NORDIC LYMPHOMA GROUP

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

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

THE ACT-1 and ACT-2 TRIALS

ACT-1 (younger patients)

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

ACT-2 (elderly patients)

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

Study Coordinator(s):		ACT-1: F. d´Amore (Nordic Lymphoma Group) ACT-2: L. Trümper (DSHNHL) F. d´Amore (Nordic Lymphoma Group)
Statisticians	**:**	H. Anderson (Nordic Lymphoma Group) and M. Kloess (IMISE)
Data Center Chair	**:**	M. Löffler (IMISE, Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig)
Randomization	**:**	Clinical Trial Office, Aarhus University Hospital, Denmark
EudraCT number	**:**	**2006-006130-17** - ACT-1-Trial (younger) **2007-000821-23** - ACT-2-Trial (elderly)
Final version	**:**	**18.09.2007**

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THE ACT-1 TRIAL

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EudraCT number	**:**	**2006-006130-17** - ACT-1-Trial (younger) **2007-000821-23** - ACT-2-Trial (elderly)
Final version	**:**	**Version 1.0: 18.09.2007** **Version 2.0: 30.01.2009, amendment #1 incorporated** **Version 3.0: 30.06.2009, amendment #2 incorporated** **Version 3.1: 20.01.2011**
Amendment #1	**:**	**30.01.2009**
Amendment #2	**:**	**30.06.2009**
Date of activation	**:**	**22.10.2007**

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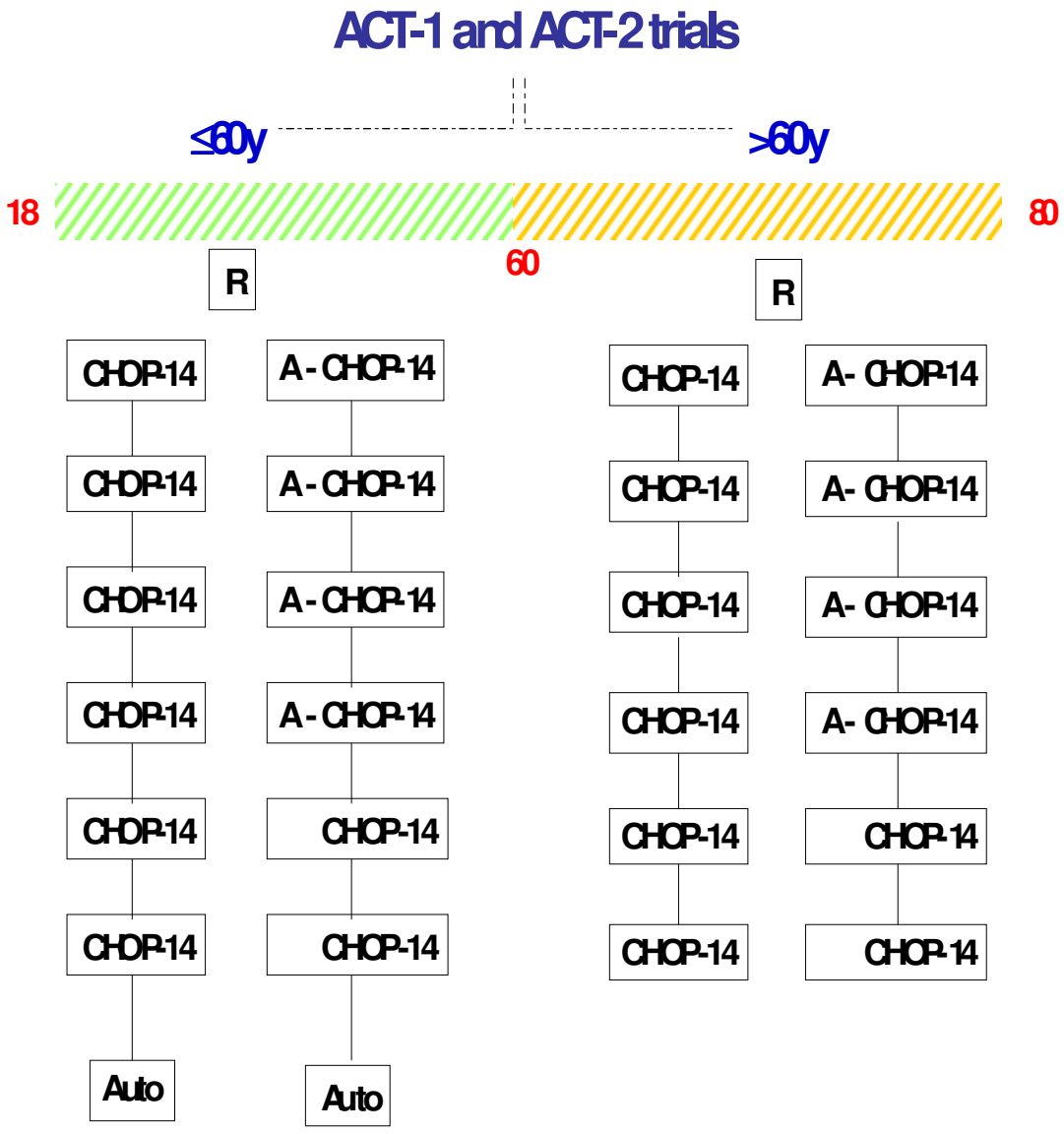
2. Scheme of the study



R= Randomization

A= Alemtuzumab (30 mg d1 of cycle1-4)

Auto= High-dose therapy (BEAM) with autologous stem cell support

PTCL= unspecified, AIL, hepatosplenic, panniculitis-like (γδ), NK/T nasal type, enteropathy associated

3. Synopsis

Project Code:	First International phase III T-cell lymphoma study (Alemtuzumab and CHOP in T-cell lymphomas, ACT)
Indication**:**	Newly diagnosed non-cutaneous peripheral T-cell lymphoma (PTCL), except *alk*-protein positive and negative anaplastic large cell lymphoma
Study objectives:	Determination of the efficacy and safety of the monoclonal antibody MabCampath® (alemtuzumab) combined with two-weekly CHOP supported by G-CSF
Primary Endpoint:	Event-Free-Survival (EFS)
Secondary Endpoints:	Efficacy: Overall Response Rate, Complete Remission and Partial Remission (ORR, CR, PR) after induction chemotherapy, ORR related to tumoral CD52 status, eligibility for ASCT after induction in the young population (≤ 60 years). Overall survival (OS). Progression-free Survival (PFS). Safety. Adherence to protocol.
Study Design:	International open-label, multicentre, randomized Phase III Study
Patient Population:	Patients ≥ 18 yrs with newly diagnosed non-cutaneous, non-leukemic PTCL, except *alk*-protein positive and negative anaplastic large cell lymphoma
Planned Sample Size:	**ACT-1:** 308 young patients (≤ 60 yrs) registered and randomized
Total Number of Centers:	This study will be proposed to main European and Australian Study Groups. Single centers from other parts of the world will be allowed to participate.
Inclusion Criteria:	♦ Previously untreated patients with newly diagnosed peripheral T-cell lymphoma of stage I bulk (≥ 7.5 cm) and stages II to IV. ♦ Patients with a confirmed histologic diagnosis of peripheral T-cell NHL according to the WHO classification (Appendix C): ✓ Peripheral T-cell lymphoma, unspecified (PTCL NOS) ✓ Angioimmunoblastic T-cell lymphoma ✓ Enteropathy associated T-cell lymphoma ✓ Subcutaneous panniculitis-like T-NHL (γδ T-cell lymphoma) ✓ Hepatosplenic T-cell lymphoma ✓ Extranodal NK/T cell lymphoma, nasal type ♦ Age 18-60 years at the time of randomization for young patients' cohort ♦ Life expectancy of 3 months or longer ♦ ECOG performance status 0, 1 or 2 at randomization (see appendix D). PS 3 acceptable if lymphoma-related. ♦ Measurable disease ♦ Written informed consent

Exclusion Criteria:	♦ Patients with NK/T-NHL of the following type: ✓ Precursor T cell lymphoblastic lymphoma/leukemia ✓ All mature T cell leukemias (T-PLL, ATLL, NK cell leukemia, T-LGL) ✓ Alk-positive and negative anaplastic large cell lymphoma ✓ Blastic NK cell lymphoma ✓ Cutaneous T-cell lymphoma, transformed or not ✓ HTLV1-positive adult T-cell leukemia ♦ Concurrent severe and/or uncontrolled medical disease (e.g. uncontrolled diabetes, congestive heart failure, myocardial infarction within 6 months prior to the study, unstable and uncontrolled hypertension, chronic renal disease, or active uncontrolled infection), which could compromise participation in the study. ♦ Known hypersensitivity to murine or chimeric antibodies or proteins ♦ Severe cardiac dysfunction (NYHA classification II-IV) or LVEF < 45 % ♦ Significant renal dysfunction (serum creatinin > 2x UNL), unless related to NHL ♦ Significant hepatic dysfunction (total bilirubin ≥ 30 µmol/l or transaminases ≥ 2.5 times normal level), unless related to NHL ♦ Impaired pulmonary functions; in this case, the patient is to be excluded if the resultant pulmonary function test shows FEV_1<50% or a diffusion capacity <50% of the reference values ♦ Suspected or documented central nervous system involvement by NHL ♦ Patients known to be HIV-positive ♦ Patients with active, uncontrolled infections, especially known seropositivity for HCV or HbsAg ♦ Patients with uncontrolled asthma or allergy, requiring systemic steroid treatment ♦ Prior treatment with chemotherapy, radiotherapy or immunotherapy for this lymphoma, except local radiotherapy in case of extranodal NK/T cell lymphoma, nasal type ♦ History of active cancer during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma ♦ Unwillingness or inability to comply with the protocol
Study Medication:	Six cycles of two-weekly CHOP plus G-CSF with or without alemtuzumab given subcutaneously 30 mg day 1 in combination with chemotherapy cycles 1-4 and no antibody in cycles 5-6. Patients in CR, CRu, or PR after the 6 cycles of CHOP14 combined or not with alemtuzumab will receive a consolidation with high-dose chemotherapy followed by autologous stem cell transplantation.
Timelines:	♦ Start of recruitment: Q2/2008 ♦ End of recruitment: Q2/2014 ♦ Last patient out of treatment: Q3-4/2014 ♦ End of observation: Q4/2016 ♦ Duration of the entire trial: Q2/2008 to Q4/2016 ♦ Interim analysis: ♦ Safety: ACT-1: after every 50 treated pts ♦ Efficacy: ACT-1: after about 2.5 years inclusion
Sponsors:	Nordic Lymphoma Group (NLG)

