide (750 mg/m^2 - IV), doxorubicin (50 mg/m^2 - IV), vincristine (1,4 mg/ m^2, with maximum of 2 mg - IV) and prednisone ()100mg absolute p.o.) with G-CSF support. All CT started from day 1 & prednisolone from day 1 - 5.
CHOP-14 is to be repeated on day 15. Prerequisites for the continuation of this therapy are:
1. Patient has passed the leukocyte and platelet nadir.
2. Leukocyte count >2500/mm^3 (or neutrophil count >= 1x10^9/l) on day 15 after discontinuation of G-CSF &
3. Platelet count >80 000/mm^3/l) on day 15
4. No active infection
5. No serious organ or other toxicity.

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

as part of the CHOP-14 regimn:
Vincristine 1,4 mg/ m2, with a i.v.
maximum of 2 mg day 1

Investigational medicinal product name	prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As part of the CHOP-14 regimn:
Prednisone 100 mg (absolute) p.o. day 1 – 5.
Tapering of prednisone: Prompt discontinuation of prednisone can result in marked fatigue, particularly in elderly patients. We recommend a gradual reduction of the prednisone dose, with administration of 50 mg on day 6, 25 mg on day 7 and 12.5 mg on day 8.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

As part of the CHOP-14 regimn:
Doxorubicin 50 mg/m2 i.v. day 1

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

As part of the CHOP-14 regimn:
Cyclophosphamide 750 mg/m2 i.v. day 1

Arm title	Experimental arm

Arm description:

After the completion of the perphase treatment; patents recieve six cycles of chemotherapy (CHOP-14): cyclophosphamide, doxorubicin, vincristine and prednisone with G-CSF support. In addition to the standard arm, patientes recieve six doses of the monoclonal CD52 antibody alemtuzumab 30 mg s.c. on day 1 of CHOP each at 14-day intervals.
If the thresholds (leukocytes >2500/mm^3 and platelets >80000/mm^3) are still not reached after a 1-week postponement of therapy (by day 22 after CHOP-14), further treatment should be delayed, with checks of blood counts every 3 days, until these values are reached.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

as part of the CHOP-14 regimn:
Vincristine 1,4 mg/ m2, with a i.v.
maximum of 2 mg day 1

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As part of the CHOP-14 regimn:
Prednisone 100 mg (absolute) p.o. day 1 – 5
Tapering of prednisone: Prompt discontinuation of prednisone can result in marked fatigue, particularly in elderly patients. We recommend a gradual reduction of the prednisone dose, with administration of 50 mg on day 6, 25 mg on day 7 and 12.5 mg on day 8.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

As part of the CHOP-14 regimn:
Cyclophosphamide 750 mg/m2 i.v. day 1

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

As part of the CHOP-14 regimn:
Doxorubicin 50 mg/m2 i.v. day 1

Investigational medicinal product name	alemtuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

30 mg s.c. in the thighs on day 1 of CHOP. In course 1 of A-CHOP, the 1st dose of alemtuzumab may be split into 10 mg on day 1 & 20 mg on day 2 to minimize drug reactions. For s.c. admin. the content of an alemtuzumab ampoule is 30 mg per ml (taken up into a 2 ml syringe). One syringe filled with 1 ml alemtuzumab solution is injected into the left or right thigh, with care being taken to avoid repeated use of exactly the same injection site. At the start of treatment, local reactions can be experienced, such as mild swelling and reddening of the skin, sometimes painful; such reactions decrease during continued therapy. Prior to the initial administration, patients are to be given paracetamol 1g & 50-100 mg diphenhydramine hydrochloride or clemastine 2 mg 30 minutes prior to the s.c. injection. If the thresholds (leukocytes >2500/mm^3 and platelets >80 000/mm^3) are still not reached after 1-week postponement of therapy (by day 22 after CHOP-14) further treatment should be delayed.

Number of subjects in period 1	standard arm	Experimental arm
Started	58	58
Completed	55	54
Not completed	3	4
Consent withdrawn by subject	-	1
Protocol deviation	3	3

Baseline characteristics

Reporting groups	
Reporting group title	standard arm

Reporting group description:

After the prephase treatment completion; patients recieve six cycles of chemotherapy (CT) (CHOP-14): cyclophosphamide (750 mg/m^2 - IV), doxorubicin (50 mg/m^2 - IV), vincristine (1,4 mg/ m^2, with maximum of 2 mg - IV) and prednisone ()100mg absolute p.o.) with G-CSF support. All CT started from day 1 & prednisolone from day 1 - 5.
CHOP-14 is to be repeated on day 15. Prerequisites for the continuation of this therapy are:
1. Patient has passed the leukocyte and platelet nadir.
2. Leukocyte count >2500/mm^3 (or neutrophil count >= 1x10^9/l) on day 15 after discontinuation of G-CSF &
3. Platelet count >80 000/mm^3/l) on day 15
4. No active infection
5. No serious organ or other toxicity.

