German High-Grade
Non-Hodgkin's Lymphoma
Study Group DSHNHL

NORDIC LYMPHOMA GROUP

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

DSHNHL 2006-1B /ACT-2

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		page
0	**Table of contents**	**2**
1	**Persons responsible for DSHNHL 2006-1B/ACT2**	**6**
1.1	Board of the DSHNHL	6
1.2	Board of the NLG	6
1.3	Scientific Advisory Board for DSHNHL 2006-1B/ACT2	6
1.4	Data and Safety Monitoring Committee (DSMC)	6
1.5	Protocol Steering Committee of DSHNHL 2006-1B/ACT-2	7
2	**Protocol DSHNHL 2006-1B/ACT-2**	**8**
2.1	General information	8
2.1.1	Persons and institutions responsible for DSHNHL 2006-1B/ACT-2	8
2.1.2	GCP Conformity	11
2.1.2.1	Acknowledgment of the Principal Investigator	11
2.1.3	Trial Synopsis	12
2.1.4	Flowchart of the Study	14
2.1.5	Treatment plan, obligatory tests and examinations	15
2.1.6	Physician`s checklist	16
2.2	Aims of the study	17
2.2.1	Primary aim of the study	17
2.2.2	Secondary aims of the study	17
2.3	Rationale of DSHNHL 2006-1B/ACT-2	18
2.3.1	Current state of the art and issue	18
2.3.2	Summary of the rationale	20
2.4	Trial protocol	21
2.4.1	Trial design	21
2.4.2	Participating institutions and number of patients	21
2.4.3	Duration of the study: treatment phase and follow-up observation	21
2.4.4	Study discontinuation	21
2.4.4.1	Discontinuation of the study for individual patients	21
2.4.4.2	Early termination of the study or closing of individual treatment arms	22
2.4.4.3	Withdrawal of trial centers	22
2.5	Eligibility	23
2.5.1	Inclusion criteria	23
2.5.2	Exclusion criteria	24
2.5.3	Gender considerations	24
2.6	Biometrical aspects of the study	25
2.6.1	Randomisation algorithm	25
2.6.2	Study end points	26

2.6.2.1	Primary end point	26
2.6.2.2	Secondary end points	26
2.6.2.2.1	Secondary end points for efficacy	26
2.6.2.2.2	Secondary end points for safety	27
2.6.2.2.3	Secondary end points for adherence to protocol	27
2.6.3	Statistical hypotheses and sample size calculation	27
2.6.4	Statistical methods	28
2.6.4.1	Definition of the evaluable study population	28
2.6.4.2	Analysis population	28
2.6.4.3	Planned methods for analysis	29
2.6.4.3.1	Primary end point	29
2.6.4.3.2	Secondary end points	30
2.6.5	Interim analyses and criteria for early discontinuation of the study	30
2.6.6	Final analysis	30
2.6.7	Biometrical report	31
2.7	Study procedures for individual patients	32
2.7.1	Staging examination	32
2.7.2	Evaluation of disease stage/risk group allocation	33
2.7.3	Patient information	33
2.7.4	Notification of patient inclusion in the study	34
2.7.5	Inclusion of patients in the study	38
2.7.6	Treatment implementation according to the protocol	39
2.7.6.1	Prephase treatment	39
2.7.6.2	CHOP-14	40
2.7.6.3	Administration of Alemtuzumab	40
2.7.6.4	Dose reduction	41
2.7.6.5	Suspected CNS involvement	42
2.7.6.6	Intrathecal therapy in CNS involvement	42
2.7.6.7	G-CSF therapy	42
2.7.6.8	Possible side effects of the protocol-conformable treatment	43
2.7.6.9	Supportive measures	43
2.7.6.10	Lab monitoring during therapy	44
2.7.6.11	Radiotherapy	45
3	**Procedures and Documentation**	**46**
3.1	Restaging and follow-up procedures	46
3.1.1	Interim Restaging	46
3.1.2	Toxicity analysis during interim restaging	46
3.1.3	Restaging on completion of chemotherapy	46
3.1.4	Restaging in case of early discontinuation of therapy	47
3.1.5	Follow-up examinations	47
3.2	Documentation of end-points	48
3.2.1	Complete remission (CR)	48
3.2.2	Complete remission with remaining uncertainty	48
3.2.3	Partial remission	48
3.2.4	No change (NC)	49
3.2.5	Progression (PRO)	49
3.2.6	Relapse	49
3.2.7	Evaluation of unmeasurable tumour or bone involvement	50

3.2.8	Treatment related mortality	50
4	**Evaluation of safety / Adverse events**	**51**
4.1	Evaluation of safety	51
4.2	Adverse events (AEs)	51
4.2.1	Definitions of expected/unexpected adverse events	51
4.2.2	Documentation of expected/unexspected adverse events	52
4.3	Serious adverse events (SAEs)	52
4.3.1	Definitions of SAEs, SARs and SUSARs	52
4.3.2	Documentation of serious adverse events	53
5	**Documentation and Monitoring**	**55**
5.1	Structure of the documentation dossier	55
5.2	Processing of completed documentations forms	57
5.3	On-site monitoring	57
5.4	SAE, SAR and SUSAR reporting	58
5.4.1	AE reporting	58
5.4.2	SAE reporting	58
5.4.3	SUSAR reporting	59
5.4.4	Annual Safety Reports	60
5.4.5	Information of Ethic Committees	60
6	**Reference evaluation**	**61**
6.1	Reference Pathology Report	61
7	**Accompanying scientific projects**	**62**
8	**Ethical aspects**	**64**
9	**Administrative aspects**	**65**
9.1	Data processing and archiving of data	65
9.2	Subsequent amendments to the protocol	65
9.3	Finances and insurance	65
9.4	Publication agreements	65
10	**References**	**66**

11 Appendix 71

11.1 Definitions – stage and extranodal involvement 71

11.2 Definition of bulky disease 72

11.3 Definitions – performance status according to Karnofsky index 73

11.4 Definitions – performance status according to ECOG scale 73

11.5 Comparison of ECOG and Karnofsky indices 73

11.6 International Prognostic Index 73

11.7 Common toxicity criteria (CTC) 74

1 Persons responsible for DSHNHL 2006-1B/ACT-2

1.1 Board of the DSHNHL

Prof. Dr. N. Schmitz, Hamburg
Prof. Dr. M. Pfreundschuh, Homburg / Saar
Prof. Dr. M. Löffler, Leipzig
Prof. Dr. L. Trümper, Göttingen

1.2 Board of the NLG

Dr. Mikael Eriksson, Lund
Dr. Harald Holte, Oslo
Dr. Helge Haarstad, Trondheim
Dr. Christian Geisler, Copenhagen
Dr. Tuula Lehtinen, Tampere
Dr. Esa Jantunen, Kuopio
Dr. Eva Kimby, Stockholm
Dr. Francesco d'Amore, Århus

1.3 Scientific Advisory Board for DSNHL 2006-1B/ACT-2

The Scientific Advisory Board decides on all scientific projects using study materials.

Members are:

Prof. Dr. L. Trümper, Göttingen (Study Coordinator)
Prof. Dr. Francesco d'Amore (Study Coordinator)
PD Dr. T. Ruediger, Karlsruhe (Pathologist)
Prof. Dr. A. Rosenwald, Würzburg (Pathologist)
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The DSMC receives information on the progress of the study at annual intervals and has the following responsibilities: review of study progress

Review of safety aspects including serious adverse events
Review of the results of interim evaluations
Review of protocol adherence. Recommendations concerning the continuation, modification or early discontinuation of the study to the Study Management

1.5 Protocol Steering Committee of DSHNHL 2006-1B/ACT-2

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(1) Representative of the Writing and DSHNHL/NLG Steering Committee
(2) Representatives of the Reference Pathology
(3) International Principal Investigators & Participants in ACT-2/2006 1B

2.1 General Information

2.1.1 Persons and institutions responsible for DSHNHL 2006-1B/ACT-2

Sponsor	Faculty of Medicine at the Georg August University, Göttingen, Germany, Stiftung Öffentlichen Rechts Represented by Prof. Dr. Cornelius Frömmel, Dekan of the Faculty, Chairman of the Board
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2.1.2 GCP Conformity

In January 1997, the International Conference on Harmonization adopted the "Note for Guidance on Good Clinical Practice" (ICH-GCP). The DSHNHL studies are planned, implemented and evaluated in accordance with the GCP principles, taking into account the available capacities. All studies are based on the recommendations of the Declaration of Helsinki.

Signature of the Principal Investigator and Biometry:

2.1.2.1 Acknowledgement of the Principal Investigator

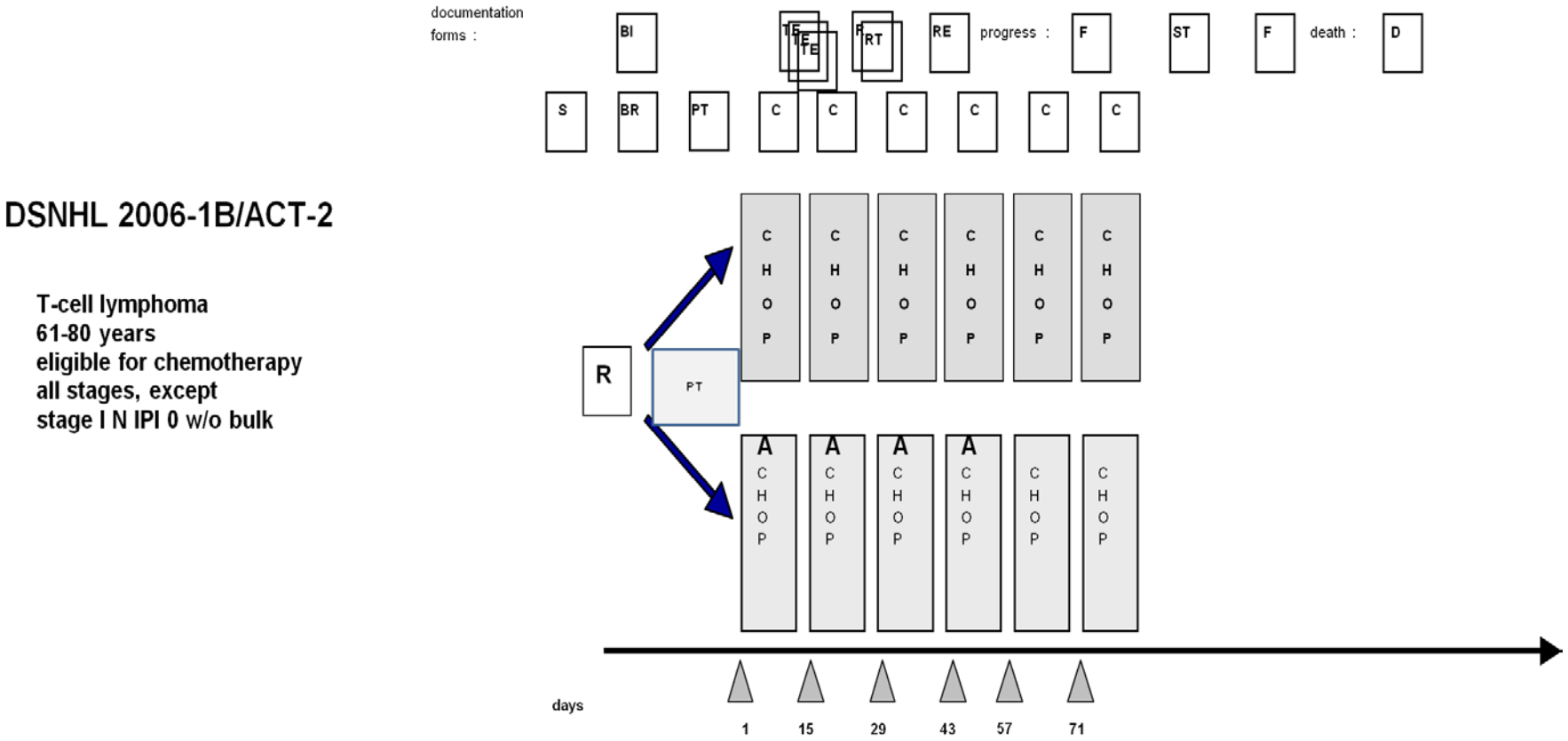
Hereby I declare that I have read, understood and agreed to the trial protocol.

2.1.3 Trial Synopsis

Principal Investigator	Prof. Dr. L. Trümper (PI acc. to AMG) Department of Haematology/Oncology University Hospital of the Georg-August University Robert-Koch-Str. 40 D- 37075 Göttingen e-mail: lorenz.truemper@med.uni-goettingen.de
European Intergroup Principal Investigator	Prof. Dr. F. D`Amore (European Coordinating PI) Department of Hematology Aarhus University Hospital DK-8000Aarhus C e-mail: frandamo@rm.dk
Short title of the study	CHOP-14 with or without the Monoclonal Anti-CD52 Antibody Alemtuzumab in Elderly Patients DSHNHL 2006-1B / ACT-2
Indication	Primary therapy of patients with Alk-negative T-NHL in patients aged 61 - 80 years
Objectives	Primary objective: 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. Comparison of +/- alemtuzumab addition concerning: further endpoints of efficacy, short term and long term side effects, adherence to protocol and withdrawal from therapy
Interventions	All patients will receive prephase treatment prior to initiation of therapy. Patients will be randomly assigned to receive six cycles chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP-14) with G-CSF support with or without four doses of the monoclonal CD52 antibody alemtuzumab 30 mg s.c. on day 1 of courses 1 through 4 of CHOP at 14-day intervals.
Key inclusion and exclusion criteria	Inclusions: patients with untreated peripheral T-cell lymphoma age 61-80 without major accompanying disorders Exclusions: cutaneous T-cell lymphoma, anaplastic large cell T-cell lymphomas
Outcomes	Primary endpoint: event-free survival (EFS) at 3 years Secondary endpoints: CR and OR rate, rate of primary progression, relapse rate, treatment-related deaths, overall survival, progression free survival, tumour control, disease-free survival, safety, protocol adherence, immune reconstitution after therapy
Study design	open-label, multicentre, prospective, randomised phase III study (treatment optimisation protocol)
Statistical analysis	Randomization at diagnosis with strata: study center, IPI-factors, bulk, histology, age > 70 Intent-to-treat analysis of treatment arms A and B by log rank test for EFS and multivariate analysis adjusting for prognostic factors

Sample Size	274 patients with peripheral T-cell lymphoma (137 per arm)
Trial Duration	First patient in: September 2007 Last patient in: September 2013 Last patient out of treatment: March 2014 End of observation: March 2016 Duration of the entire trial: September 2007 to March 2016 Interim analysis August 2011
Participating centers	Trial group centers of the DSHNHL, NLG, HOVON, EORTC, NCRI, ALG, PLRG, Austrian, CLRO lymphoma groups and further centers
BMBF Project number	GFVT 01014715
EUDRA CT number	2007-000821-23
NCI NCT number	00725231