4. Investigators and study administrative structure

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5. Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
ALAT	Alanine Amino Transferase
ASAT	Aspartate Amino Transferase
ATLL	Adult T cell Leukemia/lymphoma
BM	Bone Marrow
CD52	Cluster Defined number 52
CHOP	Cyclophosphamide, Doxorubicin, Vincristine (Oncovin), Prednisone
CHOP14	2 weekly CHOP
CMV	cytomegalovirus
CR	Complete Remission/Response
CRF	Case Report Form
CRu	Complete Remission unconfirmed
CT	Computerized Tomography
CTC	Common Toxicity Criteria
DFS	Disease Free Survival
DSMB	Data and Safety Monitoring Board
EATL	Enteropathy associated T cell Lymphoma
EBV	Epstein Barr Virus
EFS	Event Free Survival
ENT	Ear Nose Throat
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
γGT	Gamma Glutamyl Transferase
GvHD	Graft-versus-Host-Disease
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IPI	International Prognostic Index
IV	Intravenous
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
NC	No change
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NOS	Not otherwise specified
NRP	National Reference Pathologist
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood

PD	Progressive Disease
PET	Positron Emission Tomography
PO	Per Os
PPD	Product of the two largest Perpendicular Diameters
PR	Partial Response
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
SPD	Sum of the Products of the two largest perpendicular Diameters
T-LGL	T cell large granular lymphocyte leukemia
T-NHL	T cell Non-Hodgkin lymphoma
T-PLL	T cell prolymphocytic leukemia
TTTF	Time to treatment failure
US	Ultrasound
WBC	White Blood Count
WHO	World Health Organization

6. Background and Rationale

6.1 Introduction

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoid malignancies. In Western countries, PTCLs account for 10-15% of all lymphomas and almost 20% of aggressive lymphomas[1-4]. However, geographical differences in the incidence are reported, PTCL being relatively more common (35-45%) in Asia, in particular with respect to some specific histopathologic subtypes such as the NK/T-cell, nasal type. With regard to their clinical and histopathological features, a variety of different PTCL entities have been described. The World Health Organization (WHO) classification of lymphoid neoplasms recognizes 9 distinct clinicopathologic PTCL subtypes[5] that can be grouped into three main categories: leukemic, predominantly extranodal and predominantly nodal PTCLs. Subtypes with predominantly nodal presentation are: PTCL, unspecified (PTCLu), angioimmunoblastic lymphoma (AIL) and anaplastic large cell lymphoma (ALCL). PTCLu represents the most common T-cell lymphoma subtype in Western countries. It usually occurs in middle-aged to elderly patients. Patients with PTCLu commonly present with stage III-IV disease and unfavourable clinical characteristics, such as B symptoms, elevated LDH levels, bulky tumour, bone marrow involvement (up to 25% of the cases), and poor performance status. Consequently, more than a half of these patients have an unfavourable International Prognostic Index (IPI) at diagnosis[6]. Since the mid-eighties, evidence has accumulated that PTCLs are clinically more aggressive, have a poorer response to treatment and a shorter survival as compared to their histologically aggressive B-cell counterparts[6-10]. Whether the International Prognostic Index (IPI) is a better predictor of survival than the histological subtype in PTCLs is still a matter of debate[11-13]. With the exception of a*lk*-protein positive ALCL, which seems to have a significantly better prognosis than its *alk*-negative counterpart after conventional chemotherapy, there is general agreement on the unsatisfying results observed with conventional therapeutic strategies in PTCL.

6.2 Results of conventional chemotherapy in Peripheral T-cell Lymphomas

Throughout the years, PTCLs have usually been treated in the same fashion as advanced stage diffuse large B-cell lymphoma (DLBCL), i.e. with CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone) or CHOP-like regimens as the mainstay of therapy. With front-line anthracycline-based combination chemotherapy, approximately 50% of patients with PTCL achieve a complete remission and reported 5-year survival values range from 25 to 45% with some heterogeneity among histological subtypes. This poor probability of survival is partly due to primary refractory disease, but seems explained to a larger extent by a higher risk of relapse. In a study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA), relapse rates of T-cell and B-cell

derived aggressive lymphomas were compared[10]. According to this report, 43% of PTCL patients relapsed from CR compared to less than a third in the aggressive B-cell group. The relapses are mainly occurring during the first 2 years after diagnosis, 44% of the death occurring in the first 12 months and 23% in the following year[14].

However, some studies have shown an improvement in response rates and overall survival when a more dose-intense induction treatment was applied. For example, in a study of Karakas et al[15], 27 PTCL and 55 DLBCL patients were treated with a CHOP-like regimen intensified by the addition of etoposide (120 mg/m^2 on days 1-3). This resulted in a complete response (CR) rate and 5-year overall survival for PTCL similar to that of B-cell cases (77% and 62%, respectively). Furthermore, in a trial of the Nordic Lymphoma Group, where patients were randomized to either CHOP or MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycine), PTCL, although still displaying a poorer prognosis than DLBCL, had a slight survival advantage from the more dose-intense chemotherapy arm, i.e. MACOP-B[16]. As a strategy to improve the outcome for patients with malignant lymphoma of aggressive histology, 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 [17]. 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. 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 [18]. 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 may well be considered standard therapy at least in elderly patients and an acceptable basis for an induction strategy in younger patients with PTCL.

6.3. Results of High-dose Therapies in Peripheral T-cell Lymphomas

There is a debate as to whether high-dose chemotherapy followed by stem cell or bone marrow transplantation should be considered early in first remission in order to consolidate responses. Reports on the possible efficacy of high-dose therapy (HDT) with autologous stem cell transplant (ASCT) in PTCL in first CR are scarce. A retrospective analysis by Blystad et al has reported the

HDT experience in PTCL patients at two large oncologic centers in Norway and Sweden[19]. This retrospective study reports not only on chemoresistent or recurrent cases, but also on cases treated with HDT in first complete remission (11 out of 41 reported cases). In this report, HDT seems to improve outcome in PTCL (5-year overall survival: 59%) as compared to historical controls allowing long lasting remissions in patients with an aggressive clinical presentation or with a chemosensitive relapse. In another retrospective study, Rodriguez et al[20] reported a 5-year overall and disease-free survival for the approximately 100 PTCL patients transplanted in first CR of 80% and 79%, respectively. However, the patient population in this trial was young (median age: 31 yrs) and included some anaplastic large-cell lymphomas. Within the LNH87-2 trial, Mounier et al[21] found no difference between PTCL and aggressive B-cell lymphomas in terms of overall and disease-free survival after HDT with autologous stem cell transplant compared with sequential chemotherapy without transplant consolidation. However, the sample size was small (16 evaluable PTCL pts), emphasizing the importance of large prospective studies specifically designed for PTCL patients. Very recently, long-term follow-up results from a large retrospective cohort of PTCL patients reciving HDT with ASCT in 1st CR have been reported. HDT + ASCT performed in 1st CR, i.e. in chemosensitive cases, yielded a 5-yr overall survival of 68% and a progression-free survival of 63%.[22.] Two prospective trials using HDT with autologous stem cell rescue in first partial or complete remission and specifically designed for PTCL patients were performed and preliminary results recently reported. A German study investigated the feasibility and efficacy of first line autologous stem cell transplantation after 4(-6) courses of three-weekly CHOP followed by one course of Dexa-BEAM (as mobilization regimen) and consolidated by myeloablative radiochemotherapy with high-dose Cyclophosphamide and total body irradiation[23]. In 38% of the 65 evaluable patients, progressive disease occurred prior to transplantation. Among the remaining patients, at a median follow-up of 10 months post-transplant, 27% of patients experienced a relapse. In a larger PTCL-specific phase II prospective trial, the Nordic Lymphoma Group tested a dose-intensified induction schedule (6 courses of CHOEP14) followed by autologous transplant in first remission[24]. They reported a lower pre-transplant failure rate (30%) and a lower fraction of post-transplant relapses (12%), underscoring that an important issue in this disease is the ability to reach a response during the induction therapy before the consolidation with HDT.

6.4 Results of treatment of Peripheral T-cell lymphomas with Alemtuzumab

Alemtuzumab (MabCampath®) is a humanized immunoglobulin G1 anti-CD52 monoclonal antibody that binds to the CD52 antigen expressed on the cell membrane of normal and malignant B- and T-lymphocytes but not on hematopoietic stem cells. It is registered in Europe for the treatment of patients with B-cell chronic lymphocytic leukemia (CLL) who have been previously treated with alkylating agents and who have failed fludarabine therapy. Because malignant T cells have been reported to express high numbers of CD52 molecules on their surface[25], T-cell lymphomas,

including PTCL, are particularly suitable for alemtuzumab therapy. After the encouraging results obtained with alemtuzumab in patients with T-cell prolymphocytic leukemia (T-PLL)[26-29] and cutaneous T-cell lymphoma (CTCL)[30], a pilot study with alemtuzumab in patients with relapsed or chemorefractory PTCL was recently reported[31]. Forteen patients with advanced, heavily pretreated PTCL received a rapidly escalating dosage of alemtuzumab during the first week followed by 30 mg i.v. 3 times per week for an additional 12 weeks. The ORR was surprisingly high with 3 patients achieving a CR (of 2, 6 and 12 months), and 2 patients a PR. However, the infectious and hematologic toxicity observed were considerable in these poor prognosis patients. It included cytomegalovirus (CMV) reactivation in 6 patients, pulmonary aspergillosis in 2, pancytopenia in 4, and a total of 5 treatment related deaths. Given the high activity of alemtuzumab in relapsed/refractory PTCL patients, further studies using the compound more upfront or in cases with less advanced disease were performed. In a phase II trial, alemtuzumab in combination with fludarabine, cyclophosphamide and doxorubicin (Campath-FCD) and given intravenously at the dose of 30 mg twice per cycle was tested in patients with PTCL at first diagnosis or at relapse[32]. The combination was proven effective as first line treatment with a CR rate of 73%. However, in relapsed/refractory patients the efficacy results were less evident and the toxicity observed, especially haematologic and cardiac (in previously anthracylin-treated cases) was substantial. More recently, the first data on the combination of CHOP and alemtuzumab were presented[33]. Patients with untreated PTCL received 8 courses of 4-weekly CHOP combined with alemtuzumab. The antibody was escalated to 30 mg during the first week and subsequently administered subcutaneously before CHOP courses 2 to 4 (first cohort) or 2 to 8 (second cohort). After a mean follow-up of 1 year, 12 out of 18 evaluable patients were alive and 11 had achieved a CR. No drug-related deaths were recorded. CMV reactivation occurred in 12% of assessable chemotherapy cycles. This study demonstrated an acceptable safety profile and feasibility of the CHOP-alemtuzumab regimen as first-line treatment in PTCL patients. It also confirmed a good tolerance and efficacy of the subcutaneous administration route, as already observed in patients with CLL[34,35].

6.5 Rationale of the trial

We hereby propose a randomized phase III study with the goal of improving both ORRs and long term outcome in patients with systemic PTCL. The specific aim of this study will be to compare the efficacy of bi-weekly CHOP combined with subcutaneous alemtuzumab with that of bi-weekly CHOP without concomitant immunotherapy. In young patients (< 60 years), higher response rates should also translate into an improved eligibility to autologous transplant in first remission.