Reporting group title	Experimental arm

Reporting group description:

After the completion of the perphase treatment; patents recieve six cycles of chemotherapy (CHOP-14): cyclophosphamide, doxorubicin, vincristine and prednisone with G-CSF support. In addition to the standard arm, patientes recieve six doses of the monoclonal CD52 antibody alemtuzumab 30 mg s.c. on day 1 of CHOP each at 14-day intervals.
If the thresholds (leukocytes >2500/mm^3 and platelets >80000/mm^3) are still not reached after a 1-week postponement of therapy (by day 22 after CHOP-14), further treatment should be delayed, with checks of blood counts every 3 days, until these values are reached.

Reporting group values	standard arm	Experimental arm	Total
Number of subjects	58	58	116
Age categorical			
(<=70 years) versus (>70 years)			
Units: Subjects			
From 60 - 70 years	39	37	76
from 71 - 80 years	19	21	40
Age continuous			
Units: years			
median	69	69	
full range (min-max)	61 to 80	60 to 80	-
Gender categorical			
Units: Subjects			
Female	29	20	49
Male	29	38	67
Value of serum LDH			
Value for serum LDH (LDH ≤UNV vs. LDH>UNV)			
Units: Subjects			
LDH > UNV	29	27	56
LDH =< UNV	29	31	60
International prognostic IPI			
on the basis of the number of risk factors determined during examination, the patient will be allocated to one of the four risk groups using the "International Prognostic (IPI) as follows: 1. low risk group, 2. low-intermediate risk group, 3. intermediate-high risk group, 4. High-risk group.			
Units: Subjects			
IPI 0, 1	8	7	15
IPI 2	15	21	36
IPI 3	22	15	37

IPI 4, 5	13	15	28
primary pathology (T-cell) Units: Subjects			
T-cell lymphoma	3	5	8
Peripheral T-cell lymphoma, unspecified (PTCL-NOS)	22	23	45
Lennert's lymphoma	0	0	0
T-zone lymphoma	0	0	0
T-immunoblastic variant	1	0	1
Perifollicular variant	0	1	1
Follicular variant	0	0	0
T-cell lymphoma of the AIL type	23	25	48
Anaplastic large cell lymphoma ALK-neg	5	2	7
Extranodal NK/T-cell lymphoma, nasal type	1	0	1
Intestinal T/NK-cell lymphoma (± enteropathy)	3	2	5
Hepatosplenic T-cell lymphoma	0	0	0
Subcutaneous panniculitis-like PTCL	0	0	0
primary pathology 1			
With and without reference pathology (technical sufficient material)			
Units: Subjects			
With reference pathology	55	53	108
Without reference pathology	3	5	8
Reference pathology II (T-cell)			
Anaplastic large cell lymphoma ALK-neg was excluded after protocol amendment 2. PTCL, was unclassifiable with standard arm. gamma/delta T-cell lymphoma, was unclassifiable with the experimental arm			
Units: Subjects			
T-cell lymphoma	3	1	4
Peripheral T-cell lymphoma, unspecified (PTCL-NOS)	13	17	30
Lennert's lymphoma	0	0	0
T-zone lymphoma	0	3	3
T-immunoblastic variant	0	0	0
Perifollicular variant	2	1	3
Follicular variant	1	1	2
T-cell lymphoma of the AIL type	25	24	49
Anaplastic large cell lymphoma ALK-neg	4	3	7
Extranodal NK/T-cell lymphoma, nasal type	1	0	1
Intestinal T/NK-cell lymphoma (± enteropathy)	3	2	5
Hepatosplenic T-cell lymphoma	0	0	0
Subcutaneous panniculitis-like PTCL	0	0	0
other T-cell	1	1	2
no T-cell	2	0	2
without reference pathology	3	5	8
ECOG			
Performance status (ECOG = 0-1 vs. ECOG > 1)			
Units: Subjects			
ECOG = 0-1	47	46	93
ECOG > 1	11	12	23

Bulky disease Units: Subjects			
yes	6	5	11
no	52	53	105
stage of disease			
Stage (I, II vs. III, IV) stage of disease in accordance with the International Prognostic Index			
Units: Subjects			
I, II	10	10	20
III, IV	48	48	96
Number of extranodal involvements			
Number of extranodal involvements (0-1 vs. >1) in accordance with the International Prognostic Index.			
Units: Subjects			
0 - 1	45	46	91
>1	13	12	25

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

all randomized patients with study treatment
n=58 (6 x CHOP-14)
n=58 (6 x CHOP-14 + A)

Subject analysis set title	Per protocol set 1 (PPS1)
Subject analysis set type	Per protocol