2.1.4 Flowchart of the Study



2.1.5 Treatment plan, obligatory tests and examinations

Trial Phase	Staging	Random.	Pre-phase	Therapy			Interim Restaging	Therapy			Restaging	Toxicity Evaluation	Follow-up exams after final Restaging
	d-14 to d0		**-d6 to d0**	Cycle 1 **d1**	Cycle 2 **d15**	Cycle 3 **d29**	**d29 + approx d14**	Cycle 4 **d43**	Cycle 5 **d57**	Cycle 6 **d71**	**d71 + approx d14**	**d71 + -3-6 weeks**	**Every 3 months year 1 and 2; every 6 months starting year 3**
Prephase therapy			X										
Arm A 6 x CHOP-14 or Arm B 6x CHOP-14 plus 4xAlemtuzumab)				X X +A	X X +A	X X +A		X+A	X X	X X			
Patient´s history	X			X	X	X	X	X	X	X	X	X	X
Clinical examination	X			X	X	X	X	X	X	X	X	X	X
Performance status	X[2a]		X[2b], X[2c]	X	X	X	X	X	X	X	X	X	X
Toxicity tests							X[8]						
Laboratory analysis	X[3a], X[3d]			X[3b]	X[3b]	X[3b]	X[3b], X[3d]	X[3b]	X[3b]	X[3b]	X[3b] X[3d]		X[3c] X[3d]
Complete blood count during chemotherapy				X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]			
Chest X-ray , abdominal ultrasound	(X)[10]												(X)[10]
pulmonary function test, cardiac ultrasound	X												X
Complete CT scan	X						X				X		X
Bone marrow biopsy	X										X[5]		X[6]
Lumbar puncture, ENT, endoscopy	X[7]												
CTC evaluation			X	X	X	X		X	X	X		X	X[9]
Side effects assessment				X	X	X		X	X	X		X	X
Secondary disease assessment													X

[2] a: before any treatment b: beginning of pre-phase c: at end of prephase

[3] a: leukocytes, lymphocytes, mono., bas., neut., eos., platelets, Hb, BSG, LDH, GPT, AP, γGT, bilirubin, total protein, albumin, paraprotein, IgG, IgA, IgM, β 2-microgl., creat., serology for CMV, EBV, HIV, Hep A/B/C b: leukocytes, platelets, HB, LDH, GPT, AP, bilirubin, creatinine, electrolytes, CMV (pp65 or PCR) monitoring immediately prior to each cycle, and EBV (DNA qPCR) monitoring monthly; c: leukocytes, lymphocytes, mono., bas., neut., eos., platelets, Hb, LDH d: blood and bone marrow samples for scientific project (see Section 7 in protocol)

[4] leukocytes, platelets, HB, prior to cycle and at least 2 measurements in nadir range

[5] if initial involvement

[6] if initial involvement, check after end of therapy [7] in cases of high clinically suspected CNS involvement

[8] Toxicity analysis should be performed as recommended in protocol (see Section 3.1.2); [9] at first follow-up only [10] see section in protocol 2.7.1 (4.5)

2.1.6 Physician's checklist

What is required prior to initiation of therapy?

(1) Requirement: Center registered with trial office and national authorities, local ethics committee vote received?
(2) Diagnosis of the primary and referral pathologist available?
(3) Risk factors determined using the IPI?
(4) Bulky disease assessed?
(5) Trial assignment (DSHNHL 2006-1A or ACT 1 or DSHNHL 2006-1B/ACT2) decided? Originals remain at the hospital.
(6) All eligibility criteria met?
(7) No exclusion criteria apply?
(8) Patient informed, and patient´s approval for randomisation and consent obtained?
(9) All staging examinations completed?
(10) Randomisation documents, staging report form and histology results submitted on CRF by fax to the trial office?
(11) Randomisation will be performed
(12) Serum, blood and bone marrow samples forwarded to trial biomaterials bank?

Treatment procedures and staging:

(1) Chemotherapy cycles 1 - 3 + three alemtuzumab administrations in arm B
(2) Interim restaging and toxicity analysis 14 days after commencement of cycle 3
(3) Chemotherapy cycles 4 - 6 and one alemtuzumab administrations in arm B
(4) Restaging 14 days after commencement of the last chemotherapy cycle

What is required on completion of therapy?

(1) Restaging examination 14 days after commencement of the last chemotherapy cycle or last administration of alemtuzumab
(2) Regular follow-up examinations after final restaging (every 3 months in the first 2 years, thereafter every 6 months to the end of follow-up.

What is required in case of progression, NC and relapse?

Please contact the trial office and check if an alternative treatment protocol would be more appropriate for the patient

What is required on early discontinuation of therapy?

Inform the trial office of the reasons for early discontinuation. If possible, conduct a restaging examination at time of discontinuation and document treatment outcome at time of discontinuation in the restaging form. Document any subsequent follow-up examinations. No patient is “off-study”!

What is required if severe adverse events (SAEs) occur?

Fax the SAE report to the trial office within 24h of the event (0049-551-39-22810).

What is required in the event of patient death?

Document exact time of death and the suspected cause of death on the Death form and supply the post-mortem report (if available) to the trial office. Every case of death is an SAE, exceptions see 4.2.1. Complete also the SAE-CRF in case of death (see above).

What is required if a new physician takes over/patient changes center?

The patients recruited to this study should receive continuous therapy and follow-up according to this protocol at the initial trial center. In the exceptional cases of patients

changing between centers, which are both participating in this study, the trial office will be informed, who will be responsible for treatment, follow-up and documentation. In case of a patient changing to a center not participating in this study for treatment or disease-specific follow-up, the center which included the patient into the trial will retrieve the informations on follow-up and will document those informations in the CRFs of the trial. .

2.2 AIMS OF THE STUDY

2.2.1 Primary aim of the study

The aim of this study is to investigate the following question in patients aged between 61 and 80 years with untreated peripheral T- NHL in a randomised, multicentre clinical trial:

> *Does additional administration of the monoclonal CD52 antibody alemtuzumab in patients over the age of 60 years with peripheral T- lymphoma result in an improvement in treatment outcome in comparison with chemotherapy based on the CHOP-14 protocol alone?*

To be included in this clinical study are all patients with peripheral T-NHL, negative for the expression of ALK, aged 61 to 80 years, irrespective of their risk profile. Excluded are patients stage I N, IPI 0, without bulky disease. The primary endpoint is the event-free survival (EFS). The objective is to demonstrate a difference in the 3-year EFS rate of 15% (hazard ratio of 0.652), with an error probability of 5% (two-sided), at a power of 80%.

2.2.2 Secondary aims of the study

The secondary aims of the study are to collect further data in order to be able to evaluate

1. Efficacy:
   - rate of complete remission
   - overall response rate
   - rate of primary progression
   - relapse rate
   - rate of treatment-related deaths
   - overall survival
   - progression-free survival
   - tumor control
   - disease-free survival.
2. Safety
3. Adherence to protocol

2.3 RATIONALE OF THE STUDY

2.3.1 Current state of the art and issue

Peripheral T-cell non-Hodgkin lymphomas (PTCL) are rare malignancies representing 8-15% of all malignant lymphomas (Armitage, Greer, et al. 1989, Armitage & Weisenburger 1998, Melnyk, Rodriguez, et al. 1997). Depending on their lineage, the T-cell receptors are either rearranged (T-cell lymphoma) or germline (NK-cell lymphoma). Characteristically, these lymphomas express T-cell (CD2, CD3, CD5) and/or NK-cell (CD56, CD16, CD94) markers together with a variety of costimulatory molecules. PTCL are still difficult to classify, as a general principle of classification is lacking. The WHO classification favours a multi-parameter approach integrating morphologic, immunophenotypic, genetic and clinical features (Jaffe et al. 2001). Disease entities are mainly defined by their clinical presentation, in part because other parameters lack specificity. Most extranodal PTCL are classified by their characteristic site of clinical presentation (e.g. nasal NK-cell lymphoma, hepatosplenic lymphoma, intestinal T-cell lymphoma). Nodal PTCL may be classified by defining genetic abnormalities (ALK1-translocation in ALCL), a clinical syndrome (angioimmunoblastic T-cell lymphoma; AIL) or morphology (ALK1$^-$ ALCL). After these more distinctive entities of nodal PTCL have been separated out, there remains the large group of PTCL that currently cannot be reproducibly subclassified (PTCL-not otherwise specified; PTCL-NOS).

Whereas the cutaneous T-cell lymphomas take an indolent course, most PTCL follow an aggressive spontaneous progression similar to diffuse-large cell B-NHL. PTCL are usually treated in analogy to aggressive B-NHL, i.e. depending on the IPI-score (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, Shipp, et al. 1993) with six to eight courses of anthracycline-based chemotherapy like CHOP. Applying such therapies, several studies have documented a significantly worse outcome of PTCL compared to aggressive B-NHL. In the largest series summarizing 1595 patients, the french GELA (groupe d'etudes des lymphomes de l' adulte) showed a signicantly worse prognosis of 288 patients with T-NHL compare to B-NHL, independent of the fact, that these patients had a higher IPI-score than the patients with aggressive B-NHL. In this study, most PTCL were classified as angioimmunoblastic (AIL; 23%), pleomorphic medium and large T-cell (PML; 49%), or anaplastic large cell (ALCL; 20%) lymphomas according to the Kiel classification. Comparing B-NHL with PTCL patients, respectively, complete remission rates were 63% and 54%; the 5-year overall survival (OS) rates were 53% and 41%, and event-free survival (EFS) rates were 42% and 33%. Comparison of the different histological subtypes of lymphoma showed that the 5-year OS rate for T-ALCL (64%) was superior to those of other PTCL (35%) as well as B-NHL (53%). When multivariate analysis was applied using the IPI score as one factor, nonanaplastic PTCL remained an independent parameter (Gisselbrecht et al. 1998). Similar to the GELA experience, the EFS at 5 years, studies on T-NHL including ALCL were in the range of 36% to 39% (Askani et al. 1997, Melnyk et al. 1997, Lopez-Grillo et al. 1998, Kim et al. 2002). Excluding anaplastic large cell lymphoma, however, the summary from published experiences for T NHL patients treated with CHOP-21 based regimens five year EFS-rates ranges from 0% to 22% (Lippman et al. 1988, Rüdiger et al. 2002, Huang et al. 2004). The impact of patient age on OS and EFS has not been analysed separately in the majority of these studies. But as the IPI, to which patient age contributes, was found an independent adverse factor for patients with T NHL, the results for elderly patients will be equal or inferior compared to the treatment results obtained in younger patients.

As a first strategy to improve the outcome for such patients, escalating chemotherapeutic intensity was tested. Within a trial conducted on 689 patients with aggressive lymphomas aged >60, shortening of the interval in between six cycles CHOP chemotherapy from 21 to 14 days with growth factor support resulted in a significantly improved response rate, TTTF and OS for the total cohort. Five-year event-free and overall

survival rates were 32.5% and 40.6%, respectively, for CHOP-21 and 43.8% and 53.3%, respectively, for CHOP-14. In a multivariate analysis, the relative risk reduction was 0.66 (P =.003) for event-free and 0.58 (P <.001) for overall survival after CHOP-14 compared with CHOP-21, with similar toxicities of CHOP-14 and CHOP-21 (Pfreundschuh et al. 2004). Addition of etoposide to the CHOP-14 regimen, however, was associated with increased toxicities, consecutive erosion of dose intensity and inferior TTTF and OS compared to CHOP-14 in this age group (Pfreundschuh et al. 2004). For the subgroup of patients with T-NHL (n=41), there was a tendency of superior TTTF and OS for patients treated with CHOP-14, though not reaching statistical significance due to the small numbers per treatment arm. The event free survival at 3 years for all treatment groups reached 40% in this study including patients with ALK positive T NHL, comparing favourably with the results obtained in the studies mentioned above (M.Ziepert, personal communication). Thus, despite its yet unsatisfactory efficacy, six cycles of CHOP-14 have to be considered standard therapy in elderly patients with T-cell NHL.

For aggressive B-NHL, the addition of the anti-B cell monoclonal antibody rituximab to CHOP chemotherapy resulted in an improvement of overall survival of 15% for patients with aggressive lymphoma age > 60 (Coiffier et al. 1998). In line with this result, the interim analysis of the RICOVER-60 trial on the first 828 evaluable patients demonstrated a time-to-treatment failure at 26 months of 70% vs 57% (*P* = .000025) in the comparison of R-CHOP-14 vs CHOP-14 (Pfreundschuh et al. 2005). For a translation of this immunochemotherapeutic approach to the situation in patients with T-NHL, alemtuzumab (MabCampath®) appears an attractive agent, because malignant T cells express high numbers of the CD52 antigen on the cell surface (Rossmann et al. 2001). As a single agent, the humanized antibody alemtuzumab was found both feasible and effective in trials for patients with CLL and T-PLL refractory to conventional chemotherapy, as well as symptomatic progress of cutaneous T-cell lymphoma (Pawson et al. 1997, Dearden et al. 2001, Hagberg et al. 2001). With an extended dose schedule of 3x30 mg/week for up to 12 weeks established in CLL, alemtuzumab was also given to 14 patients in relapsed peripheral T-cell lymphomas (Enblad et al. 2004). While alemtuzumab was found to be effective inducing two partial and three complete remissions, a high rate of severe infections with fatal complications in four patients lead to an early closure of this trial. Prophylactic antibiotic and virostatic measures, however, prevented severe infectious complications in a further phase II clinical study applying alemtuzumab at a lower dose, i.e. 1x30 mg/week for four weeks, for consolidation after CHOP-14 induction therapy in patients with primary PTCL and AILD. The recruitment of this study ended in June 2006 with 42 patients included, and due to short observation time, the value of alemtuzumab consolidation in this setting can not yet be fully appreciated (Trümper et al., ASCO 2006). However, with a prophylaxis such as the one outlined in this trial protocol, no life-threatening viral or bacterial infections were observed.

The concept of concurrent alemtuzumab as an adjunct to chemotherapy in the treatment of PTCL is currently tested in a phase II study by Weidmann et al. In this trial, a dose of 70 mg alemtuzumab is applied with each of six courses chemotherapy with fludarabine, cyclophosphamide and doxorubicine (FCD). An interim analysis at a median observation time of 12 months showed a response in 10 of 13 patients without major toxic events (Weidmann et al. 2004). Furthermore, in a case series of ten patients with relapsed PTCL and AILD, the concurrent administration of alemtuzumab to a salvage therapy with ifosphamide, carboplatin and etoposide was feasible without major infectious complications, induced a remission in seven patients and allowed progression to high dose therapy and allogeneic transplantation in all patients (Wulf et al. 2005).

In further phase II trials (Gallamini, personal communication, 2005), CHOP was combined with standard dose alemtuzumab in newly diagnosed patients with PTCL for 6-8 cycles without severe side effects. In addition, the HOVON Dutch group (Kluin-Neelemans, personal communication) and the BNLI British group (Dearden, personal communication) are conducting phase II trials with Alemtuzumab. In summary, the humanized CD52 monoclonal

antibody alemtuzumab showed an impressive activity against T-cell malignancies. With appropriate prophylactic antibiotic and virostatic measures, its application was found feasible both as a single agent and in conjunction with chemotherapy. These data sugest, that the potential benefit of improved tumor control outweighs the increased, but manageable risk of infection through the immunsuppressive side effects of Alemtuzumab. Alemtuzumab represents a feasible, and the currently unique therapeutic tool to complement standard CHOP-14 chemotherapy with humoral immunotherapy.