A dose escalation with subcutaneous alemtuzumab during the first CHOP cycle will not be given in this phase III study according to the results of a recent published trial[36] demonstrating that it is not necessary. By analogy to a phase III study with CHOP14 in the treatment of elderly patients with

diffuse large B-cell lymphoma[37], showing that a pre-phase treatment reduces early treatment-related toxicity and mortality, a pre-phase therapy is included.

Most patients with T-NHL are already immunocompromised. Recently, a high frequency (27%) of pre-therapeutic CMV viremia and a significant correlation between higher CMV viral loads and degree of $CD8^+$ T-cell lymphopenia were found[38]. Therefore, alemtuzumab treatment should not require additional measures than the traditionally adopted ones such as prophylactic antibiotics and close monitoring of CMV reactivation (see paragraph 11.4.4).

7. Study objectives

7.1 Primary Objective:

- To assess the effect of the addition of alemtuzumab s.c. to 6 courses of 2-weekly CHOP14 in terms of Event-Free Survival (EFS) as defined in paragraph 16.1.

7.2 Secondary Objectives:

- To assess the effect of the addition of alemtuzumab s.c. to 6 courses of 2-weekly CHOP14 in term of overall survival (OS), progression-free survival (PFS) and overall response rates (ORR, i.e. CR/CRu/PR), tumor control or time to progression (TTP). Assessment of ORR means evaluating eligibility to autologous stem cell transplantation.
- To assess the overall response rates (ORR) related to the CD52 expression.
- To evaluate the safety of the addition of alemtuzumab s.c. combined with 2-weekly CHOP with respect to the incidence of severe opportunistic infections and infections due to neutropenia as well as the adherence to protocol as defined in paragraph 16.2.

8. Study design

An open label, randomized, multicenter, phase III study. Details of all treatments (dose and schedule) are given in paragraph 11.

8.1 Remission induction

Patients with peripheral T-cell lymphoma meeting all eligibility criteria (see section 9.1) will be registered and randomized on entry between:

Arm A: 6 cycles of 2-weekly CHOP14 plus G-CSF

Arm B: 6 cycles of 2-weekly CHOP14 plus G-CSF combined with s.c alemtuzumab

Patients will be evaluated for response after 3 cycles of CHOP or CHOP-alemtuzumab (all patients) and after 6 cycles of CHOP or CHOP-alemtuzumab (if applicable, otherwise after last cycle administered). All patients, who have not attained at least a NC after 3 cycles of CHOP or CHOP-alemtuzumab, will go off protocol treatment.

8.2 Consolidation with Autologous Stem Cell Transplantation for young patients (≤ 60 years)

After termination of induction, young patients only (≤ 60 years) who have reached CR/CRu or PR will be treated with a consolidation consisting of high-dose chemotherapy followed by autologous stem cell support.

9. Study population

9.1 Eligibility for registration

All eligible patients have to be registered and randomized before start of treatment (see paragraph 17).

9.1.1 Inclusion criteria

- Previously untreated patients with newly diagnosed peripheral T-cell lymphoma of stage I bulk (≥ 7.5 cm) and stages II to IV.
- Patients with a confirmed histologic diagnosis of peripheral T-cell NHL according to the WHO classification (Appendix C):
  - ✓ Peripheral T-cell lymphoma, unspecified (PTCL NOS)
  - ✓ Angioimmunoblastic T-cell lymphoma
  - ✓ Enteropathy associated T cell lymphoma
  - ✓ Subcutaneous panniculitis-like T-NHL (γδ T-cell lymphoma)
  - ✓ Hepatosplenic T-cell lymphoma
  - ✓ Extranodal NK/T cell lymphoma, nasal type
- Age 18-60 years at time of randomization
- Life expectancy of 3 months or longer
- ECOG performance status (PS) 0, 1 or 2 at the time of randomization (see appendix D). However, PS 3 will be acceptable if lymphoma-related.
- Measurable disease (defined as at least one lesion with two measurable perpendicular diameters of which at least one should be ≥ 15 mm).
- Written informed consent

9.1.2 Exclusion criteria

- Patients with NK/T-NHL of the following type:
  - ✓ Precursor T cell lymphoblastic lymphoma/leukemia
  - ✓ All mature T cell leukemias (T-PLL, ATLL, NK cell leukemia, T-LGL, HTLV1-pos ATL)
  - ✓ Alk-positive and negative anaplastic large cell lymphoma
  - ✓ Blastic NK cell lymphoma
  - ✓ Cutaneous T-cell lymphoma, transformed or not
- Concurrent severe and/or uncontrolled medical disease (e.g. uncontrolled diabetes, congestive heart failure, myocardial infarction within 6 months prior to the study, unstable and uncontrolled hypertension, chronic renal disease, or active uncontrolled infection), which could compromise participation in the study.
- Known hypersensitivity to murine or chimeric antibodies or proteins
- Severe cardiac dysfunction (NYHA classification II-IV, Appendix H) or LVEF < 45 %
- Significant renal dysfunction, i.e. serum creatinin >2 times upper normal level (UNL), unless related to NHL
- Significant hepatic dysfunction (total bilirubin >2 times UNL or transaminases ≥ 2.5 times UNL), unless related to NHL
- Impaired pulmonary functions; in this case, the patient is to be excluded if the resultant pulmonary function test shows FEV_1<50% or a diffusion capacity <50% of the reference values
- Suspected or documented Central Nervous System involvement by NHL
- Patients known to be HIV-positive
- Patients with active, uncontrolled infections, especially known seropositivity for HCV or HbsAg
- Patients with uncontrolled asthma or allergy, requiring systemic steroid treatment
- Prior treatment with chemotherapy, radiotherapy or immunotherapy for this lymphoma, except local radiotherapy in case of extranodal NK/T cell lymphoma, nasal or nasal type
- History of active cancer during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma
- Unwillingness or inability to comply with the protocol
- Simultaneous participation in any other study protocol
- Pregnant and nursing women (Women of childbearing potential should use safe anticonception (contraceptive pills, intrauterine devices, injection of prolonged gestagen, subdermal implantation, hormonal vaginal devices and transdermal patches are considered as safe contraceptive methods).

10. Pathology review

After a diagnosis has been made locally, the original tissue blocks (suitable to perform immunohistochemical stainings), including the frozen tissue, should be sent to the National Reference Pathologist (NRP). The tissue material should be accompanied by Pathology Form I (Draft in Appendix A), which identifies the patient and the tissue material, and reports the final histologic diagnosis of the referral center pathologist. The NRP will review the tissue material to confirm the diagnosis of T-cell lymphoma, will assess or re-assess (if already performed by the referral center pathologist) the expression of CD52, and define the subtype according to the WHO lymphoma classification. Confirmation of diagnosis by the referral center pathologist will usually be sufficient for randomization, unless otherwise agreed upon at country-specific level. The results of the NRP review will be reported on the Pathology Form II (Draft in Appendix B) and returned together with the original tissue block to the referral center. A copy of both pathology forms will be sent by the NRP via the trial office to the Data Management Center. The Pathology forms (form I and II) to be used will be sent from the Data Management Center, IMISE.

11. Treatments

11.1 Induction treatment

Independently of age group, patients will be randomized for the induction treatment between Arm A (CHOP14 without alemtuzumab) and Arm B (CHOP14 combined with alemtuzumab). The CHOP14 dosage and number of cycles will be identical in both arms. Pre-phase treatment and G-CSF will be given in both arms.

11.1.1 Pre-Phase Therapy

Independently of randomization arm, all patients will receive a pre-phase therapy (given only prior to the first chemotherapy cycle), consisting of:

- Vincristine 1 mg iv single dose at day -6
- Prednisone/Prednisolone 100 mg daily p.o. day -6, -5, -4, -3, -2, -1, 0

Day 1 is considered as the first day of the CHOP14 chemotherapy.

The purpose of this pre-phase treatment is to prevent tumor lysis syndrome in patients with extensive tumors, to improve the performance status of the patient and to reduce the toxicity of the first chemotherapy cycle. Pre-phase treatment is mandatory. Sufficient fluid intake should be ensured and appropriate supportive measures (see paragraph 11.4.3) should be provided.

11.1.2. Arm A: CHOP14 chemotherapy plus G-CSF

Patients will be treated with 6 cycles of CHOP every 2 weeks. CHOP14 is to be repeated on day 15. Antiemetic prophylaxis will be administered in accordance with local standards. In accordance with the 2-weekly CHOP schedule, patients will receive G-CSF between each cycle of CHOP-alemtuzumab. In cases of persistent leucopenia, G-CSF administration should be continued until recovery of the leukocyte count and achievement of the protocolled threshold for continuation of therapy. G-CSF (filgrastim) is to be administered from day 4 to day 12 (once daily s.c.) during the CHOP14 regimen, irrespective of leukocyte count:

- 300 µg/day if body weight <75 kg
- 480 µg/day if body weight ≥ 75 kg

Alternatively, lenograstim (150 µg/m^2 s.c.) day 4 through 12, or a single dose of pegfilgrastim (6 mg s.c.) once daily on day 4 can be applied.

Agent	Dose/day	Route	Days
Cyclophosphamide	750 mg/m^2	i.v.	1
Doxorubicin	50 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2, with a maximum of 2 mg	i.v.	1
Prednisone/Prednisolone	100 mg	p.o.	1, 2, 3, 4, 5
G-CSF or Peg-G-CSF	See above	s.c.	4-12 (filgrastim or lenograstim) 4 (pegfilgrastim)

11.1.3. Arm B: CHOP14 chemotherapy plus G-CSF, combined with alemtuzumab

Patients will be treated with 6 cycles of CHOP in combination with alemtuzumab every 2 weeks. CHOP14 is to be repeated on day 15. Alemtuzumab will be given subcutaneously 1 time~~s~~, i.e. day 1 at each CHOP14 cycles. In cycles 1-4, a dose of 30 mg alemtuzumab will be administered while no antibody will be administered in cycles 5-6. All patients need prophylactic medication to avoid "first-dose" reactions and reactivation of severe infections. See paragraph 11.4 for special management of alemtuzumab administration. Antiemetic and cystitis prophylaxis will be administrated in accordance with local standards. In addition, G-CSF therapy will be applied to each cycle of CHOP14 (see paragraph 11.1.2).

Agent	Dose/day	Route	Days
Cyclophosphamide	750 mg/m^2	i.v.	1
Doxorubicin	50 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2, with a maximum of 2 mg	i.v.	1

Prednisone/Prednisolone	100 mg	p.o.	1, 2, 3, 4, 5
Alemtuzumab	Cycles 1-4:30 mg Cycles 5-6: no adm.	s.c.	1
G-CSF or Peg-G-CSF	See above	s.c.	4-12 (filgrastim or lenograstim) 4 (pegfilgrastim)

11.1.4 Prerequisites for the continuation of the CHOP14 chemotherapy

CHOP14, with or without alemtuzumab 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 ≥ 2.5 x 10^9/l (or neutrophil count ≥ 1 x 10^9/l) on day 15, unless due to bone marrow involvement
3. Platelet count ≥ 100 x 10^9/l on day15, unless due to bone marrow involvement
4. No active infection
5. No serious organ or other toxicity

If these prerequisites are not fulfilled, a dose modification as detailed in paragraph 11.2. will be applicable.