Subject analysis set description:

all patients FAS with fulfilled inclusion criteria; patients randomized in arm B without any alemtuzumab therapy excluded.
n=55 (6 x CHOP-14)
n=54 (6 x CHOP-14 + A)

Subject analysis set title	Per protocol set 2 (PPS2)
Subject analysis set type	Per protocol

Subject analysis set description:

all patients PPS1 with confirmed reference pathology)
n=50 (6 x CHOP-14)
n=49 (6 x CHOP-14 + A)
(for 8 patients no reference pathology available, 2 patients with non confirmed T-cell pathology)

Reporting group values	Full analysis set (FAS)	Per protocol set 1 (PPS1)	Per protocol set 2 (PPS2)
Number of subjects	116	109	99
Age categorical			
(<=70 years) versus (>70 years)			
Units: Subjects			
From 60 - 70 years	76	72	65
from 71 - 80 years	40	37	34
Age continuous Units: years			
median	69	69	69
full range (min-max)	60 to 80	61 to 80	61 to 80
Gender categorical Units: Subjects			
Female	49	45	42

Male	67	64	57

Value of serum LDH			
Value for serum LDH (LDH ≤UNV vs. LDH>UNV)			
Units: Subjects			
LDH > UNV	56	52	48
LDH =< UNV	60	57	51
International prognostic IPI			
on the basis of the number of risk factors determined during examination, the patient will be allocated to one of the four risk groups using the "International Prognostic (IPI) as follows: 1. low risk group, 2. low-intermediate risk group, 3. intermediate-high risk group, 4. High-risk group.			
Units: Subjects			
IPI 0, 1	15	15	12
IPI 2	36	33	31
IPI 3	37	36	35
IPI 4, 5	28	25	21
primary pathology (T-cell) Units: Subjects			
T-cell lymphoma	8	8	7
Peripheral T-cell lymphoma, unspecified (PTCL-NOS)	45	41	36
Lennert`s lymphoma	0	0	0
T-zone lymphoma	0	0	0
T-immunoblastic variant	1	1	1
Perifollicular variant	1	1	1
Follicular variant	0	0	0
T-cell lymphoma of the AIL type	48	46	42
Anaplastic large cell lymphoma ALK-neg	7	7	7
Extranodal NK/T-cell lymphoma, nasal type	1	1	1
Intestinal T/NK-cell lymphoma (± enteropathy)	5	4	4
Hepatosplenic T-cell lymphoma	0	0	0
Subcutaneous panniculitis-like PTCL	0	0	0
primary pathology 1			
With and without reference pathology (technical sufficient material)			
Units: Subjects			
With reference pathology	108	101	91
Without reference pathology	8	8	8
Reference pathology II (T-cell)			
Anaplastic large cell lymphoma ALK-neg was excluded after protocol amendment 2. PTCL, was unclassifiable with standard arm. gamma/delta T-cell lymphoma, was unclassifiable with the experimental arm			
Units: Subjects			
T-cell lymphoma	4	4	4
Peripheral T-cell lymphoma, unspecified (PTCL-NOS)	30	26	26
Lennert`s lymphoma	0	0	0
T-zone lymphoma	3	3	3
T-immunoblastic variant	0	0	0
Perifollicular variant	3	3	3
Follicular variant	2	2	2

T-cell lymphoma of the AIL type	49	47	47
Anaplastic large cell lymphoma ALK-neg	7	7	7
Extranodal NK/T-cell lymphoma, nasal type	1	1	1
Intestinal T/NK-cell lymphoma (± enteropathy)	5	4	4
Hepatosplenic T-cell lymphoma	0	0	0
Subcutaneous panniculitis-like PTCL	0	0	0
other T-cell	2	2	2
no T-cell	2	2	0
without reference pathology	8	8	0
ECOG			
Performance status (ECOG = 0-1 vs. ECOG > 1)			
Units: Subjects			
ECOG = 0-1	93	87	80
ECOG > 1	23	22	19
Bulky disease Units: Subjects			
yes	11	9	8
no	105	100	91
stage of disease			
Stage (I, II vs. III, IV) stage of disease in accordance with the International Prognostic Index			
Units: Subjects			
I, II	20	20	17
III, IV	96	89	82
Number of extranodal involvements			
Number of extranodal involvements (0-1 vs. >1) in accordance with the International Prognostic Index.			
Units: Subjects			
0 - 1	91	87	80
>1	25	22	19

End points reporting groups

Reporting group title	standard arm

Reporting group description:

After the prephase treatment completion; patients recieve six cycles of chemotherapy (CT) (CHOP-14): cyclophosphamide (750 mg/m^2 - IV), doxorubicin (50 mg/m^2 - IV), vincristine (1,4 mg/ m^2, with maximum of 2 mg - IV) and prednisone ()100mg absolute p.o.) with G-CSF support. All CT started from day 1 & prednisolone from day 1 - 5.
CHOP-14 is to be repeated on day 15. Prerequisites for the continuation of this therapy are:
1. Patient has passed the leukocyte and platelet nadir.
2. Leukocyte count >2500/mm^3 (or neutrophil count >= 1x10^9/l) on day 15 after discontinuation of G-CSF &
3. Platelet count >80 000/mm^3/l) on day 15
4. No active infection
5. No serious organ or other toxicity.