This trial is designed to test the impact of alemtuzumab on treatment outcome when given as an adjunct to CHOP-14 chemotherapy. Primary aim is the improvement in the event free survival (EFS) of patients age > 60 with T-NHL receiving six courses of CHOP-14 chemotherapy.

2.3.2 Summary of the rationale

The prospects of elderly patients with ALK negative T cell lymphoma are poor, despite advances achieved by increased dose intensity in the CHOP-14 regimen. The estimated EFS at 3 years is in the range of 20 – 25% only. The aspects discussed in section 2.1, however show, that there is a promising strategy which can be pursued in order to further improve the outcome achieved with six cycles CHOP-14 in elderly patients with peripheral T- and NK-cell NHL: the additional use of the monoclonal CD52 antibody alemtuzumab. Chemotherapy with CHOP is recommended by many trial groups and has been used with an acceptable level of side effects in patients up to the age of 80 years. Shortening of the treatment interval from CHOP-21 to CHOP-14 was found feasible and effective in this population of patients with NHL, and represents the standard therapy for aggressive lymphoma. The monoclonal CD52 antibody alemtuzumab is clearly effective against T-cell lymphoma as a single agent, and was found feasible as consolidation therapy after CHOP-14. We thus propose to investigate the value of adjuvant alemtuzumab administration in a prospective randomised study, with six cycles CHOP-14 ± ~~alemtuzumab in~~ four doses alemtuzumab on day 1 of CHOP (courses 1 through 4) at 14-day intervals, in patients with untreated peripheral T-cell non-Hodgkin's lymphoma over 60 years of age. Because the tolerability of chemotherapy is poorer in patients of advanced age, patients aged 71 - 80 years will be treated in a separate stratum. Special safety criteria will apply to patients >70 years of age which will include an extensive toxicity analysis during the interim restaging. The aim is to demonstrate a 15% difference in the EFS rate. This difference is clinically relevant. We assume that, at a recruitment rate of 55 patients per year over a 4-year period, the questions asked in this study can be answered with sufficient power.

2.4 TRIAL PROTOCOL

2.4.1 Trial design

The DSHNHL study 2006-1B/ACT-2 is a prospective randomised treatment optimisation trial (investigator initiated trial). Its aim is to investigate whether results in patients aged 61 to 80 years after six cycles CHOP-14 can be further improved by the concurrent addition of the CD52 antibody alemtuzumab to the chemotherapy. 2006-1B/ACT-2 is an open-label multicenter, prospective, randomized phase III clinical trial. The Georg August University of Göttingen is the sponsor of this trial according to the GCP rules and the German AMG regulations.

2.4.2 Participating institutions and number of patients

Institutions which cooperate within the DSHNHL, the NLG, the HOVON, the EORTC, the GELA, the GOELAMS as well as several additional European centers will be participating in 2006-1B/ACT-2. National PIs (principal investigators) have been named in order to supervise and organize the local conduct of the trial within the frames of the GCP rules. We assume that the centers will be able to enrol 274 patients during the 6-year recruitment phase from September 2007 to September 2013. The protocol has been discussed and approved by an international group at three consecutive investigators meetings until December, 2006, at the ASH meeting in Orlando, FL, where final approval was given. The trial protocol has been approved by the protocol committee and the investigators of the DSHNHL at the study group meeting in May 2006 at Hamburg/Germany. European participation will be coordinated through an intergroup effort conducted by Prof. Francesco d'Amore, Aarhus, Denmark for the Nordic Lymphoma Group. Within this cooperation for the evaluation of *A*lemtuzumab and *C*hemotherapy in *T*-cell lymphoma (ACT), DSHNHL 2006-1B/ACT-2 represents the protocol for all patients older than 60 years.

2.4.3 Duration of the study: treatment phase and follow-up observation

The treatment duration of therapy arm A and B (6 x CHOP-14 without/with alemtuzumab) will be both 10 weeks. The study is to continue for a further 2 years after completion of the recruitment phase, i.e. after treatment, each patient is to be observed for a minimum of 2, and a maximum of 8 years.

2.4.4 Study discontinuation

2.4.4.1 Discontinuation of the study for individual patients

Post-randomisation exclusion: A patient will be excluded from certain outcome analyses, but not from the intent to treat analysis, if, after inclusion in the study, an exclusion criterion is found to apply or if it subsequently becomes apparent that an exclusion criterion applied at the time of inclusion. This applies to all exclusion criteria and, in particular, to any change in the histological diagnosis (Reference Pathology). **The treating physician will be informed by the Clinical Trial Consultants if a patient will be excluded from certain analyses due to ineligibility. Further documentation of patients withdrawn after randomisation is mandatory for GCP-conforming trial conduct and intent to treat analyses of the trial outcome parameters.**

Early termination of therapy: early termination of therapy may be necessary in individual patients for the following reasons:

- lack of response to treatment as defined in the protocol
- serious deviation from the protocol
- non-compliance on the part of the patient
- excessive toxicity
- in response to the wish of the patient
- decision of the treating physician
- contact broken off by the patient
- non-conformity to any eligibility criterion (e.g. reference histology)
- identification of an exclusion criterion during the toxicity analysis at the interim restaging in patients aged >70 years.

The reason for early termination of therapy must be documented in written form and notified to the clinical trial consultants in the trial office in Göttingen. Patients with early termination of therapy must continue to be documented (remission status, survival with and without lymphoma).

2.4.4.2 Early termination of the study or closing of individual treatment arms

Early termination of the study or of a treatment arm may be necessary for the following reasons:

- the occurrence of serious side effects of treatment
- excessive treatment-related mortality, i.e. 15% of enrolled patients.
- proven superiority of one treatment arm (interim analysis!)
- new information from other studies or publications
- inadequate recruitment rate
- excessive number of deviations from the protocol

Should any of the above occur, the principal investigator will notify the protocol committee of the DSHNHL 1B/ACT-2, which will then decide within 1 month whether to terminate the study or not. They will propose this to the Data and Safety Monitoring Committee that will ultimately decide on this issue. Alternatively, the DMSC will recommend termination of the trial to the principal investigator based on the results of the confidential interim analyses.

2.4.4.3 Withdrawal of trial centers

Trial centers may be deactivated after initiation for the following reasons

- decision of the local investigator
- insufficient accrual
- severe failure to comply with the rules of the GCP as applying to this trial after assessment of this failure during a site monitoring with source data verification (the centre PI will be notified by the coordinating investigators of the impending deactivation and the reasons thereof)

2.5 Eligibility

2.5.1 Inclusion criteria

1. Age: 61 - 80 years

2. Risk group: All risk groups, including stage I with bulk (≥ 7.5 cm) and stages II to IV, except stage I N without bulk and with no IPI risk factor besides the age over 60

3. Histology: Diagnosis of aggressive non-Hodgkin's lymphoma, confirmed by an excisional biopsy of a lymph node or by a sufficiently extensive biopsy of an extranodal involvement if there is no lymph node involvement. It will be possible to treat all peripheral T-lineage lymphomas with the exception of anaplastic large cell lymphoma and primary cutaneous T-cell lymphomas (Mycosis fungoides, Sezary syndrome and primary cutaneous CD30-positive lymphoproliferations, and transformed primary cutaneous T-cell lymphomas). These lymphomas comprise:

T cell -NHL:

peripheral T-cell lymphoma PTCL-NOS
- Lennert's lymphoma
- T-zone lymphoma
- T-immunoblastic variant
- Perifollicular/follicular variant

T-cell lymphoma of the AIL type
extranodal NK/T-cell lymphoma, nasal type
intestinal T/NK-cell lymphoma (± enteropathy)
hepatosplenic T-cell lymphoma
subcutaneous panniculitis-like PTCL (gamma/delta T-cell lymphoma)

4. Performance status: Performance status **ECOG 0 - 2 (Karnofsky index: 60 - 100%)**. The general status of each patient is to be assessed **at time of randomisation** and can thus take place after initiation of prephase treatment. A performance status of ECOG 3 will allow inclusion, if it is lymphoma related. **The pretreatment status is to be documented in the staging CRF; the performance after the prephase treatment is also to be documented in the relevant CRF for the prephase treatment.** A definition of the performance status is provided in the Appendix.

5. Declaration of center participation

6. written consent of the patient

7. measurable disease — defined as at least one lesion with two measurable perpendicular diameters of which at least one should be ≥15 mm

2.5.2 Exclusion criteria

1. Stage I N with IPI 0 except age > 60 and without bulk
2. Already initiated lymphoma therapy (except for the prephase treatment specified for this study)
3. Serious accompanying disorder or impaired organ function, in particular:
   - Cardiac: angina pectoris CCS >2, cardiac failure NYHA >2 and/or EF <45% or FS<25% in echocardiography/nuclear medicine examination
   - impaired pulmonary functions; in this case, the patient is to be excluded if the resultant pulmonary function test shows FeV1<50% or a diffusion capacity <50% of the reference values
   - Renal: creatinine >2 times the upper reference limit, unless related to NHL
   - Hepatic: bilirubin >2 times the upper reference limit, unless related to NHL
   - Uncontrollable diabetes mellitus (prephase treatment with prednisone!)
4. Platelets <100 000/mm^3, leukocytes <2500/mm^3
5. Bone marrow involvement >25%
6. Primary leukemic manifestation of the lymphoma
7. Known hypersensitivity to the medications to be used, especially murine or chimeric antibodies
8. Known HIV-positivity
9. Active hepatitis infection, active CMV infection, active systemic fungal infection, active infection with mycobacterium tuberculosis or atypical tuberculosis
10. Suspicion that patient compliance will be poor
11. Simultaneous participation in any other study protocol
12. Prior chemo- or radiotherapy for malignancy
13. Other concomitant malignant disease (history of active cancer during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma)

In any case of doubt, relevant supplementary examinations should be conducted (ECG, echocardiogram, pulmonary function, creatinine clearance); this applies particularly to patients aged >70 years for whom it must be established that participation in the study does not represent a risk for the individual patient.

2.5.3 Gender considerations

In the hitherto largest cohorts of patients with peripheral T-cell lymphoma, a consistent predominance of male patients was found, with male to female ratios of 69% to 31%, 62% to 38%, and 60% to 40%, respectively (Gisselbrecht et al. 1998, Ansell et al. 1997, Lopez-Guillermo et al. 1998). However, the response rates to chemotherapy were similar in both male and female patients. Thus, no specific measures for patient gender issues have to be applied.

2.6 BIOMETRICAL ASPECTS OF THE TRIAL

2.6.1 Randomisation algorithm

All patients to whom exclusion criteria do not apply and who conform to all eligibility criteria on completion of staging examinations can be included in randomisation. A minimisation method will be used for randomisation [Pocock SJ, 1983]. The randomisation algorithm will be applied using the ORACLE database. The minimisation method allows treatment arms and strata to be balanced. Patients will be randomly allocated to the two treatment arms at a ratio of 1:1 and stratified in accordance with the following criteria:

(a) Centre
(b) Value for serum LDH (LDH ≤UNV vs. LDH>UNV)
(c) Performance status (ECOG = 0-1 vs. ECOG > 1)
(d) Stage (I, II vs. III, IV)
(e) Number of extranodal involvements (0-1 vs. >1)
(f) Bulky disease (no vs. yes)
(g) Primary histology (other vs. NK/T cell nasal type)
(h) Age (<=70 years vs. >70 years)

In addition to stratification by treatment centre, patients will also be stratified by the prognostic factors LDH, performance status, stage and number of extranodal involvement in accordance with the International Prognostic Index. Patients will also be stratified according to the presence of bulky disease and histological subtype because of additional radiotherapy. Because of the higher toxicity in the elderly patients it will also be stratified by age groups: 61 - 70 years and 71 - 80 years.

All patients where - after inclusion of the patient in the study – it is found that eligibility criteria were not met at the time of randomisation although it was assumed that the patient was eligible at that time – have to be included in the Intent-to-treat analysis of the study.

2.6.2 Study end points

2.6.2.1 Primary end point

The primary end point of this study is Event-free Survival (EFS). The Kaplan-Meier method will be used to assess EFS. EFS is defined by the time between day of randomisation until one of the following events occurs, whichever comes first:

(a) Disease progression during therapy (PD)
(b) Institution of any additional unplanned anti-tumor treatment
(c) Relapse after achievement of CR/CRu
(d) Death due to any cause.

Patients who have not experienced an event at the time of analysis will be censored at the most recent date of disease assessment.
The criteria for the assessment of protocol deviations, discontinuation of therapy at the wish of the patient, discontinuation of therapy by the physician or because of other factors are to be fixed before the first interim analysis for efficacy will be performed.

2.6.2.2 Secondary end points

2.6.2.2.1 Secondary end points for efficacy

Secondary end points for efficacy are CR rate, overall response (OR) rate, rate of primary progression, relapse rate, rate of treatment-related deaths, overall survival (OS), tumour control and disease-free survival. Tumour control allows the evaluation of the biological efficacy with reduction of the influence of toxicity. Evaluation of disease-free survival makes it possible to compare the time course of the occurrence of relapse between the treatment arms.

CR rate:	Number of complete remissions and unconfirmed complete remissions (including CR/CRu in patients after early discontinuation) divided by the number of patients
OR rate:	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
Rate of primary progression:	Number of primary progressions during therapy or immediately after the therapy divided by the number of patients
Relapse rate:	Number of relapses divided by the number of patients with CR/CRu
Rate of treatment-related deaths:	Number of treatment-related deaths during therapy or immediately after the therapy divided by the number of patients
Overall survival (OS):	Time between randomisation and death due to any cause; in case of patients, who are alive, the time between randomisation and the date when the patient was last known to be alive.
Progression-free survival (PFS):	Time between randomisation and progression or death due to any cause; in the case of patients without event, the time between randomisation and the date when the patient was last known to be without event
Tumour control:	Tumour control or time to progression (TTP), similar to EFS, but events which are not tumour-related are censored
Disease-free survival:	similar to EFS, but events occurring during and immediately after therapy are assigned to time point ε= 0.01 months

2.6.2.2.2 Secondary end points for safety

Secondary end points for safety are:

- adverse events (AEs)
- serious adverse events (SAEs)
- and selected laboratory parameters
- immunoreconstitution after therapy

2.6.2.2.3 Secondary end points for adherence to protocol

- number of chemotherapy cycles
- duration of chemotherapy cycles
- cumulative dose and dose intensity of the cytostatics
- number of alemtuzumab administrations
- interval between alemtuzumab administrations
- cumulative dose and dose intensity of the monoclonal antibody alemtuzumab
- duration of G-CSF administration

2.6.3 Statistical hypotheses and sample size calculation

The following question is to be investigated in this clinical study:

- *Does the additional administration of 4 doses of the monoclonal antibody alemtuzumab with a cumulative dose of 120 mg result in an improvement of the Event-free Survival (EFS)?*

The effectiveness of the additional application of alemtuzumab at 14-day intervals with six cycles CHOP-14 has not yet been investigated in a randomised study. It is thus unknown whether increased toxicity may result from the inclusion of alemtuzumab and thus compromise the effectiveness of treatment. For this reason, a two-sided test will be used. In order to answer the study question, the following statistical hypotheses will be tested:

H_o: EFS (6 x CHOP-14) = EFS (6 x CHOP-14 and 6 x alemtuzumab)
H_A: EFS (6 x CHOP-14) ≠ EFS (6 x CHOP-14 and 4 x alemtuzumab)

Any detectable difference will emerge from failure under therapy and relapse profiles. On the basis of observed hazard rates in other study groups it is assumed that the differences between the therapy arms in respect of EFS-rate should mainly become apparent in the period up to 3 years after the commencement of therapy.
There are no data available from previous trials of the DSHNHL for a population similar to the population to be included in the planned trial. There are only few data in the literature, as outlined in the rationale. According to the data from the literature it is plausible to postulate a 20% 3-year EFS-rate for the therapy arm six cycles CHOP-14 without alemtuzumab.
Furthermore the DSHNHL study group decided on their last meeting (4./5.05.2006, Hamburg) that the demonstration of a 15% improvement in EFS-rate can be seen as relevant.