11.2 Dose modifications of CHOP

Dose modifications will not apply to the first course of chemotherapy. During the following courses modifications of the treatment schedule will only apply in case of:

a) Myelosuppression not due to lymphomatous bone marrow involvement

If leukocytes are < 2.5 x 10^9/l and/or platelets < 100 x 10^9/l, the subsequent chemotherapy course should be delayed by one week. If low leukocytes and/or platelets values persist, the dose of doxorubicin and cyclophosphamide should be reduced according to the scheme below. The subsequent course(s) should again be dosed at 100% level, if myelosuppression has recovered.

Leucocytes x 10^9/l		Platelets X 10^9/l	Cyclophosphamide	Doxorubicin	Vincristine	Prednisone	Alemtuzumab
>2.5	and	> 100	100%	100%	100%	100%	100%
2-3	and	> 100	75%	75%	100%	100%	100%
1-2	or	> 50 < 100	50%	50%	100%	100%	100%
<1	or	< 50	0%	0%	100%	100%	100%

b) Neurotoxicity

Dose modifications of vincristine are made at the discretion of the physician.

c) Cardiotoxicity

In cases of documented cardiomyopathy developed during treatment, LVEF should be repeated. In case of a reduction of LVEF value by > 15% and a resulting absolute value of <45% (e.g. from 60% to < 45%) the patient goes off protocol treatment.

11.3 Consolidation with Autologous Stem Cell Transplantation

After termination of the induction phase, patients in CR/CRu, or PR will be treated with a consolidation regimen consisting of high-dose chemotherapy followed by autologous stem cell support. The mobilization will be performed with G-CSF and the stem cells harvested between the 4^{th} and the 5^{th} cycle or between the 5^{th} and the 6^{th} cycle of CHOP14± alemtuzumab. G-CSF stimulation and stem cell harvest procedure should be performed according to local guidelines. In case of insufficient harvest, an additional leukapheresis will be performed after the 6^{th} cycle. The minimum threshold of ≥ 2.0 x 10^6/kg CD34+ cells should be reached in order to proceed with the high-dose chemotherapy and autologous stem cell transplantation. The recommended interval between the start of the 6th treatment course and the high-dose regimen is 5-7 weeks and should not exceed 10 weeks. BEAM will be the high-dose regimen used.

Conditioning Regimen BEAM

Carmustine 300 mg/m^2 i.v. on day -7
Etoposide 100 mg/m^2 i.v. x 2 daily, on days -6 to -3
Cytosine arabinoside 200 mg/m^2 i.v x 2 daily on days -6 to -3
Melphalan 140 mg/m^2 i.v. on day -2
(stem cell reinfusion = day 0)

Minor variations of the BEAM regimen may apply at different centres. The high-dose regimen should always be given according to local procedures and guidelines as well as the use of G-CSF for stem cell mobilization and after stem cell transplantation.

11.4 Special management of Alemtuzumab administration

11.4.1. Product information of MabCampath® (Alemtuzumab)

MabCampath® is a genetically modified humanized monoclonal antibody (IgG1-kappa) and is provided as a sterile, clear, colourless, isotonic solution for injection. Each single-use 1-mL vial of

MabCampath® contains 30 mg alemtuzumab, 2.7 mg sodium chloride, 0.07 mg potassium chloride, 0.07 mg monobasic potassium phosphate, 0.38 mg dibasic sodium phosphate, 0.006 mg disodium edetate, and 0.033 mg polysorbate 80. No preservatives are added.

Packaging, labelling and storage: *Genzyme will do the labelling of MabCampath* according to the GMP rules. Store at 2 to 8°C (36 to 46°F). Do not freeze. Discard vial if it has been frozen. Do not use beyond expiration date. Protect from direct sunlight.

Accountability of MabCampath: Each centre will keep account of MabCampath. Investigators are responsible for the accountability and they should keep documentation of what they have received, used and perhaps returned to Genzyme/local pharmacy or destroyed. A trial specific procedure on how to handle MabCampath will be prepared.

11.4.2. Administration of Alemtuzumab

On the days where both alemtuzumab and chemotherapy have to be given, alemtuzumab will always be given *after* the CHOP chemotherapy.

To reduce toxicity, alemtuzumab will be injected subcutaneously in the thighs[34,35]. Even using this route, side effects will occur. After subcutaneous injection, in >90% of the patients local injections site reactions will be seen, especially during the first 2 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 within one week. Generally, side effects will decrease within 2 weeks. The majority of patients will experience fever, a minority rigors, all grade I-II, and all will show diminishment of these symptoms within 2 weeks during continuation of the alemtuzumab.

During the first injection, the patient needs to be observed with an IV line that should be kept open for medications. Vital signs (blood pressure, pulse, respiration, and temperature) should be monitored every 15 minutes during the first hour or until stable and then for another hour.

Premedication with paracetamol (1000 mg) and an antihistaminic drug (e.g. clemastine 2 mg) is mandatory. Moreover, alemtuzumab should be given after the CHOP including oral Prednisolone (day 1 dose).

In most patients, injection-related adverse reactions will occur during the administration of the first dose (“first-dose reactions”). These are usually mild (grade I or II) and manageable by oral paracetamol and clemastine. If symptoms as rigors, mucosal congestion/oedema or hypotension occur at toxicity grade III or IV, i.v. steroids (e.g. 200 mg hydrocortisone) may be used. In cases where significant complications (grade III or IV) should persist at later injections, consultation with the Study Coordinators is recommended.

11.4.3. Prophylactic measures

Prophylaxis is required against so-called “first-dose” allergic reactions, against tumor lysis, against infections, and against transfusion-related GvHD.

Prophylaxis against “first-dose” reactions will include paracetamol 1 gram orally and clemastine (Tavegyl) 2 mg intravenously or orally, 30 minutes before the injections. In the absence of severe side effects, both drugs can be tapered down during the following weeks.

Prophylaxis against tumor lysis should consist of allopurinol, 300 mg, during the first month.

Prophylaxis against infections related to T-cell lymphocytopenia such as pneumocystis jiroveci and herpes infections should be initiated from the first alemtuzumab administration and consist of:

- trimethoprim/sulfamethoxazole (cotrimoxazole) 480 mg p.o. twice per day or 960 mg p.o. per day, thrice a week; during granulocytopenia, the dose can be increased to 960 mg twice daily
- valaciclovir 500 mg p.o. twice to thrice a day or famciclovir 250 mg p.o. twice daily or acyclovir 400 mg p.o. three to four times daily

Both drugs should be continued for at least 3 months (recommended 4-6 months), after transplantation or until CD4-lymphocytes >200/µl. For patients who cannot tolerate cotrimoxazole, effective alternatives include aerolized pentamidine, oral dapsone and oral atovaquone. Since the mucositis observed short after transplantation could prevent the intake of the oral prophylaxis, one aerolized pentamidine before transplantation and a switch to aciclovir or valaciclovir i.v. are recommended. A switch back to oral prophylaxis may occur as soon as the patient’s clinical conditions allow it.

Prophylactic antimicrobial treatment should be given according to local guidelines and contain at least one anti-fungal agent. In both arms, close CMV antigen monitoring is required once weekly during the 6 cycles of chemotherapy, and until 6 weeks after stem cell reinfusion. Thereafter, monitoring will be performed every second week for 6 months. Further monitoring can be performed at the investigator’s discretion. Finally all blood products need to be leukocyte-depleted, irradiated and preferably CMV negative (in patients with negative CMV serology) until 6 months after the last alemtuzumab application to prevent transfusion-related GvHD and virus transmission. Vaccinations with any live vaccines should be avoided until at least one year after the last alemtuzumab application.

11.4.4. Monitoring of CMV reactivation and recommendations for pre-emptive therapy

CMV reactivation should be monitored with an appropriate antigen or virus-DNA detection technique according to the methods of the participating hospital.

Asymptomatic patient

In case of positivity by PCR (significant number of copies according to local reference values) or antigenemia, immediate confirmation is recommended. Patients with low level antigenemia/low number of copies (according to local reference values) will be followed closely clinically and by weekly PCR/antigenemia assay. If the presence of a rising antigenemia/copy number is confirmed, the patient will be treated with oral valganciclovir (900 mg x 2) or intravenous ganciclovir (according to local guidelines), while protocol treatment is continued. If an asymptomatic patient with CMV reactivation starts showing clinical manifestations of CMV infection, therapy should, if not already initiated, be changed to ganciclovir intravenously and the protocol treatment (CHOP-alemtuzumab or CHOP) should be stopped (see below "symptomatic patient"). The patient will go off protocol and subsequently be treated/followed according to local guidelines.

Symptomatic patient

In a PCR-positive/antigenemia-positive patient with clinical symptoms of apparent CMV infection the study therapy will be discontinued and ganciclovir administered (see above). Ganciclovir should be administered intravenously 10mg/kg/day over 2 daily doses until remission of symptoms has been reached. Thereafter, the intravenous drug can be substituted by oral valganciclovir (900 mg x 2 or equivalent). In the case of documented, clinically manifest CMV infection, protocol treatment should be discontinued .

Duration of valganciclovir treatment in asymptomatic patients with CMV reactivation

Full dose valganciclovir should be given during at least ten days or until CMV PCR/antigenemia negativity and thereafter 900 mg x 1 daily as prophylaxis for the entire duration of alemtuzumab treatment.

- Neutropenia is a common side-effect of ganciclovir and valganciclovir. Monitoring of neutrophil counts is an effective and sensitive safety parameter during treatment.
- Regular monitoring of creatinine clearance for dose adaptation of ganciclovir (valganciclovir) in case of renal insufficiency is essential.
- Monitoring of neutrophil counts is essential also after discontinuation of protocol treatment.
- After study completion CMV testing will be continued monthly during at least three months.

11.4.5 Monitoring of EBV reactivation and recommendations for pre-emptive therapy

EBV reactivation should be monitored with an appropriate antigen or virus DNA detection technique according to the methods of the participating hospital. In accordance with EBMT guidelines, quantitative PCR (qPCR) is the recommended technique. The recommended monitoring frequency is described in section 13.3. Pre-emptive therapy should be initiated according to local guidelines. Alternatively, the guidelines for management of EBV reactivation

elaborated by the EBMT Working Party for Infectious Diseases are recommended (http://www.ebmt.org/5WorkingParties/IDWP/wparties-id.html).

11.5 Concomitant medication and treatment

Thus far, there are no reported interactions between alemtuzumab and other drugs.

a) Drugs

Concomitant medication(s) administered to the patient since the beginning of the treatment should be documented. Patients should receive full supportive care including blood transfusions and blood products, (which always should be irradiated), antibiotics, anti-emetics etc., where applicable and according to local guidelines.

b) 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 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.

12. Study Discontinuation

12.1 Post-randomization exclusion

A patient will be withdrawn 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 the 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 of a patient's exclusion after randomization by the study coordinator. However, since the main analyses will be performed according to the intention to treat principle, further documentation also of patients withdrawn after randomization will be necessary.