Reporting group title	Experimental arm

Reporting group description:

After the completion of the perphase treatment; patents recieve six cycles of chemotherapy (CHOP-14): cyclophosphamide, doxorubicin, vincristine and prednisone with G-CSF support. In addition to the standard arm, patientes recieve six doses of the monoclonal CD52 antibody alemtuzumab 30 mg s.c. on day 1 of CHOP each at 14-day intervals.
If the thresholds (leukocytes >2500/mm^3 and platelets >80000/mm^3) are still not reached after a 1-week postponement of therapy (by day 22 after CHOP-14), further treatment should be delayed, with checks of blood counts every 3 days, until these values are reached.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

all randomized patients with study treatment
n=58 (6 x CHOP-14)
n=58 (6 x CHOP-14 + A)

Subject analysis set title	Per protocol set 1 (PPS1)
Subject analysis set type	Per protocol

Subject analysis set description:

all patients FAS with fulfilled inclusion criteria; patients randomized in arm B without any alemtuzumab therapy excluded.
n=55 (6 x CHOP-14)
n=54 (6 x CHOP-14 + A)

Subject analysis set title	Per protocol set 2 (PPS2)
Subject analysis set type	Per protocol

Subject analysis set description:

all patients PPS1 with confirmed reference pathology)
n=50 (6 x CHOP-14)
n=49 (6 x CHOP-14 + A)
(for 8 patients no reference pathology available, 2 patients with non confirmed T-cell pathology)

Primary: EFS (Event-Free Survival)

End point title	EFS (Event-Free Survival)

End point description:

It includes:
- PD
- PR (treated), NC, unknown at the end of study therapy
- Relapse after CR/CRu
- CR/ CRu and additional treatment
- Death of any cause

End point type	Primary

End point timeframe:

It was calculated as the time from randomization to the date of the first reported event. Patients with no reported event at the time of analysis were censored at the most recent assessment date. It was

End point values	standard arm	Experimental arm	Full analysis set (FAS)	Per protocol set 1 (PPS1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58[1]	58[2]	116[3]	109[4]
Units: percentage				
36 months	24	27	25	26
48 months	18	21	20	20
60 months	10	21	16	17

Notes:

[1] - 95% CI

[2] - 95% CI

[3] - 95% CI

[4] - 95% CI

End point values	Per protocol set 2 (PPS2)			
Subject group type	Subject analysis set			
Number of subjects analysed	99[5]			
Units: percentage				
36 months	26			
48 months	20			
60 months	16			

Notes:

[5] - 95% CI

Statistical analyses

Statistical analysis title	per protocol

Statistical analysis description:

T-cell, PPS1 (n=109) EFS according to treatment arm

Comparison groups	Experimental arm v standard arm v Per protocol set 1 (PPS1) v Full analysis set (FAS) v Per protocol set 2 (PPS2)
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143 [6]
Method	Regression, Logistic

Notes:

[6] - T-cell, EFS according to treatment arm:
P=0.248 FAS (n=116).
P=0.143 PPS1 (n=109).
P=0.386 PPS2 (n=99).

Secondary: PFS (Progression-Free Survival)

End point title	PFS (Progression-Free Survival)

End point description:

it includes:
- PD
- Progression after PR, NC (untreated), unknown (untreated) at the end of study

therapy
- treated NC, treated unknown at the end of study therapy
- Relapse after CR/CRu
- Death of any cause

End point type	Secondary

End point timeframe:

It was calculated as the time from randomization to the date of the first reported event. Patients with no reported event at the time of analysis were censored at the most recent assessment date. It was analyzed for all treatment arms at 3, 4, and 5 years

End point values	standard arm	Experimental arm	Full analysis set (FAS)	Per protocol set 1 (PPS1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58[7]	58[8]	116[9]	109[10]
Units: percentage				
36 months	29	28	28	30
48 months	24	22	23	24
60 months	13	22	18	18

Notes:

[7] - 95% CI

[8] - 95% CI

[9] - 95% CI

[10] - 95% CI

End point values	Per protocol set 2 (PPS2)			
Subject group type	Subject analysis set			
Number of subjects analysed	99[11]			
Units: percentage				
36 months	29			
48 months	23			
60 months	16			

Notes:

[11] - 95% CI

Statistical analyses

No statistical analyses for this end point

Secondary: OS (Overall Survival)