It is therefore the aim of this study to demonstrate an improvement in EFS-rate from 20% to 35% (i.e. a hazard ratio of 0.652). The two-sided question will be answered with an error

probability of α= 5% and a power of 80%. According to the experience of the DSHNHL study group an α with 5% and a power with 80% for this trial will be adequate to answer the study question.

In order to calculate the required sample size, a procedure developed by Freedman [Freedman LS 1982] has been used. Calculations were performed using the software program nQuery Advisor, Version 2.0.
Calculations show that a sample size of 246 patients, i.e. 123 per treatment arm, is required for the test. If patients cannot be evaluated on completion of the study because of lack of documentation, there would be an equivalent loss of power.

In order to offset any loss of power, patients who are drop-outs (patients which cannot be adequately documented) must be replaced for the analysis. It is expected that it will be necessary to recruit therefore approximately 5% more patients. About further 5% of patients will change their inclusion criteria after randomisation e.g. if the reference pathologists change the primary diagnosis or from other reasons. To enable also a full powered 'per protocol' analysis beside the 'intent-to-treat' analysis more patients have to be included. The required total sample size would thus be approximately 10% higher. Therefore it will be necessary to include 274 patients (137 per treatment arm) in the study. It is planned to include these patients over an accrual period of 4 years and a follow-up period of 2 years.

2.6.4 Statistical methods

2.6.4.1 Definition of the evaluable study population

Prior to each analysis, the data for each patient will be evaluated by a Review Panel consisting of the main coordinating investigator, a biometrician and a data manager. The following criteria will be applied for the evaluation:

- compliance with the eligibility criteria
- confirmation of primary diagnosis (Reference Pathology)
- treated according to the randomisation
- complete documentation of therapy
- observation period at least 2 months after the completion of therapy and availability of the completed follow-up CRF
- protocol-conformable treatment
- knowledge of the reasons for early discontinuation.

The course of therapy, the final outcome of therapy and the time of completion of protocol-conformable therapy will be documented in the Confirmation of Evaluability and signed and dated by the Review Panel. Patients for whom there is a Confirmation of Evaluability can be included in the interim analysis of efficacy. All patients who received at least one dose of treatment (including prephase treatment), and for whom at least one post-baseline observation is available can be included in the interim analysis for safety.

2.6.4.2 Analysis population

The Full Analysis Set (FAS) will include all randomized patients. All patients will be evaluated for that therapy arm which they were randomly assigned, irrespective of what therapy they actually received.
The first Per Protocol Set (PPS 1) will include all randomized patients that fulfill all inclusion criteria and no exclusion criterion. All patients will be evaluated for the protocol therapy they

actually received, i.e. a patient not treated according to the arm he was randomly assigned will be excluded for this first PPS. The second PPS (PPS 2) is the same as the previous one but restricted only to patients with confirmed reference pathology.
The Safety Analysis Set (SAF) will include all patients that received at least one dose of treatment (including prephase treatment), and for whom at least one post-baseline observation is available.

2.6.4.3 Planned methods for analysis

2.6.4.3.1 Primary endpoint

All main analyses will be done in accordance with the intent-to-treat principle.
For the 'Full Analysis Set' population the log-rank test will be used in a primary analysis to compare Event-free Survival (EFS) for the two treatment arms. Kaplan-Meier curves will be used to represent the EFS. In addition, a projection of the 3-year EFS-rate with 95% confidence interval will be prepared for the two treatment arms.

In a secondary analysis, a Cox multivariate regression model will be used to test if the therapy effect that emerged from the univariate analysis remains stable after adjustment for prognostic factors. In addition, interactions between therapy effect and prognostic factors (IPI criteria and variables with prognostic relevance within this study) will be analysed in order to establish whether the treatment effect is homogeneous in the different prognostic subpopulations.
For the Cox models the estimators are given in form of hazard ratios with 95% confidence intervals and corresponding p values. If the assumed proportional hazard estimate proves inaccurate, more suitable methods of analysis will be considered.

During the analysis of efficacy, an overview will be prepared of the number of randomised patients, number of patients completing therapy, numbers of early discontinuations and of the time point of early discontinuation will be provided.
Furthermore an explorative analysis for the 'per protocol' population will be done in the same way as the analysis for the Intent-to-treat population.
The CD52-positive patient population is of special interest in the setting of PTCL and will be the object of a planned sub-group analysis at the end of the study, where CD52-status will be correlated with histological subtypes and study end-points. The ACT-1 trial, conducted by the Nordic Lymphoma Group for younger patients in parallel to this trial, has nearly the same study design. Thus, for special questions, a combined analysis of the two data sets will be performed. A detailed analysis plan will be prepared before start of the first formal efficacy interim analysis.

2.6.4.3.2 Secondary end points

The CR rates, OR rates, rates of primary progression, relapse rate and rate of treatment-related deaths will be documented, together with the corresponding 95% confidence intervals. Multivariate logistic regression model will be used to test if the therapy effect that emerged from the univariate analysis remains stable after adjustment for prognostic factors.
The further secondary end points (data on survival time) will be analysed in analogy with the primary end point. For qualitative secondary end points, such as adverse events and serious adverse events, frequency tables will be prepared. The percentage of patients with serious

adverse events will be stated. Quantitative secondary end points, such as laboratory parameters, cumulative doses of cytotoxic drugs, the antibody alemtuzumab, days in hospital, total number of days of administration of antibiotics, total number of transfusion of erythrocyte and platelet concentrates, duration of chemotherapy cycles and relative dose intensity will be described in terms of location (mean or median) and distribution (standard deviation or lower and upper quartile). Error bar graphs or box plots will be used for graphic representations. Secondary end points will also be analysed separately by therapy arm.

2.6.5 Interim analyses and criteria for early discontinuation of the study

SAE's and deaths occurring during the study will be continuously monitored by the coordinating investigator and the biometrician. For these secondary endpoints no formal criterion for early discontinuation will be defined. The safety and toxicity profile will be analyzed annually. The trial may be terminated at the discretion of the data safety and monitoring committee at any of these safety interim analyses.
For the EFS, the main endpoint of the study, a formal criterion for early discontinuation will be defined using the alpha spending function [DeMets DL & Lan KKG 1994, Lan KKG & DeMets DL 1983, Hwang IK & Shih WJ 1990]. In contrast with standard group sequential designs, this design allows adjustment to be made for the time point of interim analysis. The method suggested by O'Brien and Fleming will be used to calculate the "stopping boundary" [O'Brien PC & Fleming TR 1979]. This method requires almost conventional p values for the final analysis, but makes it difficult to terminate the study early for unjustified reasons.
[For example, with a total of 183 expected EFS-events (under investigation of 5% more patients for the 'per protocol' analysis) and τ_1=50, τ_2=70, τ_3=90, τ_4=110, τ_5=130, τ_6=150, τ_7=170, τ_8=180 events, the O'Brien/Fleming boundaries would be as follows:
$\alpha(\tau_1)$=0.00018, $\alpha(\tau_2)$=0.00153, $\alpha(\tau_3)$=0.00519, $\alpha(\tau_4)$=0.01147, $\alpha(\tau_5)$=0.02005, $\alpha(\tau_6)$=0.03040, $\alpha(\tau_7)$=0.04200, $\alpha(\tau 8)$=0.04812]

Prior to the early discontinuation of a study, a complex analysis of numerous factors must be conducted. The criteria for discontinuation proposed here can thus only serve to initiate the decision process on whether to discontinue the study or not.

It is not expected that conclusive interim evaluation of efficacy will be possible within the initial 2 years of this study. For this reason, the first planned interim analysis of efficacy will be performed 2.5 years after commencement of recruitment when it is assumed that approximately 38% of the expected events will have already occurred (probably in 2011). No further interim analyses of efficacy are definitely planned at present. As the proposed alpha spending function is flexible with respect to the number of interim analyses conducted, the Study Management Committee can decide when to conduct a further interim analysis during the on-going study.

2.6.6 Final analysis

A final analysis can be performed when the planned number of events has occurred and documented, or at the latest after the end of the study in 2016.

2.6.7 Biometrical report

A report on each analysis will be prepared by the responsible biometrician.
The results of the final analysis will be presented in a final report. This will provide a description of the patient population for each treatment arm, the feasibility of the treatment, the safety of therapy (particularly in respect of the occurrence of adverse and serious adverse events), adherence to protocol, cases of early discontinuation and the results of the efficacy analysis

2.7 TRIAL PROCEDURES FOR INDIVIDUAL PATIENTS

2.7.1 Staging examination

a) Obligatory examinations

1. Patient history (onset of symptoms, B symptoms, ECOG index)
2. Clinical examination
3. Laboratory tests:
   - complete haematogram with differential blood cell count
   - ESR
   - LDH
   - GPT
   - alkaline phosphatase (serum)
   - γ-GT
   - bilirubin
   - total proteins and albumin with protein electrophoresis and immunoelectrophoresis (paraprotein)
   - immunoglobulins IgG, IgA, IgM
   - beta2-microglobulin
   - creatinine
   - HIV serology, hepatitis serology, CMV status, EBV status
4. Chest X-ray in two planes of the patient in upright position (recommended, but not mandatory
5. Abdominal ultrasound (recommended, but not mandatory)
6. complete CT scan (neck/thorax/abdomen/pelvis)
7. Bone marrow biopsy (histology and cytology)
8. Lumbar puncture with CSF cytology in cases of involvement of the cranium viscerale, the bone marrow or the testes.
9. Echocardiography (or alternatively: determination of the ejection fraction by MUGA scan) prior to initiation of treatment
10. pulmonary function including diffusion capacity

b) Optional tests to be decided by investigators based on individual patients' characteristics

1. Full body bone scan
2. Gastroscopy (obligatory in case of tonsillar involvement)
3. Examination by an ENT specialist (obligatory in cervical involvement)
4. Haemoccult test
5. Lumbar puncture with CSF cytology, if not obligatory (see 5.1.a)
6. Gallium scintigraphy, PET scan, NMR tomography, cervical node ultrasound
7. Liver biopsy.

2.7.2 Evaluation of disease stage/risk group allocation

The results of the staging examination are to be used to classify the stage of the disease in accordance with the criteria of the Ann Arbor Conference (cf. Appendix). In addition, 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, cf. Appendix) as follows: 1. low risk group, 2. low-intermediate risk group, 3. intermediate-high risk group, 4. High-risk group. The criteria of the IPI and the definitions of "bulky disease" and "E involvement" can be found in Appendix of the study protocol.

2.7.3 Patient information

The treating physicians will provide patients with information on the study prior to starting prephase therapy. Treating physicians will provide patients with information (in the presence of a witness where appropriate) in comprehensible terms on the diagnosis of peripheral T- cell lymphoma and the current status of knowledge about the diagnosis and treatment of this disease and on the aims of the study. Patients will also be informed about the expected and possible effects and side effects of treatment and about the insurance cover which they will have as study participants. The risk-benefit considerations of this trial have to be explained to the patient. It must be ensured that patients are fully aware that they are free to decide whether to participate or not, that they can cancel their decision to participate at any time and that there will be no disadvantages for them if they do not participate. Patients will also be informed that, if they consent to participate in the study, they retain the right of access to their patient records, and that personal data required for the scientific monitoring of the disease will be collected and assessed. The aim and purpose of the collection of data will be explained to the patient. In addition, the patients are to be asked to immediately report all impairments to their health which may occur during or after treatment and which could be associated with treatment (e.g. later alterations to blood counts) to the treating physician. The patients will also be informed that regular follow-up examinations, which will be in their own interest (and particularly in that of future patients), are to be conducted over a period of many years and that the results of these examinations will be notified to the trial office.

Patients have to confirm their consent to participate in written form and the consent form must also be signed by the physician providing the patient with information. The form will explicitly specify consent to the collection of patient data, including full name, date of birth and address, and consent to the accompanying scientific investigations. In addition, patients must consent to being directly contacted by the trial office, if the trial office is no longer able to obtain the required information from the treating physician.

The Patient Information and Informed Consent Form must be signed by the patient and the physician. The originals of the Patient Information and Informed Consent Form are to be retained by the treating physician. The patients will be given the copies of these forms with a copy of the Patient Information Leaflet. In addition, the patients will receive a copy of the insurance policy.

2.7.4 Notification of the inclusion of a patient in the study

The treating physician must notify the clinical consultants at the trial offices or the consultant of the national study group (see below) by faxing the completed randomisation documents including the Baseline and Staging forms (BR,B1+2, S1+2, Patho I signed only by authorised person listed in the site Delegation log. After transmission of these documents by fax they have to be sent to the Trial Office Göttingen via mail, one copy has to be retained in site.

The complete version of the patient information and the signed and dated Informed Consent must be present at the site and will remain there.

Upon approval, the Clinical Consultant has to notify the trial office in Göttingen, which performs the registration of the patient in the database after having checked all documents for completeness and correctness.

The trial office will then fax the randomisation forms to the Data Management at IMISE, Leipzig (see below), where randomisation will be performed.

A copy of the Centre Participation Contract (see Appendix) and the EC approval must be provided to the trial office before randomisation of the first patient.

Randomisation should be done prior to the commencement of the prephase treatment. However, randomisation can be postponed until after the commencement of the prephase treatment, but must be accomplished prior to the commencement of CHOP (or alemtuzumab) therapy.

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The following information is required for randomisation:

- name of institution and treating physician
- name of pathologist and referral pathologist
- name of the radiologist, if radiotherapy is planned
- identification of the patient
- age
- sex
- histopathologic subtype (WHO classification) from primary pathologist
- confirmation that patient conforms to eligibility criteria
- confirmation that no exclusion criteria apply
- IPI criteria: - LDH and upper normal limit of LDH in the respective laboratory
  - performance status ECOG score (Karnofsky index)
  - Ann Arbor stage

- presence of extranodal involvement (number, site)
- presence of bulky disease (site)
- sites of lymphoma involvement
- haematological status.