12.2 Early termination of therapy

Early termination of therapy may be necessary for the following reasons:

1. Progression after 3 or 6 cycles of CHOP14-alemtuzumab or after 3 or 6 cycles of CHOP14
2. lack of response to treatment as defined in the protocol

3. Manifest cardiomyopathy (absolute reduction of ejection fraction >15% with a resulting absolute value of <45%). This condition is recommended to be managed as anthracycline-induced cardiomyopathy according to local guidelines.
4. Excessive toxicity requiring stopping of the protocol treatment.
5. Patient´s refusal to continue treatment or major compliance problems.
6. Contact broken off by the patient
7. Non-conformity to any eligibility criterion (e.g. reference histology)
8. Major protocol violation
9. Decision of the treating physician

The reason for early termination of therapy must be documented in written form and notified to the Study Coordinator. Like patients excluded after randomization, patients with early termination of therapy must continue to be documented (remission status, survival with and without lymphoma).

13. Required clinical evaluation

13.1 Observations prior to start of treatment

- History (including B symptoms, defined according to Ann Arbor criteria, see Appendix E)
- Physical examination (including ECOG performance status, see Appendix D)
- Laboratory tests: Minimal panel to be reported in the CRF include Hb, WBC and differential, platelet count, creatinine, uric acid, bilirubin, alkaline phosphatase, ALAT, LDH, albumin, immunoglobulin IgG, IgA, IgM and C-Reactive-Protein (CRP). Additional tests to be performed according to local guidelines.
- Imaging (incl. Chest X-ray, CT neck, thorax, abdomen and/ or MRI neck thorax Abdomen/ abdominal ultrasound)
- Lymph node or tissue of biopsy of involved site for morphology, immunopathology
- Immunophenotyping of biopsy of involved site according to pathology forms (Appendix A and B)
- Cryopreservation of lymphoma involved tissue for external pathology review as well as cytogenetics, gene expression profiling, and BAC array CGH
- Bone marrow aspirate and biopsy (marrow fields minimal 2 cm length) within 6 weeks before registration/treatment
- ABO and RhD blood group, irregular antibody screening
- ECG and left ventricular ejection fraction (LVEF) or cardiac ultrasound/Doppler
- Pulmonary function test including diffusion capacity
- CMV Ig antibodies and CMV antigen in peripheral blood, HIV, HBV and HCV serologies

- EBV serology: IgM and IgG against Early Antigen and IgG against Epstein-Barr Nuclear Antigen.
- EBV-DNA in peripheral blood
- Peripheral blood immunophenotyping: CD4, CD8, CD56/CD16, CD19, CD52/CD4/CD8
- Pregnancy test within 2 weeks of treatment, in women of childbearing potential
- Lumbal puncture for CSF analysis (only if found indicated by the treating physician)
- Other investigations if indicated (e.g. skeletal scintigraphy, gastroscopy, liver biopsy)

13.2 Observations after each cycle of CHOP-alemtuzumab

- Blood count (at least 1 measurement during nadir). Additional tests to be performed according to local guidelines.
- CMV antigen monitoring is required once weekly during the 6 cycles of chemotherapy, and until 6 weeks after stem cell reinfusion.
- Samples for pharmacokinetics (PK) examining the initial and subsequent terminal half-life after CHOP-alemtuzumab (only applicable for selected centers and in total 20 patients in each cohort)

13.3 Observations after 3 and 6 cycles of CHOP or CHOP-Alemtuzumab (or after last cycle, if treatment stopped earlier)

- History (including B symptoms defined according to Ann Arbor Criteria, see Appendix E)
- Physical examination (including ECOG performance status)
- Laboratory tests (including Hb, WBC and differential, platelet count, creatinine, uric acid, bilirubin, alkaline phosphatase, ALAT, LDH, albumin). Additional tests to be performed according to local guidelines.
- Imaging of involved areas (incl. chest X-ray, CT or MRI thorax and abdomen and echography of the cervical lymph node stations), PET scanning in case of residual abnormalities if available
- Bone marrow aspirate and biopsy / peripheral blood if initially positive
- LVEF by cardiac ultrasound/Doppler or MUGA-scan after 3 cycles in case of initial abnormality - and, for all patients, after 6 cycles of chemotherapy
- EBV-DNA in peripheral blood should be tested monthly until end of therapy.

13.3.1. Response assessment after cycle 3 and cycle 6 (or after last cycle, if treatment stopped earlier)

Response will be formally evaluated in both arms after cycles 3 and 6 according to the criteria of response, or evaluated after last cycle if treatment stopped earlier. The response criteria are in appendix I. PET scanning or histology/cytology of the residual lesion at end of protocol is strongly advised in case of residual abnormalities. A patient with PET (or histology) negative residual abnormalities on CT may be considered as CRu. All relevant information on drug dose, measurable lesions, tumor response and treatment related toxicity will be collected.

13.4 Observation after autologous stem cell transplantation

- History (including B symptoms)
- Physical examination (including ECOG performance status)
- Laboratory tests (including Hb, WBC and differential, platelet count, creatinine, uric acid, bilirubin, alkaline phosphatase, ALAT, LDH, albumin). Additional tests to be performed according to local guidelines.
- Imaging of involved areas (incl. chest X-ray, CT or MRI thorax and abdomen and echography of the cervical lymph node stations), PET scanning in case of residual abnormalities if available
- Bone marrow aspirate and biopsy / peripheral blood if initially positive
- LVEF by cardiac ultrasound/Doppler or MUGA-scan, after 3 and 6 cycles of chemotherapy
- EBV-DNA in peripheral blood

13.5 Observations during follow up

Follow up for patients in CR/CRu, or PR after completion of treatment schedule, will be every 3 months during the first two years, every 6 months during the next 2 years and annually thereafter until the completion of the study and planned observation period. Patients who have not achieved CR/CRu, or PR after induction and relapsed patients will be followed for at least 2 years according to local guidelines or until the completion of the study and planned observation period.

Follow-up examinations will comprise:

- Physical examination (including ECOG performance status)
- Blood count, LDH
- Test of EBV-DNA in peripheral blood is recommend until 12 months after end of therapy at each follow up visit.
- Any clinically indicated examinations (appropriate scans annually for the first 2 years)

- Any documentation of abnormal events (e.g. serious late infections, cardiac abnormalities, secondary malignancies)

13.6 Time of clinical evaluations

- At entry: at time of randomization, within 14 days prior to start cycle 1
- Prior to each cycle: within 14 days prior to each cycle
- After cycle 3: within 7 days before cycle 4 (no delay)
- End of the 6 cycles: 3 to 6 weeks after end of cycle 6 (or earlier if treatment stops)
- After ASCT: 8-12 weeks after ASCT
- Follow-up: every 3 months during the first 2 years, every 6 months during the next 2 years and annually thereafter until the completion of the study and planned observation period

	At entry	Prior to each cycle	Weekly during the 6 cycles	After cycle 3 (Interim restaging)	After cycle 6 (First Restaging)	After ASCT (Second Restaging)	Follow up
Medical history	X	X		X	X	X	X
Physical examination incl. PS	X	X		X	X	X	X
Blood tests:							
Hematology	X[1]	X[2]	X[2]	X[1]	X[1]	X[1]	X[1]
Flow cytometry of PBMNC	X				X		
Blood chemistry	X[3]	X[4]		X[4]	X[4]	X[4]	X[4]
HIV, HBV, HCV, EBV antibodies	X						
CMV-Antigenemia	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[9]
EBV serology	X						
EBV-PCR in PB[10]	X			X	X	X	X
PB/serum storage future studies[11]	X			X	X		
Urine Analysis	X			X	X		
Bone marrow biopsy	X			X[6]	X[6]	X[6]	X[7]
BM storage future studies	X			X[6]	X[6]	X[6]	
Specific investigations:							
ECG and LVEF/cardiac ultrasound	X			X	X	X[7]	X[7]
FEV_1+FEV_2	X						
Chest X-ray and CT scan (or MRI) neck/thorax/abdomen	X			X	X	X[7]	X[7]
PK samples				X[8]	X[8]		

[1] Hb, WBC and differential, platelet count

[2] Hb, WBC, platelet count: at least 1 measurement during nadir

[3] creatinine, uric acid, bilirubin, AP, ALAT, LDH, albumin, immunoglobulin IgA, IgG, IgM, CRP

[4] creatinine, uric acid, bilirubin, ALAT, albumin, AP, LDH, CRP

[5] weekly in both arms, by either immunocytology for pp65 or PCR and until 6 weeks after SC reinfusion

[6] if initially positive

[7] at the physician´s discretion (if appropriate)

[8] One week after each cycle in the first 20 patients

[9] Six weeks after SCT:every second week for 6 months and thereafter at the physician's discretion

[10] Test monthly until end of therapy

[11] SOP can be requested from the Clinical Trial Office

14. Toxicities

CHOP is a common used chemotherapeutic regimen with well-known side-effects. The most frequent side-effect is myelosuppression which may hamper patient adherence to the projected schedule of CHOP.

Side effects of subcutaneously administered alemtuzumab may include fever (frequent, grade I-II during the first 2 weeks), rigors (about 25%, grade I-II, during the first 2 weeks), mucosal congestion or edema (rare), and drop in systolic blood pressure (rare). Most patients will experience local reactions at injection sites varying from grade I erythema only (can measure till 30 cm in diameter), local mild pain or local mild pruritus.

An important issue remains the opportunistic infections. In a pilot study in patients with relapsed or chemorefractory heavily pretreated PTCL patients[31], the infectious toxicity observed was considerable, including cytomegalovirus (CMV) reactivation in 6 out of 14 patients (43%), pulmonary aspergillosis in 2, pancytopenia in 4, and a total of 5 treatment related deaths. However, this rate was lower when Alemtuzumab was given as first-line treatment in PTCL patients: CMV reactivation occurred in 12% of assessable chemotherapy cycles when alemtuzumab was combined with CHOP28[33]. Major infections included JC virus reactivation in one patient, invasive pulmonary aspergillosis in 2 patients, Staphylococcus sepsis in one patient and pneumonia in 2 patients.

Cardiotoxicity should be carefully monitored by physical examination and LVEF monitoring (preferably after cycle 3 and 6). In case of a reduction of >15% (absolute value, corrected to the pre-LVEF value) and a decline of the LVEF <45% (e.g. reduction from 60% to <45%), the patient should go off treatment. If the patient develops symptomatic cardiomyopathy, the LVEF should be repeated and the patient should go off protocol treatment during a decline of the LVEF or if NYHA grade 3 or 4 develops.

Special management is provided in 11.4. Toxicities will be scored according to the NCI Common Terminology Criteria for Adverse Events, CTCAE version 3 (see Appendix G).

15. Evaluation of safety

15.1 Definition of Adverse Events (AEs)

An Adverse event (AE) is any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs during or following treatment regardless of the causal relationship. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the treatment.