End point title	OS (Overall Survival)

End point description:

- Death of any cause

End point type	Secondary

End point timeframe:

It was calculated as the time from randomization to the date of the first reported event. Patients with no reported event at the time of analysis were censored at the most recent assessment date. It was analyzed for all treatment arms at 3, 4, and 5 years

End point values	standard arm	Experimental arm	Full analysis set (FAS)	Per protocol set 1 (PPS1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58[12]	58[13]	116[14]	109[15]
Units: percentage				
36 months	56	37	47	50
48 months	56	25	42	44
60 months	39	25	33	35

Notes:

[12] - 95% CI

[13] - 95% CI

[14] - 95% CI

[15] - 95% CI

End point values	Per protocol set 2 (PPS2)			
Subject group type	Subject analysis set			
Number of subjects analysed	99[16]			
Units: percentage				
36 months	47			
48 months	41			
60 months	31			

Notes:

[16] - 95% CI

Statistical analyses

No statistical analyses for this end point

Secondary: complete remission rate (CR rate)

End point title	complete remission rate (CR rate)

End point description:

End point type	Secondary

End point timeframe:

at the end of the therpay according to treatment's arm

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58[17]	58[18]	116[19]	
Units: percentage	43	60	52	

Notes:

[17] - 25 / 58 (43%)
95% CI: 30%; 57%

[18] - 35 / 58 (60%)
95% CI: 47%; 73%
[19] - 60 / 116 (52%)
95% CI: 42%; 61%

Statistical analyses

No statistical analyses for this end point

Secondary: Number of given chemotherapy cycles

End point title	Number of given chemotherapy cycles

End point description:

End point type	Secondary

End point timeframe:

at the end of the therpay according to treatment's arm

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	58	116	
Units: cycles				
1 cycle	5	2	7	
2 cycles	3	0	3	
3 cycles	0	4	4	
4 cycles	2	4	6	
5 cycles	2	5	7	
6 cycles	46	43	89	

Attachments (see zip file)	Duration of chemotherapy cycles/duration of CT cycles.png

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response (OR)

End point title	Overall response (OR)

End point description:

Number of complete remissions, unconfirmed complete remissions and partial remissions (including CR/Cru, PR in patients after early discontinuation) divided by the number of patients

End point type	Secondary

End point timeframe:

at the end of the therpay according to treatment's arm

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58[20]	58[21]	116[22]	
Units: percentage	60	72	66	

Notes:

[20] - 35/58 (60%)
95% CI: (47%; 73%)
[21] - 42/58 (72%)
95% CI: (59%; 83%)
[22] - 77/116 (66%)
95% CI: (57%; 75%)

Statistical analyses

No statistical analyses for this end point

Secondary: Leukocytopenia

End point title	Leukocytopenia

End point description:

to follow the Possible side effects of the protocol-conformable treatment. The results represent the percentage of cycles per each treatment arm that affected with Leukocytopenia.
CTC results are withen nadir interval: day 8 - 10

End point type	Secondary

End point timeframe:

over all treatment cycles

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	58	116	
Units: percentage				
CTC= 0 (>=4*10^3/mm^3)	19	11	14	
CTC=1 (<4*10^3/mm^3)	5	9	7	
CTC=2 (<3*10^3/mm^3)	11	9	10	
CTC=3 (<2*10^3/mm^3)	20	20	20	
CTC=4 (<1*10^3/mm^3)	44	49	49	

Statistical analyses

No statistical analyses for this end point

Secondary: Thrombocytopenia

End point title	Thrombocytopenia

End point description:

The results represent the percentage of cycles per each treatment arm that affected with Thrombocytopenia.
CTC results are withen nadir interval: day 8 - 10

End point type	Secondary

End point timeframe:

over all treatment cycles

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	58	116	
Units: percentage				
CTC= 0 (>=4*10^3/mm^3)	62	55	58	
CTC=1 (<4*10^3/mm^3)	14	23	19	
CTC=2 (<3*10^3/mm^3)	14	10	11	
CTC=3 (<2*10^3/mm^3)	4	11	8	
CTC=4 (<1*10^3/mm^3)	5	2	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Anaemia

End point title	Anaemia

End point description:

The results represent the percentage of cycles per each treatment arm that affected with anaemia.

End point type	Secondary

End point timeframe:

over all treatment cycles

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	58	116	
Units: percentage				
CTC= 0 (>=4*10^3/mm^3)	34	32	33	
CTC=1 (<4*10^3/mm^3)	22	22	22	
CTC=2 (<3*10^3/mm^3)	40	39	39	
CTC=3 (<2*10^3/mm^3)	4	8	6	
CTC=4 (<1*10^3/mm^3)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Haematological toxicity per patient

End point title	Haematological toxicity per patient

End point description:

The results represent the percentage of patients per each treatment arm.
the number of laboratory values within nadir interval for Thrombocytopenia (CTC) is small!