Note:

As the randomised study stratifications in the DSHNHL 2006-1B/ACT-2 T-NHL study are based on the International Prognostic Index score [Shipp et al. 1993], stage, performance status, number of extranodal involvements and LDH value must be known at the time of randomisation and this information must be documented! The LDH value given at randomisation must be the value measured prior to treatment, i.e. prior to the initiation of the prephase treatment. Care must be taken to ensure that the result is not influenced by haemolysis. The reference values used by the laboratory in question must also be stated.

2.7.5 Inclusion of patients in the study

After the central trial office has been notified of the inclusion of a patient, the randomisation of patients will be performed by the Data Management office in Leipzig. The results of the randomisation will be reported to the recruiting physician as soon as available by ***a written confirmation*** **of the result of the randomisation** ***by e-mail.*** **In addition, the treating institution will be notified by a phone call from** the trial office.

Immediately after randomisation, the documentation dossier (CRF) for the included patient will be sent from Leipzig to the recruiting physician.

In Germany, the primary pathologist is requested to forward tissue samples for reference pathological analysis to one of the DSHNHL reference pathologists (Chapter 6.1). The German national reference pathologist for this trial is

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E-mail: path161@mail.uni-wuerzburg.de

In addition, the reference pathologist is informed about new patients included in the study by using the reference pathology server (daily update).

Within the context of the randomisation procedure, the recruiting physician will be informed about the requirement of patient material for accompanying investigations conducted under the supervision of the Scientific Advisory Board. The physician will receive logistic support from the Study Management Panel for the submission of this material. In the Patient Information and Informed Consent Form, patients are requested to consent to these scientific procedures and to allow primary lymph node material to be made available to the Study Management Centre for this purpose.

Reference pathology procedures will apply to each participating country or trial group, where a coordinating reference pathologist will be named who will receive the necessary data (Pat ID, recruitment date, primary pathologist) in order to start the reference pathology evaluation.

2.7.6 Treatment implementation according to the protocol

Prephase treatment is obligatory and must precede the main phase therapy with CHOP-14 with/without alemtuzumab. Prephase treatment can be started prior to randomisation. The main therapy phase (CHOP and CHOP + alemtuzumab, respectively), however, must not be initiated before randomisation, and must directly follow the prephase treatment. Thus, commencement of the prephase treatment in cases of emergency, e.g. in cases of extensive tumour size or poor performance status, is permitted prior to notification of the trial offices in Göttingen. Interim restaging will take place after cycle 3. Salvage therapy will be recommended to all patients who show no response to treatment at this point of time (PRO). Salvage therapy should also be given within a prospective study. This will be regulated in a separate study protocol for salvage therapy (available on request). Fourteen days after commencement of the last cycle of chemotherapy or after the last administration of alemtuzumab, the definite restaging will take place. Patients, who have not achieved CR or CRu after completion of the entire treatment according to the protocol, require further treatment and can be given salvage therapy. As a rule, salvage therapy will consist of a different type of chemotherapy, but may consist of radiotherapy if the treating physician considers this appropriate.

In view of the advanced age of the patients to be included in this study, very close clinical monitoring is recommended. Patients should be examined on a weekly basis by an experienced physician so that any clinical side effects of chemotherapy (e.g. mucositis, polyneuropathy, deterioration of general status) are recognised at an early point of time and appropriate treatment can be provided. Because of the possible reactions to alemtuzumab and the increased toxicity of chemotherapy in the elderly patients, we would recommend a close observation, at best as an in-patient, of the patient during the first chemotherapy cycle until the nadir of the leukocyte count has been passed.

2.7.6.1 Prephase treatment

All patients will receive a prephase treatment in the form of a 1-week course of prednisone with vincristine:

Vincristine	1 mg	i.v.	day* -6 (single dose)
Prednisone	100 mg	p.o.	day* -6 through day 0

*day 1 = day 1 of CHOP 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. **Prephase treatment is mandatory.** Sufficient fluid intake should be ensured and appropriate supportive measures (see below) should be provided.

2.7.6.2 CHOP-14

The CHOP-14 dosage and number of cycles will be identical in both arms (Flowchart of the study).

CHOP-14 schedule:

Cyclophosphamide	750 mg/m^2	i.v.	day 1
Doxorubicin	50 mg/m^2	i.v.	day 1
Vincristine	1,4 mg/ m^2, with a maximum of 2 mg	i.v.	day 1
Prednisone	100 mg (absolute)	p.o.	day 1 – 5
(administration of G-CSF)			

Recycle: CHOP-14 on day 15.

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.

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 $\geq$ 1x10^9/l) on day 15 after discontinuation of G-CSF and
3. Platelet count >80 000/mm^3 on day 15
4. No active infection
5. No serious organ or other toxicity.

If the threshold counts for leukocytes and platelets on day 15 are not achieved, the commencement of the next cycle will be initially postponed for 3 days - if the threshold counts are still not achieved by this time, the next chemotherapy cycles can be postponed for a further 3 - 4 days. In these cases, administration of G-CSF is to be continued. If a postponement exceeding 1 week is required, dose reduction will be necessary (see below).

2.7.6.3 Administration of alemtuzumab

Courses 1-4 ~~6~~ of A-CHOP: application of Alemtuzumab 30 mg subcutaneously in the thighs on day 1 of CHOP chemotherapy, after application of the cytostatics including prednisone. In course 1 of A-CHOP, the first dose of alemtuzumab may be split into 10 mg on day 1 and 20 mg on day 2 to minimize drug reactions.
Before use, the contents of the alemtuzumab ampoule should be checked to ensure that no precipitation or discoloration has occurred; if this is the case, then the ampoule should not be used. For subcutaneous administration the content of an ampoule of alemtuzumab (1 ml., containing 30 mg alemtuzumab) is taken up into a 2-ml syringe. As alemtuzumab solution contains no preservatives, attention must be paid to maintain sterility in handling and administration. One syringe filled with 1 ml alemtuzumab solution (containing 30 mg alemtuzumab) is injected into the left or right thigh, with care being taken to avoid repeated use of exactly the same injection site (i.e. alternating left/right sides at successive visits). Before administration of the injection, the skin should be disinfected. At the start of

subcutaneous treatment, local reactions can be experienced, such as mild swelling and reddening of the skin, sometimes painful; such reactions decrease during continued therapy.
During the first injection patients need to be observed with an iv line that should be open for medications. Adequate hydration of patients should be ensured and patients should receive premedication with allopurinol. Vital signs should be monitored every 15 minutes during the first hour or until stable and then for another hour. Prior to the initial administration of alemtuzumab, patients are to be given paracetamol (1000 mg) and 50 - 100 mg diphenhydramine hydrochloride or clemastine 2 mg 30 minutes prior to s.c. alemtuzumab injection. It should be ensured, that epinephrine and diphenhydramine hydrochloride are available in case an allergic reaction occurs. All necessary equipment for the treatment of anaphylactic shock should be readily available. Patients may develop fever and chills after application of alemtuzumab. If these symptoms are observed, the administration of the antibody should be discontinued.
Alemtuzumab will be supplied by the manufacturer, Genzyme via a distributor as labelled trial drug free of charge to the hospital pharmacy of the investigator specifically for a patient randomized to Arm B. Alemtuzumab is provided in glass ampoules, each containing 1 ml of a colorless solution of 30 mg alemtuzumab with the additives disodium ethylene diamine tetraacetate, polysorbate 80 and phosphate-buffered saline comprising potassium chloride, sodium chloride, disodium phosphate, potassium dihydrogen phosphate and water for injection. The ampoules have a rubber septum for withdrawal of the contents by hypodermic needle. Alemtuzumab vials must be kept refrigerated at 2–8 °C. They must be protected from light and must not be frozen. If Alemtuzumab is taken out of the vial in splitted portions, appropriate cooling at 4°C of the vials has to be ensured.

2.7.6.4 Dose reduction

If the thresholds (leukocytes >2500/mm^3 and platelets >80 000/mm^3) are still not reached after a 1-week postponement of therapy (i.e. by day 22 after CHOP-14), further treatment should be delayed, with checks of blood counts every 3 days, until these values are reached. The next cycle should then be given at a reduced dose:

1. Postponement of therapy by 0 - 7 days:

No reduction

2. Postponement of therapy by 8 - 14 days:

Cyclophosphamide	75%
Doxorubicin	75%
Vincristine	100%
Prednisone	100%

3. Postponement of therapy by >14 days:

Cyclophosphamide	50%
Doxorubicin	50%
Vincristine	100%
Prednisone	100%

In addition, dose reduction of individual medications can be considered if other toxicities (e.g. polyneuropathy, severe mucositis) occur. In case of neurotoxicity, dose modifications of vincristine are made at the discretion of the physician. In cases of documented cardiomyopathy developed during treatment, LVEF should be repeated. If LVEF values are reduced > 15% resulting in an absolute value < 45%, the patient goes off protocol treatment. In such cases, prior consultation with the Study Management Committee is recommended.

If possible, administration of alemtuzumab should be synchronised with chemotherapy. In the rare instances in which alemtuzumab may have already been administered for the new cycle, but postponement of chemotherapy is necessary for unforeseen reasons, the next dose of alemtuzumab should be postponed accordingly, i.e. be given only with the following chemotherapy cycle. When the chemotherapy has to be discontinued completely, application of alemtuzumab should also be stopped. If alemtuzumab has to be stopped due to allergic reactions, chemotherapy should be completed according to protocol.

2.7.6.5 Suspected CNS involvement

In cases of a clinically suspected involvement of the CNS, CNS imaging by MRT scan and liquor analysis are recommended. In case of involvement, intrathecal therapy should be implemented (see below). A routine CNS prophylactic treatment in all patients is not recommended.

2.7.6.6 Intrathecal therapy in CNS involvement

In patients with lymphoma cells demonstrated in their cerebrospinal fluid, intrathecal therapy should be given on days 1, 5 with 15 mg methotrexate (with folinic acid, see above), 40 mg cytosine arabinoside and 4 mg dexamethasone and continued at weekly intervals until results for the CSF are negative. With normalisation of the CSF cell count, at least two further treatments should be provided. Directly after the completion of the first chemotherapy cycle, patients with confirmed evidence of a cerebral lymphoma mass will receive radiotherapy of the whole cranium at a maximum cumulative reference dose of 36 Gy with subsequent individual boosts to 50.4 Gy.

2.7.6.7 G-CSF therapy

In order to ensure that the next therapy cycle can be initiated on day 15, patients will be given G-CSF daily from day 4 to day 12 (with subsequent discontinuation of G-CSF). A single dose of pegfilgrastim (6 mg s.c.) once on day 4 is sufficient to permit re-cycling on d 15.

In cases of persistent leukopenia, G-CSF administration should be continued until the recovery of the leukocyte count. G-CSF should be continued until the leukocyte threshold stipulated for continuation of therapy is reached.

G-CSF (filgrastim) is to be administered ***from day 4 to day 12*** (once daily s.c.) during CHOP-14, irrespective of the leukocyte count:

300 µg/day if bodyweight <75 kg
480 µg/day if bodyweight ≥75 kg.

By alternative, lenograstim (150 µg/m^2 s.c.) may be given similarly on days 4 though 12

2.7.6.8 Possible side effects of the protocol-conformable treatment

Alemtuzumab: After subcutaneous injection, in > 90% of the patients local injection site reactions will be seen, especially during the first two weeks. These may consist of erythema/edema (grade I) or be accompanied by pruritus and slight pain (grade II). The erythema can measure up to 30 cm in diameter in some patients, but will always disappear before the next injection. The majority of patients will experience fever, a minority rigors, all grade I-II, but side effects will decrease within two weeks.

Cyclophosphamide: myelosuppression, nausea/vomiting, alopecia, haemorrhagic cystitis

Doxorubicin: myelosuppression, nausea/vomiting, alopecia, cardiomyopathy (after max. cumulative dose: 550 mg/m^2), necrosis after paravasal injection

Vincristine: peripheral polyneuropathy, paralytic ileus, necrosis after paravasal injection

Prednisone: restlessness, stomach upset, increased appetite, osteoporosis, myopathy, corticosteroid-induced diabetes mellitus

G-CSF: bone pain, elevated body temperature or fever in rare cases

Radiotherapy (NK cell lymphoma): nausea, vomiting, impaired swallowing, headache, tiredness, leukocytopenia, thrombocytopenia, anaemia, skin alterations and alopecia in the irradiated area. Also possible are reactions to irradiation of the lungs (dyspnoea), of the intestine (diarrhoea), of the pericardium (effusion), and impairment of intellectual performance after irradiation of the CNS.

2.7.6.9 Supportive measures

1. *Selective intestinal decontamination:* not required as a rule; however, prophylactic oral administration of one dose 500 mg ciprofloxacin (Ciprobay) per day is recommended in the presence of leukocytopenia <1000/mm^3

2. *Pneumocystis carinii/toxoplasma gondii prophylaxis:* Starting on day 8 of therapy through 2 months after completion of the last chemotherapy or alemtuzumab application, oral medication with Co-Trimoxazol 960 mg p.o. twice daily on three days a week is compulsory. In case of an allergic reaction to Co-Trimoxazol, application of penthamidine 300 mg p.i. once every 30 days after an initial saturation with 300 mg p.i. on three consecutive days.

3. *Cystitis prophylaxis:* ensure adequate fluid intake particularly on day 1 of therapy or provide fluids by infusion with cardiopulmonary monitoring. Uromitexan (MESNA) prophylaxis can be given in accordance with local standards.

4. *Antiemesis:* metoclopramide (Paspertin) or alizapride (Vergentan), one ampoule i.v., hours: 0, 4, 8. Use of serotonin antagonists (e.g. ondansetron, dolasetron) is not generally indicated but is certainly permitted; administration in accordance with investigator's own local operating procedures is recommended.

5. *Oral hygiene:* a good standard of oral hygiene is to be maintained: this applies particularly to patients with dental prostheses. Prophylactic mouth rinsing with chlorhexidine (e.g. Hexoral) or similar medicines and nystatin (Amphomoronal) after each meal is recommended in patients with sensitive oral mucosa.

6. *CMV (antiviral) prophylaxis:* Starting on day 8 of therapy through at least 3 months after completion of the last alemtuzumab application or until CD4 recovery > 200/µl, oral medication one of the following virostatics is **compulsory**:
   Famaciclovir 250 mg p.o. twice daily
   Valaciclovir 500 mg p.o. twice to threetimes daily
   Aciclovir 400 mg p.o. fourtimes daily
   Valganciclovir 2x450 mg p.o. threetimes weekly

7. *Blood products:* All blood products need to be leukocyte-depleted, irradiated and CMV negative (in patients with negative CMV serology) until 6 months after the last alemtuzumab application to prevent transfusion-related GvHD and virus transmission.

8. *Vaccinations:* Vaccinations with live vaccines are to be avoided for at least one year after the last alemtuzumab application.