The following events are AEs, but are expected in association with therapy:

- Myelosuppression
- Nausea/vomiting
- Alopecia
- Infections, particularly during phases of leucopenia
- Haemorrhagic cystitis
- Cardiomyopathy
- Necrosis after paravasal injection
- Peripheral neuropathy, paralytic ileus
- 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 1. 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 vein 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.

15.2 Reporting of Adverse Events (AEs)

All expected and unexpected AEs must be carefully documented.
The intensity of the AEs will be graded according to the NCI Common Toxicity Criteria grading system in the toxicity that have recommended grading (see Appendix G). Adverse events not explicitly included in the NCI Common Toxicity Criteria list should be described in details and graded according to the four point system below:

- Grade 0 = “none”
- Grade 1 = “mild” (discomfort noticed but no disruption of normal daily activity)
- Grade 2 = “Moderate” (discomfort sufficient to reduce or affect normal daily activity)
- Grade 3 = “Severe” (incapacitating with inability to work or perform normal daily activity)
- Grade 4 =”life-threatening”
- Grade 5 = “death”

Due to the expected toxicity of the treatments, only grade 3, 4 and 5 toxicities (CTCAE) or grade 2 for infections, and toxicities (grade 1 to 5) related to a Serious Adverse Event as described below, must be reported as “Adverse Events” in the appropriate CRF pages. All “Alopecia” toxicity and hematological toxicities without fever will never be recorded as “Adverse Event”.

All adverse events occurring during the treatment period and until 3 months after the last restaging examination will be recorded on the toxicity forms and sent via the trial office to the Data Management Center.

15.3 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

Serious Adverse Events (SAEs) are defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment. A serious adverse event is any untoward medical occurrence that:

- results in death or
- is life-threatening (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- requires hospitalization or prolongation of hospitalization
- results in severe/permanent disability
- Is a congenital anomaly/birth defect

Note that any death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

The term severe is a measure of intensity, thus a severe adverse event is not necessarily serious. For example "nausea of several hours" duration may be severe but may not be clinically serious.

- Hospitalization for previously planned procedure or convenience will not be considered as reportable SAE
- A febrile neutropenia with hospitalization below 8 days is not considered as SAE
- Adverse event related to progression of disease is not to be declared as a SAE

Unexpected Serious Adverse Events are those SAEs of which the nature or severity is not consistent with information in the relevant source documents. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as a source document in that country.

The following events are classified as expected serious adverse reactions (SARs):

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

Consultation with the trial office and the principal investigator/co-investigator is necessary if other events occur which are not listed above and which treating physician evaluates as serious.

15.4 Reporting of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

Reporting of SAEs

During the treatment period and the first 3 months until 1. follow-up, all SAEs must be documented on the SAE report forms and must be reported to the Clinical Trial Office in Aarhus by fax **within one working day from the initial observation of the event**. All details should be documented on the **Serious Adverse Event Form and, if applicable, the Death Form**. In circumstances where it is not possible to submit a complete report, an initial description may be made giving only the mandatory information according international guidelines (e.g. CT3 "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on

medicinal products for human use"). If additional data concerning the SAE become available at later time points, these, too, have to be reported to the trial office immediately.
In case of early disease progression and implementation of salvage therapy, SAE reporting within this study ends.

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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Aarhus University Hospital
Clinical Trial Office
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Indgang 3A, 3. sal
8000 Aarhus C
Denmark
Fax-No. + 45 8949 7597

Initial reports must be followed-up by a complete report within a further 14 calendar days and sent by the site investigator directly to the Data Management Center in Leipzig. All SAE Reports must be dated and signed by the responsible site investigator or one of his/her authorized staff members.

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.

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. The Clinical Trial Office will forward the SAE form and the Assessment sheet to the IMISE, Leipzig University, within two working days.

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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.

Reporting of SUSARs

The drug safety management at IMISE submits all information available about a SUSAR immediately, and at the latest within 15 days after the event becomes known to the Clinical Trial Office. This report will be sent 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/her site are informed about the occurrence of the SUSAR.

In the case of death or a life-threatening condition caused by a SUSAR the competent regulatory authorities, the responsible ethics committee 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 Clinical Trial Office. Additional information has to be given within further 8 days.
At any time, but no later than 24 months after end of therapy, after the completion of protocol treatment, *unexpected* Serious Adverse Events that are considered to be possibly related to

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

protocol treatment and ANY death (regardless the cause) must also be reported to the Clinical Trial Office in Aarhus using the same procedure, **within one working day from the initial observation of the event**.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator using the following criteria:

RELATIONSHIP	DESCRIPTION
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
NOT RELATED	

In parallel to the information of the competent authorities, the IMISE will also inform the provider of the investigational drug alemtuzumab, Genzyme BV, about the occurrence of SAEs and SUSARs, at Genzyme Global Patient Safety and Risk Management at: pharmacovigilancesafety@genzyme.com (preferred) or fax +1 (617) 761-8506.

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,

  - 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.

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.

Information of Ethic Committees

Because of the procedures concerning SUSAR-reporting 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.

15.5 Follow-up of Serious Adverse Events (SAEs)

The Data Management Center will forward all reports within 24 hours of receipt to the sponsor and the study central data manager. The report of an SAE will be the signal for the central data manager to ask the investigator or the responsible local data manager to complete and send as soon as possible all relevant CRF's for the involved patient with details of treatment and outcome. It is of utmost importance that all SAE's (including all deaths due to any cause) are reported in a timely fashion. Patients without a report of an SAE are implicitly considered alive without SAE. This

information will be used in monitoring the incidence of SAE's, the estimation of overall survival and monitoring of safety of experimental treatments. If there is an excessive frequency of SAEs in one of the two therapy arms or the frequency of SAEs appears excessive, it may be necessary to terminate the study earlier.

Patients withdrawn from the study due to any adverse event will be followed at least until the outcome is determined or resolves and even if it implies that the follow-up continues after the patient has left the trial. In case of a SAE, the patient must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. It may imply that this follow-up will continue after the patient has left the trial.

Sponsor is responsible for reporting the SUSARs within required timelines promptly as well as to send the annual safety reports with aggregate summary tabulation of all suspected SARs (including SUSARs) of the trial to the health authorities and ethical committees of different countries. According to European laws, in case of SUSAR, all participating centers will be informed by the Data Management Center.

16. Endpoints

16.1 Primary endpoint

The primary endpoint is the Event-free Survival (EFS). The EFS is defined by the time between day of randomization until one of the following events occurs, whichever comes first:

- Disease progression during therapy
- Relapse after achievement of CR/CRu
- Institution of any additional unplanned anti-tumor treatment
- 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.

16.2 Secondary endpoints

1. Overall survival (OS) measured from the time of randomisation to death due to any cause; in the case of patients, who are alive, the time where the patient was last known to be alive.
2. Progression-free survival (PFS), defined as the duration from randomisation to the date of first progression/relapse after achievement of CR/CRu, or death of any cause.
3. Overall response rate (ORR), defined as the proportion of complete remissions, unconfirmed complete remissions and partial remissions (CR/CRu and PR, including CR/CRu and PR in patients after early discontinuation) measured during the staging performed after the induction chemotherapy, i.e. the percentage of patients proceeding to autologous stem cell

transplantation, and divided by the number of patients. The remission criteria are defined on the basis of Cheson et al. [39]. (see Appendix I)

4. Overall response rate (ORR) related to the CD52 expression
5. Tumor control or time-to-progression (TTP), defined as the time from randomization to progression/relapse after achievement of CR/CRu or any unplanned anti-tumor treatment after achievement of CR/CRu. Not tumor-related events will be censored.
6. Safety with following endpoints: adverse events (AEs), serious adverse events (SAEs). (according to Appendix G)
7. Feasibility of successful stem cell harvest ($\geq 2x10^6$ CD34-positive cells)
8. Adherence to protocol defined by:
    - 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 alemtuzumab
    - Cumulative G-CSF dose and duration of G-CSF administration

17. Registration and Randomization

The patient should be registered and randomized immediately after satisfactory completion of screening tests and obtaining informed consent, and before the start of chemotherapy. Patients need to be registered at the Clinical Trial Office.

The following information will be requested at randomization:

1. Protocol number
2. Institution name
3. Name of caller/responsible investigator
4. Patient's initials or code
5. Patient's hospital record number
6. Sex
7. Date of birth
8. Date of diagnosis of NHL
9. WHO classification
10. Pathology result from referral/reference pathologist
11. Eligibility criteria (i.e. all inclusion and exclusion criteria)

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number. Patient study number will be given immediately by phone and confirmed by fax or email. Patients will be randomly allocated to one of the two therapy arms at a ratio 1:1 by means of a minimization algorithm with the following stratifying factors:

a) Centre
b) Value for serum LDH (LDH ≤ Upper Normal Value versus LDH > Upper Normal Value)
c) General status of patient (ECOG performance status 0 and 1 versus >1)
d) Stage I and II versus III and IV
e) Number of extranodal involvements (0-1 vs >1)
f) Bulky disease (no vs yes)
g) Histology (other vs NK/T cell nasal type)

The treatment allocation of a new patient is based on data for these factors for all previous patients and thus takes use of the central study data base. The technique secures that the patients will be balanced between therapy arms for the stratifying factors.

18. Documentation, Data Collection and Monitoring

The participating institutions will have to ensure thorough and complete documentation of the course of disease for each patient. After inclusion of a patient in the study, the treating physician will receive a documentation dossier with the case report forms (CRF) from the Data Management Center.
The documentation dossier contains:

- Certificate of randomization
- Form for the procurement of patient´s material for accompanying research projects
- Flowchart of the study
- List of contact persons
- Instructions for completing the documentation forms
- Address labels for the forwarding of the completed CRFs
- CRFs (excluding Baseline Registration and Baseline Information forms, the Staging forms and the Reference Pathology Confirmation form which must be submitted prior to patient randomization)
- Forms for reporting SAEs
- Forms for the documentation of radiotherapy (where appropriate)

- CRFs for the inclusion of the next patient (BR, B, S, RPC)

The completed original documentation forms and 2 copies are to be sent to the trial office and will from there be forwarded to the Data Management Center.

Data will be collected on Case Report Forms (CRF) to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

- inclusion and exclusion criteria
- baseline status of patient including medical history and stage of disease
- timing and dosage of protocol treatment
- adverse events
- parameters for response evaluation
- any other parameters necessary to evaluate the study endpoints
- survival status of patient
- reason for end of protocol treatment

Each CRF page will be identified by a pre-printed trial number, and a unique combination of patient study number (assigned at registration), hospital and patient name code (as documented at registration) to be filled out before completing the form.

The CRF will be completed on site by the local investigator or an authorised staff member. Each page must be dated and signed by the local investigator upon completion. All CRF entries must be based on source documents. The CRF, the schedule for filling out of forms, and written instructions for completing the CRF will be provided by the Data Management Center.