End point type	Secondary

End point timeframe:

over all treatment cycles per patient

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	58	116	
Units: percentage				
Leukocytopenia CTC= 4	54	70	63	
Thrombocytopenia CTC= 3, 4	13	19	17	
Anaemia CTC= 3, 4	19	29	24	

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events during chemotherapy per patient

End point title	Adverse events during chemotherapy per patient

End point description:

The results represent the number of cycles with CTC grade 3 - 5 / number of documented cycles

End point type	Secondary

End point timeframe:

during chemotherapy over all cycles per patient

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	58	116	
Units: percentage				
Nausea	5	3	4	
Vomiting	3	2	3	
Diarrhoea	3	9	6	
Constipation	0	3	2	
Mucositis/ stomatitis	0	5	3	
Cardiac arrhythmia	0	2	1	

Cardiac general	2	7	4	
Haemorrhage/ bleeding	2	2	2	
Renal/ genitourinary	9	5	7	
Neuropathy sensory	70	9	8	
Mood alteration	0	2	1	
Allergic reaction/ hypersensitivity	0	2	1	
Infection	21	40	30	

Statistical analyses

No statistical analyses for this end point

Secondary: Types of infections

End point title	Types of infections
End point description: (grade 3-5). several types of infections can be specified for one infection	
End point type	Secondary
End point timeframe: during chemotherapy	

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58[23]	58[24]	116[25]	
Units: percentage				
Bacterial	59	32	40	
Fungal	6	10	9	
Viral	0	50	34	

Notes:

[23] - Total no. of infection (n=17)

[24] - total no. of infection (n=38)

[25] - total no. of infection (n=55)

Statistical analyses

No statistical analyses for this end point

Secondary: Therapeutic intervention during chemotherapy / Cycles

End point title	Therapeutic intervention during chemotherapy / Cycles
End point description: results represent the percentage of cycles	
End point type	Secondary
End point timeframe: over all chemotherapy cycles	

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58[26]	58[27]	116[28]	
Units: percentage				
Red blood cell transfusions	14	21	17	
Platelet transfusions	1	2	2	

Notes:

[26] - n= 300

[27] - n=313

[28] - n=613

Statistical analyses

No statistical analyses for this end point

Secondary: Therapeutic intervention during chemotherapy / Patients

End point title	Therapeutic intervention during chemotherapy / Patients

End point description:

the results represent the percentage of patients

End point type	Secondary

End point timeframe:

over all chemotherapy cycles

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	58	116	
Units: percentage				
Red blood cell transfusions	40	62	51	
Platelet transfusions	7	10	9	

Statistical analyses

No statistical analyses for this end point

Secondary: cause of death 1

End point title	cause of death 1

End point description:

Several causes of death can be specified for one patient. The result of (other) is defined as 1 pat. accident, 1 pat. hemiparesis.
Every case of death occurring within the first 2 months after final restaging is considered treatment related, if there is no clear evidence of disease related death. In cases of death later than 2 months after final restaging, the treating physician has to decide whether it was caused by therapy (primary or salvage), by lymphoma (or both) or by an intercurrent disease. If in doubt death should be reported as

therapy related. Every case of death to has to be reported to the trial office within one working day by fax if classified as an SAE.

End point type	Secondary

End point timeframe:

until completion pf the study (treatment and follow-up period)

End point values	standard arm	Experimental arm	Full analysis set (FAS)	Per protocol set 1 (PPS1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58[29]	58[30]	116	109
Units: percentage				
Tumour related	70	62	65	62
Therapy related	10	15	13	13
Concomitant diseases	10	13	12	11
Secondary neoplasia	7	8	7	8
Other	7	0	3	3
Unknown	3	8	6	6

Notes:

[29] - intent-to-treat principle

[30] - intent-to-treat principle

End point values	Per protocol set 2 (PPS2)			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: percentage				
Tumour related	64			
Therapy related	12			
Concomitant diseases	10			
Secondary neoplasia	8			
Other	3			
Unknown	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Cause of death 2

End point title	Cause of death 2

End point description:

these results show the patients who faced one main cause of death (single).
The results of (other) are defined as 1 pat. accident, 1 pat. hemiparesis

End point type	Secondary

End point timeframe:

treatment and follow-up period

End point values	standard arm	Experimental arm	Full analysis set (FAS)	Per protocol set 1 (PPS1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58	58	116	109
Units: no. of patients				
only tumour	19	22	41	37
Only therapy	2	5	7	7
Concomitant disease	2	4	6	6
Secondary neoplasia	2	3	5	5
Other	2	0	2	2
Unknown	1	3	4	4