2.7.6.10 Lab monitoring during therapy

on a regular basis twice weekly: blood counts (leukocytes, platelets, Hb) with differential blood counts (note: it is expected that the leukocyte nadir will be reached on day 8 - 10 [on the basis of experience with CHOP-14 in the NHL-B study]); in the case of cytopenia CTC $\geq$ 3 with the necessity for erythrocyte or thrombocyte transfusions, more frequent blood counts may be necessary and should be scheduled according to GCP

on a regular basis weekly for patients seropositive for CMV: CMV monitoring by either immunocytology for pp65 or quantitative PCR weekly during the six cycles of chemotherapy. Thereafter, monitoring will be performed every second week for 3 months.

prior to each cycle: clinical examination (in particular: lymph node status, exclusion of polyneuropathy, mucositis), blood counts (leukocytes, platelets, Hb), LDH, GPT, AP, bilirubin, creatinine, electrolytes, evaluation of EBV copy numbers (DNA qPCR) in the peripheral blood should be performed monthly during therapy

two months after last alemtuzumab: measurement of T-cell subsets in the peripheral blood (CD4, CD8, CD56/CD16, CD19); in case of peripheral CD4 counts < 200/µl, continuation of antiviral therapy and repetition of T-cell counts every 4 weeks

If progression of the disease occurs (indicated, e.g. by an increasing size of involved lymph nodes), the patient should be classified as a non-responder already prior to the interim restaging after 3 cycles and should be withdrawn from the study therapy. In such cases, we would recommend consultation with the Study Coordinators and commencement of salvage therapy, whenever appropriate. However, patients with early termination of therapy must continue to be documented (remission status, survival with and without lymphoma) and are not excluded from the study. In case of clinically asymptomatic CMV-reactivation detected by pp65 and/or CMV-PCR, antiviral prophylaxis (as well as Alemtuzumab) is stopped and a preemptive therapy with valganciclovir 900 mg twice daily or intraveneous gangciclovir started and given for at least 10 days or until CMV PCR/antigenemia negativity. When peripheral blood leukocytes are above the threshold of 2.500/µl, CHOP chemotherapy should be applied without delay. After documentation of two CMV negative samples, valganciclovir is reduced to the prophylactic dose of 900 mg 1x daily for the entire duration of alemtuzumab treatment that will then be commenced again. 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. After study completion CMV testing will be continued monthly during at least three months.

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.

2.7.6.11 Radiotherapy

Radiotherapy before start or during protocol treatment is recommended for patients with extranodal NK/T cell lymphoma, nasal type, only. A routine application of radiotherapy to initial bulk manifestations, extranodal disease except CNS manifestations (see above) or residual tumor mass is not recommended. If, however, the treating physician should consider special indications for consolidation radiotherapy for individual patients, the trials office has to be contacted before randomisation. In all other cases, radiotherapy given in addition to the protocol treatment will be counted as events unless otherwise specified.

3 Procedures and Documentation

3.1 Restaging and follow-up procedures

3.1.1 Interim restaging

Approximately **2 weeks after the commencement of cycle 3:**

- patient history
- clinical examination (lymph node regions!)
- laboratory parameters as during the staging examination
- CT scan of neck/thorax/abdomen/pelvis (in case of primary involvement)
- evaluation and documentation of success of therapy and side effects

3.1.2 Toxicity analysis during interim restaging

It is recommended that a detailed toxicity analysis is conducted for all patients during the interim restaging; **a detailed toxicity analysis is obligatory for all patients aged 71 years and older.** Therapy may be continued only if there is compliance with the following:

1. Evidence that no exclusion criteria related to chemotherapy-related toxicity except hematopoietic impairment have subsequently developed; in particular, no serious accompanying disorders or impairment of organ function; it must be particularly ensured that:
3 ECOG performance status is **0 - 2**
4. Heart: no angina pectoris CCS >2, no cardiac failure NYHA >2 and/or EF <50% or FS<25% in echocardiography/nuclear medicine examination
5. Lungs: no abnormal blood gases; if these are pathological, the patient is to be withdrawn if the resultant pulmonary function test shows FeV1<50% of reference values or a diffusion capacity <50% of the reference value.
6. Kidneys: creatinine may not be >2 times the upper reference limit
7. Liver: bilirubin may not be >2 times the upper reference limit
8. No uncontrollable diabetes mellitus under corticosteroid therapy

In any case of doubt, relevant supplementary examinations should be performed (ECG, echocardiogram, pulmonary function, creatinine clearance). Local guidelines regarding these supplementary examinations during or after chemotherapy should of course be observed.

3.1.3 Restaging on completion of chemotherapy

Approximately 14 days after the commencement of cycle 6 CHOP in DSHNHL 2006-1B/ACT-2, examinations are to be performed for disease reevaluation:

- patient history
- clinical examination
- laboratory parameters as for the primary staging examination
- electrocardiogram, echocardiogram if clinically indicated
- CT scan of neck/thorax/abdomen/pelvis (in case of primary involvement)

- appropriate evaluation of other primary manifestations (e.g. BM biopsy)
- evaluation and documentation of results of therapy and side effects

The restaging procedure after chemotherapy represents the final restaging. For the patients with NK/T-cell lymphoma, nasal type, who receive radiotherapy before or in parallel to the chemotherapy, the restaging should be performed after completion of both chemo- and radiotherapy.

3.1.4 Restaging in case of early discontinuation of therapy

In cases of early discontinuation of therapy (e.g. at the wish of the patient or because of excessive toxicity), a restaging examination should be conducted *as soon as possible* to determine the success of therapy at the time of discontinuation: procedures should be the same as those for the restaging on completion of chemotherapy.

3.1.5 Follow-up examinations

Follow-up of patients will continue until the completion of the study and planned observation period, i.e. at least until March 2016.

Follow-up examinations will be performed during the initial 2 years after the final restaging after therapy every 3 months, thereafter every 6 months within this protocol. Thereafter, annual follow-ups by the primary physician are recommended. Follow-up examinations consist of a clinical examination, laboratory analysis, imaging techniques and documentation of remission status and of therapy-induced disorders and secondary neoplasia and are to be conducted as detailed in the therapy plan and recorded in the follow-up CRFs. EBV monitoring by direct detection assays (quantitative PCR) is recommended at each follow-up in the first year after completion of chemoimmunotherapy.

3.2 Documentation of end points

The effect of therapy will be evaluated on the basis of the results of the final restaging examination as soon as these are available. The remission status must be evaluated on the basis of the results of the final restaging on completion of therapy complying with the response criteria defined below. These criteria should be appropriately applied for the interim restaging and follow-up examinations, too. The remission criteria have been defined on the basis of the recommendations of the published *International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas* [Cheson et al. 1999] and have been appropriately modified for application within a large-scale multicentre trial in aggressive lymphomas.

3.2.1 Complete remission (CR)

CR means the disappearance of all disease symptoms (clinical, radiological and laboratory [LDH]). In this case, the result of therapy is to be classified as "CR with complete regression" (abbreviation: CR). All enlargements of organs (spleen, liver, kidneys) attributable to lymphoma must have regressed and no more lymphoma masses should be detectable. If there was involvement of bone marrow, bone marrow biopsy must be performed and optical microscopy must confirm that bone marrow is free of signs of lymphoma. On completion of therapy, the patient must be in CR from the time point of the final restaging examination for at least 2 months.

3.2.2 Complete remission with remaining uncertainty (CRu)

If all requirements for CR are met, but signs of residual lymphoma are still detectable by imaging techniques, the result of therapy has to be classified as "CR with remaining uncertainty" (abbreviation: CRu). If re-biopsy shows that there are persistent lymphoma cells, the result of therapy cannot be classified as CRu. As in the case of CR, the patient must be in CRu from the time point of the final restaging examination for at least 2 months. If the result is classified as CRu on completion of therapy, this means that the treating physician considers that no further treatment is required at the time of evaluation.

3.2.3 Partial remission (PR)

The following criteria must be met in partial remission:

1. Lymphoma tissue still present (histological confirmation in all doubtful cases), but a clear reduction at all involved sites and reduction of the total lymphoma volume by at least 50%
2. No new lymphoma manifestations
3. Normalisation of blood counts.

Notes:

1. As a rule, PR should be accompanied by a tumour cell kill rate of several orders of magnitude. The definition of PR assumes that the disease is basically curable. If the result is classified as PR after six cycles of chemotherapy this implies that the treating physician

considers that use of additional treatment (assuming that there are no contraindications) extending beyond that of the protocol is indicated (e.g. salvage therapy). *A working classification of PR indicates that the treating physician considers further treatment appropriate; in view of the growth dynamics of aggressive lymphomas, however, it must also be assumed that in any case of supposed CRu in which active tumour tissue is still present, there may be renewed tumour development within 2 months during a therapy-free interval, so that the actual outcome would be revealed as PD.* This will be taken into account in the evaluation and final definition of the effects of therapy by the Study Management Committee. In any case of doubt or uncertainty, particularly with respect to the differentiation between CRu and PR, it is advisable to contact the trial office.

1. The above definition assumes that the kinetics of the remission of large, well-defined lesions can provide an indication of the remission of <u>all</u> lesions (including small, well-defined lesions and diffuse involvement). Thus, the measurement of <u>all</u> sites of involvement is not required. An exception to this is bone involvement, as no complete disappearance of all signs in follow-up diagnostic imaging techniques is to be expected.

3.2.4 No change (NC)

Continuous presence of lymphoma signs with only a slight reduction in size or slight increase in size of involved lymph nodes or organs (exclusion of PD and PR). The treatment result is to be classified as NC if:

- the largest diameter of any lymphoma has not increased by more than 25%
- the regression of lymphoma involvement does not conform to the criteria for PR (i.e. reduction <50%).

3.2.5 Progressive disease (PD)

There is progression of the disease if:

- there is recurrence of disease symptoms
- there is development of new lymphatic or extralymphatic lesions
- there is a marked increase in lymphoma manifestation size by more than 25% in comparison with baseline.

3.2.6 Relapse

There is relapse if, after at least 2 months CR or CRu (from the time point of the final restaging examination), one or more of the following criteria are met:

- there is recurrence of disease symptoms
- there is development of new lymphatic or extralymphatic lesions
- there is a marked increase in lymphoma manifestation size by more than 25%.

If the interval is shorter, the case is to be classified as PD. **In case of relapse, a new histological confirmation is recommended.**

Notes:

- Patients classified as CR, PR or NC during interim restaging 14 days after start of cycle 3 will receive three additional cycles CHOP-14/ A-CHOP-14.
- Non-responders (PD) will be given salvage treatment.
- Patients not in CR/CRu on completion of the whole treatment will receive salvage therapy.

3.2.7 Evaluation of unmeasurable tumour or bone involvement

Where tumours or bone involvement cannot be measured, the result can be classified as CR if all pathological signs disappear for at least 2 months (from the time point of the final restaging examination); the result is CRu if there is a marked remission of all pathological signs and no evidence of residual activity for at least 2 months (from the time point of the final restaging examination): if there is remission of all pathological signs, but evidence of activity or an increase in size within 2 months, the case is to be classified as PD. *In all cases of doubt as to the definition of results of therapy, we recommend consulting the trial office.*

3.2.8 Treatment related mortality

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.

4 EVALUATION OF SAFETY / ADVERSE EVENTS

4.1 Evaluation of safety

During staging examinations, the laboratory parameters relevant for therapy as listed on the CRFs will be documented. These will again be documented during the interim restaging examination after three cycles of chemotherapy, and within the restaging examination on completion of systemic therapy. Blood counts will be monitored on initiation of chemotherapy cycles and at least twice during each cycle, particularly during the nadir phase. The performance status of the patient (ECOG) will be determined prior to therapy, before each chemotherapy cycle scoring the minimal performance experienced, before radiotherapy, if applicable, and at the final restaging.

Also recommended is **a detailed toxicity analysis during the interim restaging examination: obligatory for patients aged 71 years and over**. This is required to ensure that chemotherapy has not caused functional impairment of the major organs and that there is no risk of such major impairment if chemotherapy is continued.

4.2 Adverse events (AEs)

4.2.1 Definition of expected/unexpected adverse events

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical or medical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding or example), symptom or disease temporally associated with the use of a medicinal (investigational) or medicinal product, whether or not it is considered to be related to the medicinal (investigational) product. (ICH-Guideline E2A). Adverse events are to be classified in accordance with the Common Toxicity Criteria (CTC) 3.0

Any adverse events which are not explicitly included in the CTC list should be classified as "Other" and evaluated, in analogy with the other AEs, using the following four point system:
Grade 0 = "none"
Grade 1 = "mild"/"slight"
Grade 2 = "moderate"/"clear"
Grade 3 = "severe"/"marked"
Grade 4 = "life-threatening"
Grade 5 = “death”

The following events are adverse events related to therapy (AR), but are expected in association with therapy:

- myelosuppression
- nausea/vomiting
- alopecia
- infections, particularly during phases of leukopenia
- haemorrhagic cystitis
- cardiomyopathy
- necrosis after paravasal injection

- peripheral polyneuropathy, paralytic ileus
- radiation damage to the lungs, pericardium or intestines
- allergic reaction to alemtuzumab (skin rash, systemic reactions)

In addition, unexpected adverse events may occur. All expected and unexpected adverse events occurring during therapy and the first 3 months until the first follow-up must be carefully documented. Therapy according to this protocol ends with documentation of disease relapse and implementation of salvage therapy.

There are also events which should be considered as disease-specific adverse events and not as drug-related adverse reactions. Those events should be documented only as AEs, irrespective of event severity. Such events are:

- any event solely attributable to tumor progression
- deep veine thrombosis / pulmonary embolism / arterial embolism
- infection grade III/IV prior to initiation of chemotherapy
- secondary malignancy detected during CHOP/A-CHOP chemotherapy.

The documentation as SAE is only necessary, if there is a possible causal relationship to the investigational medicinal product.

4.2.2 Documentation of expected/unexpected adverse events

The grade of severity of the adverse events classified in accordance with the CTC criteria should be documented in the fields provided in all chemotherapy and radiotherapy toxicity forms and the first follow-up CRF. If side effects occur which are not explicitly mentioned in the documentation forms, the relevant CTC number of the adverse event and the grade of severity should be classified as specified in Protocol Appendix and recorded in the CRFs with the relevant CTC number. Adverse events which do not appear in the CTC list should be described in detail and the grade of severity should be documented in analogy with the CTC criteria as defined.
Intercurrent disorders which do not conform to CTC criteria should be specified in written detail.
Relevant fields are provided in the follow-up CRFs for the documentation of complications which occur after the completion of therapy. In the case of adverse events of a particular grade of severity, the duration of the event, the required treatment measures, and the causal connection with therapy or the lymphoma disease are to be documented.

In this study, this will apply to the following events:

- all CTC grade 4/5 toxic events (excluding alopecia and haematological parameters)
- intercurrent disorders which cannot be characterised by CTC criteria
- unplanned hospitalisation.

As outlined above, disease-specific events are to be documented as AEs.

4.3 Serious adverse events (SAEs)

4.3.1 Definition of serious adverse events, serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs)

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening

Note: The item “life-threatening” in the definition of “serious” refers to an event in which the patient was actually at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect or
- other medical important condition (see below):

Note: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. (see ICH Guideline E2A, section IIB)

Exceptions to these criteria, which apply specifically to this study, are listed under 4.2.1.