Copies of the CRF will be kept on site. The original CRF pages and 2 copies must be sent to the trial office at the requested time-points. How and when to send in forms is described in detail in the CRF header and the CRF instructions.
In order to be able to closely monitor the occurrence of untoward events it is of utmost importance that the CRF's regarding induction treatment, for all patients, are submitted in a timely fashion i.e. within one month of completion of the induction treatment.
All CRFs will be subject to initial medical assessment at the trial office, who will make spot checks consider the following:

- Deviations from study protocol
- Occurrence of adverse events

- Occurrence of serious adverse events

Once the original CRFs are forwarded to the Data Management at the IMISE, Leipzig, all data from the CRF will be entered into the study database.
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 IFS by fax on a regular basis.
An audit trail of all changes in the contents of the study database will be automatically recorded.

When all documentation of therapy and the reference pathology report is available, study manager, monitor and biometrician of the Data Management Center will decide on the evaluability of each individual patient and will assess the significance of any protocol violations.

On-site monitoring visits will be performed and the participating institutions will allow monitors and representatives from national medical authorities and ethical committees access to original patient documentation (case records, laboratory sheets, original images etc.).

19. Statistical considerations

19.1 Patient number and power considerations

The objective of this phase III is to evaluate the impact of alemtuzumab combined with the CHOP14 chemotherapy. In the experimental arm (Arm B), the combination CHOP14-alemtuzumab is given as induction whereas the control arm (Arm A) contains only CHOP14. Both arms will be followed by a consolidation with HDT and autologous stem cell transplantation.
The sample size calculations of the design are based on the primary endpoint event-free survival (EFS). The null hypothesis is that the EFS distributions of the two arms are equal. Assuming exponential distributions, 3-year EFS equal to 35% in the control arm and 50% in the experimental

arm, a two-sided level α=5% logrank test requires 182 events to disprove this null hypothesis with a power of 80%. With constant inclusion and events rates and approx. 10% dropout, N=308 patients should be randomized during an accrual time of 4 years and followed 2 extra years to reach this number[40].

19.2 Statistical analysis

All main analyses will be done in accordance with the intention-to-treat principle.

19.2.1. Analysis sets

The Full Analysis Set (FAS) includes all randomized patients. The patients will be evaluated according to the therapy arm to 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, and were treated according to the allocated arm. 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, and for whom at least one post-baseline observation is available.

19.2.2. Patient characteristics and treatment

Demographic and prognostic characteristics as well as treatment data will be presented by treatment arm for the Full Analysis Set and the Per Protocol Sets, using descriptive statistical methods.

19.2.3. Efficacy analysis

All time-to event endpoints will be analyzed by the two-sided log-rank test and corresponding Kaplan-Meier curves will be displayed. Cox regression analysis will be used to determine the effect of selected prognostic factors and to investigate if the treatment effect is stable after adjustment.
The binary endpoint ORR will be analyzed by the chi-square test and Cochran-Mantel-Haenzel tests and/or logistic regression techniques in relation to clinical and pathological prognostic factors.
The main efficacy analyses will be performed for the Full Analysis Set. For exploratory and supporting reasons, all efficacy analyses will also be performed for the two Per-Protocol Sets.
The homogeneity of the treatment effect over subgroups defined by prognostic, demographic, and geographic factors will be presented by means of descriptive statistical methods,

19.2.4. Safety analysis

The safety and toxicity profile will be analyzed by descriptive statistical methods, based on the Safety Analysis Set.

19.2.5. Planned sub-set analysis

The CD-52-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 CD-52-status will be correlated with historical subtypes and study end-points.
The design of the induction therapy phase of ACT-1, with six cycles of CHOP-14 +/- Alemtuzumab, is parallel to the design of ACT-2, and hence a combined analysis of ORR is possible, and will be performed. The increased power enables studies on prognostic factors and treatment effect in subgroups based on e.g. CD-52 status.

19.3 Interim analysis and stopping rules

The safety and toxicity profile will be analyzed after every 50 treated patients. The trial may be terminated at the discretion of the data safety monitoring board for safety concerns at any of these safety interim analyses.
One efficacy interim analysis is planned after about 2.5 years inclusion, joint with the efficacy interim analysis of ACT-2. The alpha spending function approach DeMets DL & Lan KKG, 1994) will be used, with stopping boundary according to the O'Brien/Fleming strategy[41,42].
The study will be analysed after 182 primary events, and at the planning stage it is assumed that this will happen after n=308 patients have been evenly included during four years and followed two years extra. About half a year before planned stop of inclusion the event rate of the combined treatment arms will be analysed and the number of primary events predicted two-three years ahead, If it is improbable that the goal, 182 events, will be reached, the number of patients should be reconsidered,

19.4 Data and safety monitoring board

An independent data and safety monitoring board (DSMB) will be installed before start of the study. The DSMB will receive information of the progress of the study at regular intervals and has the following responsibilities:
- Review of study progress
- Review of safety aspects including serious adverse events
- Review of the results of the interim analysis

- Review of protocol adherence
- Give recommendations concerning continuation, modification or premature study closure to the Study Management. The addresses of the members are given on p.9.

Results of all planned interim analyses, and eventually other unplanned interim analyses, will be presented confidentially to the DSMB. Only if the DSMB recommends that the study should be stopped or modified, the results will become available to the principal investigator for further decisions. The presented report will include:

1) the number of entered
2) the number of evaluable patients
3) the treatment given
4) the number of failures
5) the type of failures
6) the incidence of SAE´s
7) the incidence of other adverse events

and these factors will be correlated to each treatment arm.

About half a year before the recruitment goal of 308 patients will be reached, a prediction will be made of the point in time when the total number of primary events (n=182) is expected to be reached. Based on this, the DSMB will advise the sponsor whether to increase the number of patients or not.
The DSMB is common for ACT-1 and ACT-2, and since the efficiency and safety issues are similar in the two studies, it is important that the interim analyses are synchronized as much as possible.

20. Ethics

20.1 Independent ethics committee or Institutional review board

The study protocol, and any amendment that is not solely of administrative nature, will need to be approved by an Independent Ethics Committee or Institutional Review Board in each participating country. The principal investigator in each country is responsible for all communication with the local Ethical Committee and the local Medical Authorities.

20.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP Guidelines. The local principal investigators are responsible for ensuring that the

study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical Practice (GCP) and applicable local regulatory requirements. This includes e.g. information on study-related additional investigations (blood tests, biopsy policy, diagnostic imaging and frequency of hospital visits during and after treatment) and a risk-benefit evaluation.

With regard to the latter, and as pointed out in the section 'Background and Rationale (see 6.1 to 6.5), the expected benefits of the investigational therapeutic approach justify the possible toxic side effects of the experimental treatment schedule. Based on an assessment of existing literature data (section 6.1), a rather broad clinical experience has been gathered over the last few years on the combined modality treatment using the antibody alemtuzumab together with different types of combination chemotherapy. An analogue chemo-immunotherapy approach has been adopted with successful results in the setting of aggressive B-cell lymphomas.

20.3 Patient information and consent

A written informed consent should be obtained from the patient before enrolment in the study. The side effects, and the potential risks and benefits of the experimental treatment will be explained to the patient orally and in writing.

21. Trial insurance

An insurance program covering all patients from participating centers will have to be contracted in each participating country.

22. Administrative Procedures

22.1 Curriculum Vitae

An updated copy of the curriculum vitae of each investigator and co-investigator of each center will be provided to the trial office prior to the beginning of the study.

22.2 Secrecy Agreement

All materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this protocol, the patient case report forms are the exclusive property of the sponsor (Nordic Lymphoma Group). They may not

be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of the sponsor.
It is specified that the submission of this protocol and other necessary documentation to the Ethics Committee or a similar body (IRB, CCPPRB, MREC….) is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.
The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

22.3 Record retention in investigating centers

In each center, the investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice. However, national regulations should be taken into account, the longest time having to be considered. For trials performed in the European Community, the investigator is required to arrange for the retention of patient identification codes for at least 15 years after the completion or discontinuation of the trial.

22.4 Ownership of data and publication policy

The Nordic Lymphoma Group, sponsor of the ACT-1, has the ownership of the data. In consequence, the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.
Manuscripts based on this protocol will be written according to the fifth edition of the “Vancouver System: Uniform Requirements for Manuscripts Submitted to Medical Journals” (1997).
The writing committee is expected to contribute with the planning and writing of the protocol and with the interpretation of the data on the basis of the statistical analysis performed at the Data Management Center. The chairman of the writing committee will be responsible for writing the first draft of the manuscript reporting treatment results and for editing the manuscript according to the critical review by the writing committee, the Data Management Center as well as by all co-authors. After this revision the manuscript will be sent to a peer reviewed scientific journal. Co-authorship will be decided on the basis of the Vancouver System criteria of active participation in the study (planning, patient inclusion, and analysis). All publications, abstracts or oral presentations based on data from patients included in this study must be approved by the study coordinator and by the writing committee. This is applicable to any individual patient registered in the trial, or any

subgroup of the trial patients. Such a publication cannot include any of the study end-points unless the final results of the trial have already been published.
Other manuscripts focusing on e.g. epidemiologic aspects, pretreatment biological features, prognostics factors etc. will be planned within the Working Group on T-cell lymphomas.
Reports focusing mainly, or entirely, on the results of special studies (e.g. molecular analyses) will be written by the person in charge of the specific analyses (first author) and co-authorship will be decided on the basis of the Vancouver System criteria reflecting substantial contribution to the generation of the data in question. All manuscripts with any relation to the present protocol must be circulated for general information and comments to the Study Coordinator and to the members of the Writing Committee prior to submission for publication.
All manuscripts will be distributed to all participating clinical departments and all study contributors (e.g. pathology and laboratory departments). Representatives of all departments will, regardless of the number of patients included by their department, be listed in a special section of the article/-s.

22.5 Protocol amendments

It is specified that the appendices attached to this protocol and referred to in the main text of this protocol, form an integral part of the protocol. No changes or amendments to this protocol may be made by the investigator or by the sponsor after the protocol has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the investigator and the sponsor. Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be appended to this protocol. Approval/advice of amendments by Ethic Review Committee or similar body (e.g. IRB) is required prior to their implementation, unless there are overriding safety reasons. If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the patient´s rights, full approval/advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the patient´s rights, approval/advice may be obtained by expedited review, where applicable. In some instances, an amendment may require a change to a consent form. The investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment. Prior to initiating the changes, protocol amendment must be submitted to regulatory agencies, where applicable, except under emerging conditions.

23. Financial issues

The present study is supported by an unrestricted grant from Genzyme. The financial support allows to cover following study related expenses:

- Clinical Trial Office personnel
- Data management and statistics
- Application-related expenses and insurances
- Patient fee
- Monitoring-related expenses

Additional funding will be applied for from governmental sources and private foundations.

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A. Pathology Form I

NLG	A-CHOP-14 (younger) [ACT-1] Prof. F. d' Amore, Aarhus University Hospital Nordic Lymphoma Group (NLG)	
	Pathology Form I	**Patho I**

⌊⌋⌊⌋ - ⌊⌋⌊⌋⌊⌋ - ⌊⌋⌊⌋⌊⌋⌊⌋ - ACT-1 Country-ID - Hospital-ID - Patient-ID - Study code	**Address of treating investigator:** Name/Institution: ..... Street: ..... Postal code - city: ..... - ..... Country: .....