End point values	Per protocol set 2 (PPS2)			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: no. of patients				
only tumour	37			
Only therapy	6			
Concomitant disease	5			
Secondary neoplasia	5			
Other	2			
Unknown	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Prephase treatment

End point title	Prephase treatment

End point description:

All patients in both arms were to receive prephase treatment prior to initiation of therapy. The purpose of the prephase treatment is to prevent tumour lysis syndrome in patients with extensive tumours, to improve the performance status of the patient and to reduce the toxicity of the first chemotherapy cycle. This treatment consists of:
Vincristine: 1 mg i.v. day -6 (single dose), where day 1 = day 1 of CHOP therapy.
Prednisolone: 100 mg p.o. day -6 through day zero, where day 1 = day 1 of CHOP therapy.
The main therapy phase (CHOP and CHOP + alemtuzumab, respectively), must not be initiated before randomisation, and must directly follow the prephase treatment.

End point type	Secondary

End point timeframe:

a 1-week course, preceding the main phase therapy of CHOP-14 with / without alemtuzumab.

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	58	116	
Units: no. of patients	54	55	109	

Statistical analyses

No statistical analyses for this end point

Secondary: Vincristine as prephase treatment

End point title	Vincristine as prephase treatment

End point description:

Vincristine: 1 mg i.v. day -6 (single dose), where day 1 = day 1 of CHOP therapy.

End point type	Secondary

End point timeframe:

a 1-week course, preceding the main phase therapy of CHOP-14 with / without alemtuzumab.

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54	55	109	
Units: percentage				
0 mg given	9	16	13	
1 mg given	85	76	81	
2 mg given	6	7	7	

Statistical analyses

No statistical analyses for this end point

Secondary: prednisolone as prephase treatment

End point title	prednisolone as prephase treatment

End point description:

Prednisolone: 100 mg p.o. day -6 through day zero, where day 1 = day 1 of CHOP therapy.

End point type	Secondary

End point timeframe:

a 1-week course, preceding the main phase therapy of CHOP-14 with / without alemtuzumab.

End point values	standard arm	Experimental arm	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54	55	109	
Units: mg				
median (full range (min-max))	700 (300 to 1300)	700 (280 to 1400)	700 (280 to 1400)	

Statistical analyses

No statistical analyses for this end point

Post-hoc: EFS per gender (Female)

End point title	EFS per gender (Female)

End point description:

End point type	Post-hoc

End point timeframe:

It was calculated as the time from randomization to the date of the first reported event. Patients with no reported event at the time of analysis were censored at the most recent assessment date. It was analyzed for all treatment arms at 3, 4, and 5 years

End point values	standard arm	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	20		
Units: percentage				
3 years	31	49		
4 years	31	49		
5 years	12	49		

Statistical analyses

Statistical analysis title	full set
Comparison groups	standard arm v Experimental arm
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.095
Method	Regression, Cox

Post-hoc: EFS per gender (male)

End point title	EFS per gender (male)

End point description:

End point type	Post-hoc

End point timeframe:

It was calculated as the time from randomization to the date of the first reported event. Patients with no reported event at the time of analysis were censored at the most recent assessment date. It was analyzed for all treatment arms at 3, 4, and 5 years

End point values	standard arm	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	35		
Units: percentage				
3 years	17	15		
4 years	6	8		
5 years	0	0		

Statistical analyses

Statistical analysis title	full set
Comparison groups	standard arm v Experimental arm
Number of subjects included in analysis	67
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.301
Method	Regression, Cox

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reported adverse events represent the period of the chemotherapy over all cycles and the first 3 months until first follow-up.

Adverse event reporting additional description:

it is based on a full-set analysis (n=116)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	standard arm

Reporting group description:

After the prephase treatment completion; patients recieve six cycles of chemotherapy (CT) (CHOP-14): cyclophosphamide (750 mg/m^2 - IV), doxorubicin (50 mg/m^2 - IV), vincristine (1,4 mg/ m^2, with maximum of 2 mg - IV) and prednisone ()100mg absolute p.o.) with G-CSF support. All CT started from day 1 & prednisolone from day 1 - 5.
CHOP-14 is to be repeated on day 15. Prerequisites for the continuation of this therapy are:
1. Patient has passed the leukocyte and platelet nadir.
2. Leukocyte count >2500/mm^3 (or neutrophil count >= 1x10^9/l) on day 15 after discontinuation of G-CSF &
3. Platelet count >80 000/mm^3/l) on day 15
4. No active infection
5. No serious organ or other toxicity.