The following events are to be classified as expected serious adverse reactions (SARs) for DSHNHL-1B/ACT-2:

- persistent (i.e. continuing for more than 3 months after completion of therapy) anaemia and thrombocytopenia requiring transfusion therapy
- life-threatening infection
- severe cardiomyopathy and /or arrhythmias (NYHA stage III/IV)
- therapy-induced secondary neoplasia (particularly leukaemia and MDS)
- severe organ toxicity (CDC III/IV) following allergic drug reaction
- life-threatening allergic drug reaction

Consultation with the trial office is necessary if other events occur which are not listed above and which the treating physician evaluates as serious.
Any events which are solely attributable to tumour progression are not to be classified as SAEs. The reporting of SAEs is obligatory.

4.3.2 Documentation of serious adverse events

All serious adverse events occurring during therapy and the first 3 months until first follow-up must be documented on the SAE report forms and must be faxed to the trial offices in Göttingen, respectively, **within one working day**.

The investigator has to notify the corresponding addresses (see below) of the occurrence of ANY serious adverse event (including death) immediately (within 24h), at latest the next working day. If additional data concerning the SAE become available at later time points, these, too, have to be reported to the trial office immediately. All SAE which are not subject of the immediate reporting are defined in 4.2.1.

The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects (Patient-ID) rather than by the subjects' names, personal identification numbers, and/or addresses.

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Automated SAE monitoring with follow up information until the resolvement or termination of the SAE will be conducted through the data management office. Incomplete or delayed SAE reporting by a trial center will automatically result in a monitoring visit with source data verification. Violations of compliances with SAE reporting rules by a trial center will be assessed by the trial coordinators and the steering committee and may result in the exclusion of trial center from further accrual of patients to this protocol.

If there is an excessive frequency of SAEs in one of the two treatment arms or the frequency of SAEs appears excessive, it may be necessary to terminate the study early.

Any events which are solely attributable to tumour progression are not to be classified and are not to be documented as SAEs. In case of early disease progression and implementation of salvage therapy, SAE reporting within this study ends.

5 DOCUMENTATION AND MONITORING

5.1 Structure of the documentation dossier

The participating investigational sites will be obligated to ensure thorough and complete documentation of the course of disease of each patient. To be able to include a patient in the study, all participating investigational sites will receive a “starter kit” in advance of the first patient inclusion. The “starter kit” will be handed out to the investigator at the official investigator kick-off meeting or send by mail in case of centers participating at later timepoints..

The “starter kit” consists of:

- the final study protocol
- patient information and patient informed consent sheet
- patient insurance contract
- randomisation forms (Baseline and Staging)
- reference/referral pathology confirmation form
- form for reporting serious adverse events
- instructions for completing the documentation forms
- a list of contact persons
- address labels for forwarding the completed forms

The complete Investigator Site File (ISF) will be delivered by the Trial Office (T-NHL) Göttingen.

After inclusion of a patient in the study, the treating physician will receive a documentation dossier with the clinical report forms (CRF) immediately from the IMISE data center in Leipzig.

The documentation dossier contains:

- certificate of randomisation
- forms for the procurement of patient´s material for accompanying research project (for German patients)
- a flowchart for the study
- instructions for completing the documentation forms, including a list of contact persons
- address labels for the forwarding of the completed forms
- case report forms for the randomised patients
- forms for reporting serious adverse events
- randomisation forms for the next patient to be included

The CRF will be prepared by the Data Management, IMISE Leipzig and printed on 4-part, no carbon required (NCR) paper. The completed original CRF pages and two copies are to be sent to the trial office in Göttingen, and one copy is retained at the trial site.

All entries in the CRFs must be made clearly with black ball-point pen, to ensure the legibility in self-copying or photocopied pages. Corrections are made by placing a single horizontal line through the incorrect entry, in a way that it can still be seen, and placing the revised entry

beside it. The revised entry must be initialled and dated by trial staff authorized to make CRF entries. Correction fluid may not be used.

The main investigator at the site or an authorised person will review the CRF for completeness and accuracy, sign and date all relevant CRF pages and any changes therein.

The signatures serve to attest that the information contained in the CRF is true and has not been falsified. In case of a major correction or missing data, the reason for it has to be given in the investigator comment field on the CRF. The investigator must assure completion, review and approval of all CRFs. At all times the principal investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the CRF. Even if there are no changes from a previous examination the questions which are repeated in each section of the case report forms should be answered completely.

As source data are regarded:

- all data contained in the patient's medical record
- all laboratory data provided by the central laboratory

5.2 Processing of completed documentation forms

The completed original documentation forms are to be sent to the trial offices, one copy is retained at the site.

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The submitted documentation forms will be processed in several steps in accordance with the methods specified in the SOPs:

Step 1 (pre-checking):

All documentation forms will be subject to initial medical assessment by the study physician at the trial offices in Göttingen, who will consider the following:

1. Deviations from study protocol
2. Occurrence of adverse events
3. Occurrence of serious adverse events (faxed SAE reports).

This will allow any medical problems to be identified at an early stage so that appropriate queries can be initiated by the Data Management, IMISE Leipzig. In addition, forms will be checked for plausibility and completeness. The originals of all documentation forms will then

be forwarded to the Data Management in Leipzig for data entry and query management. One copy will be forwarded to the IFS in Göttingen and one copy remains at the trial office.

Step 2 (data entry, query management and reminder):

Once the original CRFs are transferred to the Data Management at the IMISE, Leipzig, they will be registered upon arrival and placed in central files by the responsible data management staff for processing.

For creation of the study database, the study management software Oracle Forms will be used. The database will be validated according to the Standard Operating Procedures (SOPs) of the KKS/IMISE Leipzig prior to data capture.

Data items from the CRFs are entered into the study database by double data entry. Both data entries will automatically be compared and differences that show up will be checked by Data Management staff.

After data entry, all data will be checked for plausibility and completeness. Errors or omissions will be entered on data query forms, which will be returned to the investigational site for resolution. A copy of the answered and signed query is to be kept with the copies of the CRF at the site and the original query answer will be send to the trial office via mail. The trial office will forward the original query answer to the Data Management, IMISE Leipzig, where it will be entered into the database.

Reminders for outstanding CRFs and query answers, respectively, will be sent to the investigational sites as well as to the monitor by fax on a regular basis.

An audit trail of all changes in the contents of the study database will be automatically recorded.

Step 3 (evaluability):

When all documentation of therapy and the reference pathology report is available, study physician, monitor and biometrician will convene to decide on the evaluability of each individual patient and will assess the significance of any protocol violation.
Once the database has been declared complete and accurate before the final analysis, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between the coordinating investigator, the biometrician and the data manager.

5.3 On-site monitoring

Monitoring on site will be performed by members of the Institut für anwendungsorientierte Forschung und klinische Studien (IfS) in Göttingen or contract research organisations (CROs) as delegated by the national principal investigators according to trial specific SOPs. Because of the anticipated number of trial sites (approx. 100) and the small number of patients per site the following monitoring procedures will be implemented.

Before start of the trial, a kick-off meeting will be performed, to inform the investigators and their key trial personnel on the relevant trial procedures. In addition, extensive written guidance will be provided with the investigator site file. Inclusion of the first patient will be allowed without prior initiation visit. Every trial site will be visited for initiation, either immediately after the first patient received the 2nd course of CHOP-14. The participating institutions are obligated to allow monitors access to original patient documentation (signed patient information, informed consent, case records, laboratory sheets, original images etc.).

At this visit the study monitor will review the protocol and case report forms (CRFs) with the investigators and their staff and explain the trial process in detail.
During the trial the monitor holds regular telephone contact with all sites. For cause visits are possible if there are problems with regulatory documents, CRF documentation, CRF transmission, delayed SAE-reporting or severe protocol violations. Request for missing data or further information will be made in writing, by telephoning or –if necessary- by visiting the participating institutions. Furthermore, site visits will be performed, when significant delays in documentation or major protocol violations occur. During these visits the monitor will conduct source data verification (SDV) by random: 100% SDV carried out for compliance in- and exclusion criteria, informed consent, main target criterion, documentation and reporting of AEs, SAEs, age, sex, initials and number of the patients. 5% SDV is verified for patient history data, lab values and other parameter. Patient records and Investigator Site File will be checked for completeness, plausibility and correctness by random.
An additional visit will be arranged for close out. During these visit the monitor will check all trial-related documents for archiving and instruct the investigator about the procedure and periods thereof. To every contact a report is written by the monitor describing occurred difficulties and the progress of the study.
The investigator and key trial personnel must be available to assist the monitor during these visits. The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the CRF entries. Further information about the monitoring will be described in the study specific monitoring standard operating procedures (SOP) of the IfS.
The monitoring will be performed by the staff of the IfS in Göttingen or respective national contract research organisations for centers outside Germany.

5.4 AE, SAE and SUSAR reporting

5.4.1 AE reporting

The occurrence of all adverse events (AE) not qualifying as serious (see 4.3.2) will be documented in the CRFs.

5.4.2 SAE reporting

The investigator at each study site has to report any SAE as described in 4.3.2. If in case of the death of a patient additional information will be required, the investigator has – on demand - to forward all information to the leading ethics committee, as well to all involved ethics committees, as well as to the competent regulatory authorities and to the Coordinating investigator/Sponsor. Further SAE handling and reporting takes place in collaboration between trial office in Göttingen, and drug safety management at IMISE. Based on the SAE-CRF the clinical study consultant at the trial office will complete an SAE assessment sheet including an english narrative of the medical assessment of the SAE. The clinical study consultant documents the causal relationship between the SAE and the investigational medicinal product and the expectedness of the SAE. He will send the SAE-CRF and the Assessment sheet to the IMISE, Leipzig within 24-48 hours.

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The electronic data collection of the SAEs takes place at the drug safety management at IMISE and will be done with eSafetyNet, an SAE-Management-Tool of the company eResearch Technology. Beyond the data of the CRF, also the results of the medical assessment of the clinical study consultant will be entered. After data entry diagnoses and reactions are coded with MedDRA.

5.4.3 SUSAR-Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are side effects (probably or definitely connected with the administration of the investigational product), the nature or severity of which are inconsistent with the information available about the product. Information about the trial product are contained in the Investigator's Brochure/the SmPC (Summary of medicinal Product Characteristics) should be used to verify if the adverse reaction has been previously described. The drug safety management at IMISE submits all information available about a SUSAR immediately, the latest within 15 days after the event becomes known to the sponsor, to the responsible ethics committee[1], the competent regulatory authorities, and to all main investigators at each participating trial site. The main investigator at each trial site is responsible that all co-investigators at his site are informed about the occurrence of the SUSAR.

In the case of death or a life-threatening condition caused by a SUSAR the concerned ethic committee, the competent regulatory authorities and all main investigators at each participating trial site must be informed by the sponsor within 7 days after the event becomes known to the sponsor. Additional information has to be given within further 8 days.

In parallel to the information of the competent authorities, the IMISE will also inform the provider of the investigational drug alemtuzumab, Bayer Schering Pharma AG, about the occurrence of SAEs and SUSARs, at Bayer Schering Pharma AG, Global Medical Safety Surveillance, Müllerstrasse 178, 13353 Berlin, Phone +49 30 468 12998, Faxnumber:+49 30 468 96765, E-mail: GMS_DataManagement@schering.de.

Other safety issues must also be reported, if they might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the clinical trial, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected SAR, which is judged to be clinically important,
- post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor
- new events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects, such as:

  - SAEs, which could be associated with the trial procedures and which could modify the conduct of the trial,

  - a significant hazard to the subject population such as lack of efficacy of an investigational medicinal product used for the treatment of a life-threatening disease,

  - a major safety finding from a newly completed animal study,

[1] The responsible Ethic committee is the Ethic committee of the Member State of the subject with the occurred SUSAR.

- any anticipated end or temporally halt of a trial for safety reasons and conducted with the same investigational medicinal product in another country be the same sponsor

- recommendations of the DMSC, if any, where relevant for the safety of the subjects

The PI in consultation with the steering committee and the DMSC have to judge if the rate of occurrence or the qualitative changes of expected SARs represents a safety issue that need to be reported.

Upon decision of the PI, the drug safety manager at the IMISE submits also all other safety issues as described above to the competent authority and the Ethics Committee in the concerned Member States as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

The drug safety manager at the IMISE uses the CIOMS I form for the paperbased submission of SUSARs and relevant SARs. This form will be created after data entry and MedDRA-coding with eSafetyNet and is electronically stored as well as in the trial master file. Together with a cover letter the CIOMS I form is sent to the named organisations and persons. The date of the submission is stored in eSafetyNet.

5.4.4 Annual Safety Reports

The sponsor writes an annual (or upon request) safety report (following the “detailed guidance on the collection, verification and presentation of adverse events reports arising from clinical trials on medicinal products for human use). This report comprises a detailed risk-benefit-analysis, a list of all documented SARs – serious adverse reactions (Line Listing), as well as a summary table containing all documented SARs in the course of the trial.

The Line Listing and the Summary tabulations are created with eSafetyNet in the IMISE and sent to the Sponsor upon request.

The sponsor submits this report detailing the safety of the tested medicinal products to the concerned ethics committees as well as to the competent regulatory authorities.

The reporting time frame for the annual safety reports starts with the date of the first authorisation of the clinical trial by a competent authority.

5.4.5 Information of Ethic Committees

Because of the procedures concerning SUSAR-reporting (see 5.4.3) it’s necessary that:

All SUSARs from other Member States are periodically reported at least every 6 months as a line listing accompanied by a brief report by the sponsor highlighting the main points of concern. Those periodic reports should only include SUSARs reported within the period covered by the report. Any changes increasing the risk to subjects and any new issues that may affect adversely the safety of the subjects or the conduct of the trial should also be provided as soon as possible, but no later than 15 days. This SUSAR Listing for the Ethic Committees is created with eSafetyNet in the IMISE and sent to the Sponsor upon request. The sponsor submits the listing to all concerned ethics committees and a copy should be sent to the concerned competent authority.

If there is an excessive frequency of SAE, SAR or SUSAR in one of the study arms, DMSC will be informed and early termination of the study must be considered.

6 REFERENCE EVALUATIONS

6.1 Reference Pathology Report

The primary histological diagnosis will be made by a local pathologist on the basis of the examination of a biopsy from a completely excised lymph node. Alternatively, in cases without lymph node involvement, the diagnosis can be based on the histologic examination of the biopsy of an appropriate sample of another involved organ. The diagnosis "peripheral T-cell NHL" by the local pathologist is required before recruitment of the patient for the study and randomisation. Surgeons and medical oncologists are urged to obtain fresh frozen material of all lymph nodes for further analysis as the quality is superior to formalin fixed lymph node materials. Procedures for processing and courier transport are to be found on the BMBF-KML website www.lymphome.de.

In cases with a tentative diagnosis of peripheral T-cell lymphoma, the primary pathologist will send all biopsy material to the respective reference pathologist to confirm the diagnosis. In addition, upon diagnosing any peripheral T-cell lymphomas in their consultation practice, the reference pathologists will notify the treating physicians about this trial in order to increase recruitment. On receipt of the samples, the reference pathologist will either confirm or disapprove the diagnosis of peripheral T-cell non-Hodgkin's lymphoma. Diagnostic workup includes conventional stains (H&E, Giemsa, PAS) and immunohistochemical stains for B-and T-cell markers (CD 3, 5, 20, 30, 52), T-cell subsets (CD4, 8, 56, 57, granzymeB, Perforin, TIA1, FOXP3, CXCL13), dendritic cells (CD21) and proliferation (Ki-67). Individual cases will need additional stains (e.g. ALK1) to exclude differential diagnoses. To confirm clonality of the T-cell proliferation, the rearrangement of the T-cell receptor beta and gamma chains will be investigated applying the Biomed2 protocol. Diagnoses will be rendered according to the WHO classification. The reference pathologist will *immediately* communicate the result to the local pathologist and the trial office on the pathology form 1. Confirmation of the diagnosis is mandatory for patient inclusion in this trial.