Reporting group title	Experimental arm

Reporting group description:

After the completion of the perphase treatment; patients recieve six cycles of chemotherapy (CHOP-14): cyclophosphamide, doxorubicin, vincristine and prednisone with G-CSF support. In addition to the standard arm, patientes recieve six doses of the monoclonal CD52 antibody alemtuzumab 30 mg s.c. on day 1 of CHOP each at 14-day intervals.
If the thresholds (leukocytes >2500/mm^3 and platelets >80000/mm^3) are still not reached after a 1-week postponement of therapy (by day 22 after CHOP-14), further treatment should be delayed, with checks of blood counts every 3 days, until these values are reached.

Serious adverse events	standard arm	Experimental arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 58 (46.55%)	38 / 58 (65.52%)	
number of deaths (all causes)	30	39	
number of deaths resulting from adverse events	6	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			

subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory anaemia with an excess of blast			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Fatigue			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 58 (5.17%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 58 (1.72%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 58 (8.62%)	6 / 58 (10.34%)	
occurrences causally related to treatment / all	7 / 7	10 / 10	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 58 (0.00%)	3 / 58 (5.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ataxia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 58 (1.72%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 58 (1.72%)	3 / 58 (5.17%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	7 / 58 (12.07%)	5 / 58 (8.62%)	
occurrences causally related to treatment / all	9 / 9	6 / 6	
deaths causally related to treatment / all	1 / 1	1 / 1	
Histiocytosis haematophagic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 58 (5.17%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland disorder			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 58 (1.72%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BK virus infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 58 (0.00%)	7 / 58 (12.07%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 58 (1.72%)	3 / 58 (5.17%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 58 (5.17%)	3 / 58 (5.17%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia fungal			
subjects affected / exposed	1 / 58 (1.72%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary sepsis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	standard arm	Experimental arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 58 (51.72%)	52 / 58 (89.66%)	
Cardiac disorders			
Arrhythmia	Additional description: Cardiac arrhythmia		
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
cardiac general			
subjects affected / exposed	1 / 58 (1.72%)	4 / 58 (6.90%)	
occurrences (all)	1	4	
Nervous system disorders			
neuropathy sensory			
subjects affected / exposed	4 / 58 (6.90%)	5 / 58 (8.62%)	
occurrences (all)	5	6	
Blood and lymphatic system disorders			
Haemorrhage	Additional description: Haemorrhage/ bleeding		
subjects affected / exposed	1 / 58 (1.72%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
Immune system disorders			
allergic reaction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 58 (3.45%)	1 / 58 (1.72%)	
occurrences (all)	6	1	
Nausea			
subjects affected / exposed	3 / 58 (5.17%)	2 / 58 (3.45%)	
occurrences (all)	7	2	
Diarrhoea			
subjects affected / exposed	2 / 58 (3.45%)	5 / 58 (8.62%)	
occurrences (all)	2	7	
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	
Stomatitis	Additional description: Mucositis/ stomatitis		

subjects affected / exposed	0 / 58 (0.00%)	3 / 58 (5.17%)	
occurrences (all)	0	5	
Renal and urinary disorders			
genitourinary	Additional description: Renal/ genitourinary		
subjects affected / exposed	5 / 58 (8.62%)	3 / 58 (5.17%)	
occurrences (all)	5	3	
Psychiatric disorders			
Mood alteration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
Infections and infestations			
Infection	Additional description: p-value = 0.026		
subjects affected / exposed	12 / 58 (20.69%)	23 / 58 (39.66%)	
occurrences (all)	17	38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2010	Based on the experiences in in the ACT-1 trial, in which an increased rate of opportunistic infections had been observed, an extraordinary safety analysis was performed as soon as the 30th patient had completed the full treatment course in the ACT-2 trial. This safety analysis was discussed with the DSMB and the trial steering group, leading to a temporary hold of recruitment communicated to the trial centers on 08 April 2010. An amendment reducing the dose of alemtuzumab was prepared and submitted to EC as well as the competent authorities. As of 26 May 2010 and 02 June 2010, respectively the German national authority (PEI) and the lead EC in Goettingen approved the amendment of the trial, with the exclusion of anaplastic large cell from this trial and the reduction of alemtuzumab to 30 mg per cycle in the first 4 cycles of the experimental A-CHOP arm of the trial. There was another previous amendment to the protocol on January 26, 2009. As per initial protocol of the trial, recruitment into the trial was planned for a period of 4 years. Based on the experience of significant patient accrual delay in the first year of the trial due to center activation, the time period for recruitment was extended to 6 years in the 2nd amendment, as 26 April 2010.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 April 2010	emporary trial hold: 08 April 2010 through 02 June 2010: Based on the experiences in in the ACT-1 trial, in which an increased rate of opportunistic infections had been observed, an extraordinary safety analysis was performed as soon as the 30th patient had completed the full treatment course in the ACT-2 trial. This safety analysis was discussed with the DSMB and the trial steering group, leading to a temporary hold of recruitment communicated to the trial centers on 08 April 2010.	02 June 2010

Notes:

Limitations and caveats

None reported