The diagnosis will be made available within two weeks after receiving the material in the reference pathology laboratory.

In Germany, the collection of the reference pathology case numbers and diagnoses will be assisted by the pathology server. All personal patient data entered into the database upon registration of a patient will automatically be matched to the data in the reference pathology databases via the pathology server supported by the KML lymphoma network.
The reference pathologist who received material of a study patient will thereby be easily identified and can thus be actively contacted by the DSHNHL coordinating reference pathologist in Würzburg (or the trial office) to deliver the reference diagnosis by completing an according CRF-form for the patient using the Patient-ID. The documented reference diagnosis will be forwarded to the DSHNHL coordinating reference pathologist who will check the diagnosis and send the reference documentation form via the trial office to the Data Management at the IMISE, Leipzig.

Within this prospective therapeutic trial, the national reference pathology also serves as a tissue bank for associated scientific investigations. Tissue not needed to establish the diagnosis will therefore be made available for scientific studies and tissue microarrays

(TMAs) will be assembled for individual diagnostic categories. The scientific advisory board of the trial will decide on the scientific investigations to be performed.

Whenever possible, fresh biopsy material should be obtained to support scientific studies on peripheral T-cell lymphoma. The transport of this fresh material should be individually organized in collaboration with the trial office or the reference pathologists. Whenever feasible, the material will be collected directly after diagnostic tissue biopsy. This allows an optimum preservation of tissue for scientific projects, including the asservation of viable cells and classical cytogenetic studies. The sterile lymph node will be dissected in the pathology institute and top of priority will be to establish the diagnosis. Alternatively, fresh material should be shock-frozen (liquid nitrogen) in plastic tubes. Material deep-frozen for immediate intraoperative diagnosis should also be made available for molecular biological and immunohistochemical analyses.

7 ACCOMPANYING SCIENTIFIC PROJECTS

At predefined time points during the study (initial staging, interim and final restaging, follow-up), samples for analysis in accompanying projects are to be obtained and forwarded. The sampling procedures are clinically indicated at the planned time points and will not represent additional procedures, investigations, site visits etc. for the patients. All investigations will be performed in accordance with local EC and IRB votes and the relevant data safety procedures in effect according to national legislation.

Thanks to the close cooperation between several research groups within a multicenter clinical trial, it is possible to correlate experimental and clinical data and thus determine the clinical value of experimentally obtained data. Such projects may e.g. comprise:

- the analysis of alemtuzumab pharmacokinetics on the first 20 patients, who will have received alemtuzumab;
- the determination of absolute numbers and subsets of T-, B-lymphocytes, and NK cells as determined by flow cytometry prior to therapy, and at several time points during therapy;
- assessment of Fcγ-receptor polymorphisms from peripheral blood lymphocytes by allele-specific PCR; assessement of ADCC activity from alemtuzumab with autologous NK cells (effector cells) and PHA-transformed T-lymphocytes or EBV-transformed B-lymphocytes (targets);
- from serum samples: assessment of the concentrations of sCD44, sFAS, VEGF, TNF-R1, TNF-R2, sIL-4R and thymidine kinase prior to the initiation of therapy; correspondingly determination of genetic polymorphisms for TNF-R1, TNF-R2 and IL-4R from all patients at initial staging; univariate and multivariate analyses with the five IPI factors for primary endpoint and secondary endpoints.
- The collection of fresh tissue serves two purposes:
    - (1) The sequence of the T-cell receptor beta chain locus rearranged in the clone can be defined and used to investigate primary blood-borne dissemination or minimal residual disease
    - (2) The tissue will allow clinico-pathological correlations in a number of approaches (c-DNA microarrays, FACS to define tumor cell phenotype, proteomics). Giving the acquisition of fresh tissue a high priority, we expect fresh tissue from 10% of the patients (n=43), which will be one of the largest series ever collected.

By signing the consent form, patients will also confirm that they agree to these accompanying projects, providing that these are **not** conducted for commercial purposes. Lymph node material and blood samples will be obtained from patients and forwarded to the reference pathology and the trial office, respectively. Patients may at any time withdraw their consent to these tests, without any influence on their participation in this trial.

The treating physicians will be requested to supply the material to the appropriate collection addresses during staging, restaging and follow-up.

Depending on their nature, these materials are to be forwarded to different addresses.

1) **Blood, serum, bone marrow (10 cc each)**

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2) **Fresh lymph node material**: National Reference pathology Center (c.f. 6.1)

3) **Shock-frozen fresh material**: National Reference Pathology Center (cf. 6.1)

The primary pathologists should send paraffin sections/shock-frozen fresh material to the Reference Pathology Centers. DNA obtained from paraffin sections will be stored at the national reference pathology laboratory

The *Scientific Advisory Board of ACT-2 trial* will consider, in consultation with the Study Steering Committee, applications for material submitted by research groups. In addition to the representatives of the Study Management Committee, the Reference Pathology Panel and Biometry, the Advisory Board will consist of experts in the relevant fields.

If applications for obtaining patients materials are approved, the members of the Advisory Board will consult the Data Centre to specify which samples (or patient populations) are to be included in the analysis and what data are to be provided to the Data Center by which deadlines. The research groups will be provided with clinical data for their investigations. Clinical and biometrical data will be released by the Study Management Center only for the use in projects which have been approved by the Scientific Advisory Board of the ACT-2 trial. The progress of these projects will be assessed at annual investigators meetings.

8 ETHICAL ASPECTS

This clinical study will be conducted in accordance with ICH GCP guidelines. All participating institutions are obliged to comply with the requirements of the Declaration of Helsinki.

The protocol for this study was approved by the Protocol Committee of the DSHNHL and the participating institutions at the meeting held on 04/05 May 2006. Version 2.0 and the amended version 3.0 of the study protocol had been submitted for evaluation by the local ethics committee, the Ethics Committee of the Georg-August-Universität Göttingen, for the master ethics vote.

The Ethics Committee will also be notified immediately of any future proposed changes or amendments to this protocol (changes of dosage, prolongation of treatment duration, prolongation of the study, changes in eligibility criteria, increase in sample size, etc.). These changes or amendments shall come into force only after they have received the positive approval of the Ethics Committee. Should there be evidence of an increased rate of serious adverse events (SAEs), the Ethics Committee will be informed and their opinion obtained as to whether there are reservations concerning the continuation of the study or one of the study arms.

Participating institutions in other regions should note that they must notify their local Ethics Committee of the study and establish whether they require a separate approval. If this is the case, patients may only be included in the study if the approval of the local Ethics Committee has been obtained!

9 ADMINISTRATIVE ASPECTS

9.1 Data processing and archiving of data

The data provided in CRF will be entered in an Oracle database using data entry templates. After data entry, data quality will be checked regarding completeness and plausibility by means of programmed query checks. The study database will be checked for errors and validated by the data base clerk in cooperation with the biometrician and the data manager and then released for use. A back-up of all data will be made on a daily basis. Grades of access authorisation will be allocated on the basis of hierarchical roles to completely prevent unauthorised access to patient data. The system in place will ensure that the anonymity of data is maintained during the analysis. The documentation forms will be retained for at least 10 years at the trial offices in Göttingen, Aarhus and the Data Center in Leipzig. The electronically stored data will be retained for at least 20 years by the Data Centre in Leipzig. The interim and final analysis reports will be retained at the trial offices in Göttingen or Aarhus for 20 years.

The treating physicians at the participating centres should retain the study documentation (Patient Consent Forms, Patient Information Confirmation Form, completed and submitted documentation forms including CRF's, Data Correction Forms and query answers) until the final analysis report for the study will be prepared.

9.2 Subsequent amendments to the protocol

Any subsequent amendments to the protocol must be approved by the Protocol Committee. The Protocol Committee shall also decide when such amendments are to come into force. If major amendments to the protocol are required, i.e. modification of a therapy arm, eligibility or exclusion criteria, numbers to be recruited and duration of the recruitment phase, or should it be necessary to discontinue a therapy arm or the study as a whole, the approval of the DMSC must be obtained. The Ethics Committee in charge must also approve any subsequent protocol amendments. If there is no objection to proposed amendments, the participating institutions will be informed in writing. In addition, the date of approval of the amendment by the Protocol Committee, the Decision of the Ethics Committee, notification of the participating institutions and the date on which the amendment came into force will be documented. The amendment will also be incorporated in the study protocol.

9.3 Finances and insurance

The trial is supported by a grant of the Bundesministerium für Forschung und Technologie.

All participating patients will be covered by a study subject insurance policy taken out with the Allianz, the insurer of the Sponsor of the Trial. A copy of the insurance conditions is to be handed out to patients.

9.4 Publication agreements

The results of this study are to be published in the international scientific journals. The protocol will upon approval be submitted to the NIH clinical trials database. The Protocol Committee of ACT-2 shall decide on authorship. To be taken into account are the contribution with respect to study planning and the active participation in the study (to be assessed on the basis of numbers of recruited patients). Manuscripts may only be submitted for publication when all authors have approved the contents. The main author will assume

that contents have been approved by the co-authors if no requests for alteration have been received from the co-authors within 4 weeks after receipt of the draft manuscript.

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11 APPENDIX

11.1 Definitions - stage and extranodal involvement

The following modified version of the Ann Arbor system should be used for classification of stage. The regions used in the Ann Arbor system are as follows:

Region 1: right - cervical, supraclavicular, occipital, pre-auricular, nuchal, submandibular
Region 2: left - cervical, supraclavicular, occipital, pre-auricular, nuchal, submandibular
Region 3: right - infraclavicular
Region 4: left - infraclavicular
Region 5: right - axillary/pectoral
Region 6: left - axillary/pectoral
Region 7: mediastinal (including thymus)
Region 8: right - pulmonary hilus
Region 9: left - pulmonary hilus
Region 10: mesenteric
Region 11: para-aortal (including spleen and hepatic hilus)
Region 12: right - iliac
Region 13: left - iliac
Region 14: right - inguinal/femoral
Region 15: left - inguinal/femoral

Stages:
I,N: nodal involvement in one region
I,E: presence of one single extranodal focus

II,N: nodal involvement in two or more regions on one side of the diaphragm
II,N,E: presence of one or more nodal involvements in regions and one extranodal focus on one side of the diaphragm

III,N: nodal involvement in two or more regions on both sides of the diaphragm
III,N,E: presence of one or more nodal involvements in regions and one extranodal focus on both sides of the diaphragm

IV,E: diffuse involvement of one or more extranodal foci, or more than two extranodal foci. Involvement of the liver and / or the bone marrow is stage IV,E.
IV,N,E: IV,E with additional involvement of nodal regions

Definition of extranodal involvement (E): involvement of extranodal tissue, due to direct growth of an involved lymph node or because of close anatomical association

For the IPI, involvement of paired organs counts as one E-manifestation. As one E-manifestation each also count: bone marrow, spleen, lung, liver, pleura, pericardium, CNS, stomach, small intestine, colon, and further E-foci (s. code). Exceptions:

- skin and soft tissue e-foci count as E-manifestations each
- skeletal: e-foci above and below the diaphragm count as two manifestations.

Codes for extralymphatic foci sites:

ORB = orbita
PNS = paranasal sinuses (jaw, forehead, ethmoidal sinus)
MNC = main nasal cavity
MR = mouth region (oral cavity, lips, pharynx)
TOG = tongue
SG = salivary glands (ear, low jaw salivary glands)
TG = thyroid gland
MG = mammary gland
P = peritoneum
PAN = pancreas
K = kidney
AG = adrenal gland
UB = urinary bladder (including urethra, urinary tract)
TES = testes (including epididymis)
OVA = ovary
UT = uterus
SKN = skin
WR = Waldeyer´s ring including the tonsils
ST = soft tissues (including muscles, connective tissue and fat tissue)
ASC = ascites.
OTH = other (please specify)

Definitions of general symptoms:

Stages I to IV should be suffixed **B**, if one or more of the following general symptoms are present, and suffixed **A** if these are not present.

General symptoms are:
- otherwise unexplained fever over 38° C
- otherwise unexplained night sweating (making change of night clothes necessary)
- otherwise unexplained loss of weight by more than 10% of bodyweight within 6 months.

11.2 Definition of bulky disease

Bulky disease is present if:
- there is massive lymphoma development in a lymph node with a greatest diameter of ≥7.5 cm or a conglomerate tumour with a greatest diameter ≥7.5 cm
- there is a mediastinal tumour with a diameter ≥7.5 cm, whereby the hili and the pericardium should not be included in the measurement.

The dimensions of bulky disease must be documented in detail in the Staging Report Form. Bulky disease can involve several **neighbouring** regions (conglomerate tumour).

11.3 Definitions – Performance Status according to the Karnofsky index

100%: capable of normal activities, no symptoms, no manifest signs of illness
90%: normal performance status, minimal symptoms or signs of illness
80%: normal activities only possible with effort, mild signs of illness, no symptoms
70%: unable to perform normal activities or work, still self-sufficient
60%: occasional support required, but still largely self-sufficient
50%: constant support and care required, physician's help often required
40%: largely bedridden, special care and help required
30%: constantly bedridden and severely handicapped, trained nursing care required (admission to hospital indicated)
20%: status extremely ill, admission to hospital necessary, active supportive treatment required
10%: moribund

11.4 Definitions – Performance status according to the ECOG scale

General status (ECOG):

Grade 0: fully functional, no symptoms
Grade 1: ambulatory patient with symptoms, able to carry out light work
Grade 2: patient with symptoms, less than 50% of daytime in bed, self-sufficient
Grade 3: patient with symptoms, more than 50% of daytime in bed, requires some help from others
Grade 4: completely bedridden and reliant on help from others

11.5 Comparison of ECOG and Karnofsky indices

ECOG	Karnofsky
0	100%
1	90%
	80%
2	70%
	60%
3	50%
	40%
4	30%
	20%
	10%

11.6 International Prognostic Index

The International Prognostic Index (IPI) designed by [Shipp 1993] is based on five prognostic factors. These include age (≤60 years vs. >60 years), LDH value (≤ upper reference value vs. >upper reference value), stage (I,II vs. III,IV), the number of extranodal involvements (0-1 vs. >1) and performance status (ECOG 0-1 vs. ECOG 2 - 4).

11.7 Common Toxicity Criteria (CTC): Classification of acute side effects of chemotherapy and radiotherapy

Reporting of adverse events as side effects of the study trial will be performed using the CTC terminology codes. The Common Terminology Criteria for Adverse Events v3.0 (CTCAE) is provided in the investigator´s site file, or can be downloaded from the website of the Cancer Therapy Evaluation Program under: http://ctep.cancer.gov/reporting/ctc.html