To be **filled out by the primary pathologist** and to be **confirmed by the referral or national reference pathologist***

* National pathology panel representatives (see overleaf)

Note for primary pathologist:	**Note for referral/ national reference pathologist:**
Please fill out this form as soon as possible and send it together with **the original paraffin block (-s) and slides on which the diagnosis was based, and a copy of the original pathology report** to the referral or reference pathologist (national pathology panel representative) to confirm the diagnosis. **The protocol requires a review before randomisation** of the patient in the study trial for peripheral T-cell lymphomas! The original slides will be returned to your department along with the final review result. Any additional slides that are prepared will be kept by the national representative of the Central Pathology Panel. **The study is conducted according to the declaration of Helsinki, and the patient has consented to the central review of the specimen and to performance of additional studies. Thank you for your help.**	Please review the primary diagnosis and send the completed form as soon as possible to the treating investigator (original + 2 copies) as well as to the primary pathologist and the trial office: **Fax to trial office:** **Århus University Hospital 45-8949/ 7597** Please note that the patient cannot be included in the trial **before your confirmation of the diagnosis**.
Date of assessment: __/__/20__ dd mm yyyy	**Date of review:** __/__/20__ dd mm yyyy
Histology-No:	**Histology-No:** .....

Histological diagnosis:	**by primary pathologist**	**by referral/ national reference pathologist**
ALK-negative T-cell lymphoma, specification of subtype listed below not yet possible	❍	❍
Peripheral T-cell lymphoma, unspecified (PTCL-NOS)	❍	❍
Lymphoepithelioid cell variant (Lennert lymphoma)	❍	❍
T-zone variant	❍	❍
T-immunoblastic variant	❍	❍
Perifollicular variant	❍	❍
Follicular variant	❍	❍
Angioimmunoblastic T-cell lymphoma (AILT)	❍	❍
Anaplastic large cell lymphoma, ALK-negative	❍	❍
Extranodal NK/T-cell lymphoma, nasal type	❍	❍
Enteropathy-type T-cell lymphoma	❍	❍
Hepatosplenic T-cell lymphoma	❍	❍
Subcutaneous panniculitis-like T-cell lymphoma	❍	❍

Submitted specimen: ☐ Nodal ☐ Extranodal, localisation: ..... ☐ Other, localisation: ..... **Frozen tissue/ cells available:** ❍ Yes ❍ No, If yes: Amount: ..... Type: ..... Comment:	❍ none of the above diagnoses Specify: ..... Comment: .....
Diagnosis confirmed by primary pathologist: Name (printed): ..... Signature:	**Diagnosis confirmed by referral/ national reference pathologist:** Name (printed): ..... Signature: .....

	Date (dd/ mm/ yyyy)	**Signature**
Trial office:	__/__/20__	

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Pathology Committee - National Representatives

Country	Name
Denmark	S. Hamilton-Dutoit
Norway	J. Delabie
Sweden	C. Sundström
Finland	M. Vornanen
Germany	T. Rüdiger
France	P. Gaulard
	E. Martin
Belgium	L. de Leval
Netherlands (EORTC)	D. de Jong
Netherlands (HOVON)	J. Oudejans
Czech Republic	L. Boudova
Poland	G. Rymkiewicz
Austria	A. Chott
Australia	D. Ellis
Portugal	J. Cabeçadas
Israel	E. Okon

B. Pathology Form II and III

NLG

A-CHOP-14 (younger) [ACT-1]
Prof. F. d' Amore, Aarhus University Hospital
Nordic Lymphoma Group (NLG)

Pathology Form II **Patho II** page 1 of 2

_ _ - _ _ _ - _ _ _ - ACT-1
Country-ID - Hospital-ID - Patient-ID - Study code

Note for referral or national reference pathologist:
Please fill out this form and send the original form to the trial office of the study and a copy to the primary pathologist.

Trial office: Clinical Trial Office ACT-1, Department of Hematology, Aarhus University Hospital, Tage Hansens Gade 2, Entrance 3C, 1 floor, DK-8000 Aarhus C

Date of review: _ _ / _ _ / 2 0 _ _ (dd mm yyyy) **Histology-No:** .....

Submitted specimen:

- ☐ Nodal
- ☐ Extranodal, localisation: .....
- ☐ Other, localisation: .....

Date of diagnostic biopsy: _ _ / _ _ / 2 0 _ _ (dd mm yyyy)

Molecular studies

Have molecular studies been performed? ❍ Yes ❍ No ❍ Unknown,
If yes, please specify:

	Done	Not done	
Ig	☐	☐	If done, specify: .....
TCR	☐	☐	If done, specify: .....
Cytogenetics	☐	☐	If done, specify: .....
Other studies	☐	☐	If done, specify: .....

Histological diagnosis:

- ❍ AKL-negative T-cell lymphoma, specification of subtype listed below not possible
- ❍ Peripheral T-cell lymphoma, unspecified (PTCL-NOS)
  - ❍ Lymphoepithelioid cell variant (Lennert lymphoma)
  - ❍ T-zone variant
  - ❍ T-immunoblastic variant
  - ❍ Perifollicular variant
  - ❍ Follicular variant
- ❍ Angioimmunoblastic T-cell lymphoma (AILT)
- ❍ Anaplastic large cell lymphoma, ALK-negative
- ❍ Extranodal NK/T-cell lymphoma, nasal type
- ❍ Enteropathy-type T-cell lymphoma
- ❍ Hepatosplenic T-cell lymphoma
- ❍ Subcutaneous panniculitis-like T-cell lymphoma
- ❍ Primary cutaneous γδ T-cell lymphoma

- ❍ None of the above, specify: .....

Comments: .....

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NLG

A-CHOP-14 (younger) [ACT-1]
Prof. F. d' Amore, Aarhus University Hospital
Nordic Lymphoma Group (NLG)

Pathology Form II **Patho II** page 2 of 2

_ _ - _ _ _ - _ _ _ - ACT-1
Country-ID - Hospital-ID - Patient-ID - Study code

List of stains performed.
Stains marked in gray are considered mandatory
Please specify using one of the following numbers: **0**: negative tumor cells; **1**: > 50% positive tumor cells; **2**: < 50% positive tumor cells; **3**: Scattered non-neoplastic; **4**: Not done; **5**: Technically unsatisfactory

Subtypes / Stains	PTCL, NOS	AILT	ALCL, ALK -	Extranodal NK/TCL, nasal type	Entero-pathy-type TCL	Hepato-splenic TCL	primary cutaneous γδ-TCL	Other diagnosis .....
ALK	_	_	_	_	_	_	_	_
Beta F1	_	_	_	_	_	_	_	_
CD 1	_	_	_	_	_	_	_	_
CD 2	_	_	_	_	_	_	_	_
CD 3	_	_	_	_	_	_	_	_
CD 4	_	_	_	_	_	_	_	_
CD 5	_	_	_	_	_	_	_	_
CD 8	_	_	_	_	_	_	_	_
CD 10	_	_	_	_	_	_	_	_
CD 20	_	_	_	_	_	_	_	_
CD 25	_	_	_	_	_	_	_	_
CD 30	_	_	_	_	_	_	_	_
CD 52	_	_	_	_	_	_	_	_
CD 56	_	_	_	_	_	_	_	_
CD 79	_	_	_	_	_	_	_	_
Cytotoxic								
- TIA-1	_	_	_	_	_	_	_	_
- Granzyme B	_	_	_	_	_	_	_	_
- perforin	_	_	_	_	_	_	_	_
EBER	_	_*	_	_	_	_	_	_
EBV (LMP1)	_	_	_	_	_	_	_	_
EMA	_	_	_	_	_	_	_	_
FDC (mandatory, one marker is sufficient)								
- CD 21	_	_	_	_	_	_	_	_
- CD 23	_	_	_	_	_	_	_	_
- CD 35	_	_	_	_	_	_	_	_
- CNA.42	_	_	_	_	_	_	_	_
FoxP3	_	_	_	_	_	_	_	_
TdT	_	_	_	_	_	_	_	_
Follicular helper T-cells (mandatory, one marker is sufficient)								
- PD1 (PDCD1)	_	_	_	_	_	_	_	_
- CXCL13	_	_	_	_	_	_	_	_
- NFATC1	_	_	_	_	_	_	_	_
Other (specify)	_	_	_	_	_	_	_	_
Other (specify)	_	_	_	_	_	_	_	_
Other (specify)	_	_	_	_	_	_	_	_

*Specify which cells: .....

	City	Date (dd/ mm/ yyyy)	Name (printed)	Signature
Pathologist:		_ _ / _ _ / 2 0 _ _		
Trial office:	–	_ _ / _ _ / 2 0 _ _	–	

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NLG

A-CHOP-14 (younger) [ACT-1]
Prof. F. d' Amore, Aarhus University Hospital
Nordic Lymphoma Group (NLG)

Pathology Form III — Patho III

_ _ - _ _ _ - _ _ _ - ACT-1
Country-ID - Hospital-ID - Patient-ID - Study code

Note for pathology panel representative:

Please fill out this form and send the original form to the trial office of the study.

Trial office: Clinical Trial Office ACT-1, Department of Hematology, Aarhus University Hospital, Tage Hansens Gade 2, Entrance 3C, 1 floor, DK-8000 Aarhus C

Date of review: _ _ / _ _ / 2 0 _ _ (d d m m y y y y) **Histology-No:** .....

Submitted specimen:

- ☐ Nodal
- ☐ Extranodal, localisation: .....
- ☐ Other, localisation: .....

Histological diagnosis:

- ❍ AKL-negative T-cell lymphoma, specification of subtype listed below not possible
- ❍ Peripheral T-cell lymphoma, unspecified (PTCL-NOS)
  - ❍ Lymphoepithelioid cell variant (Lennert lymphoma)
  - ❍ T-zone variant
  - ❍ T-immunoblastic variant
  - ❍ Perifollicular variant
  - ❍ Follicular variant
- ❍ Angioimmunoblastic T-cell lymphoma (AILT)
- ❍ Anaplastic large cell lymphoma, ALK-negative
- ❍ Extranodal NK/T-cell lymphoma, nasal type
- ❍ Enteropathy-type T-cell lymphoma
- ❍ Hepatosplenic T-cell lymphoma
- ❍ Subcutaneous panniculitis-like T-cell lymphoma
- ❍ Primary cutaneous γδ T-cell lymphoma

- ❍ None of the above, specify: .....

Comments: .....

	City	Date (dd/ mm/ yyyy)	Name (printed)	Signature, Member of the Panel
Pathologist:		_ _ / _ _ / 2 0 _ _		
Trial office:		_ _ / _ _ / 2 0 _ _	–	

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C. WHO classification of tumors of lymphoid tissues (4th edition, 2008), T/NK-cell neoplasms only

♦ = Eligible for trial entry

2001 3rd edition		2008 4th edition	
WHO category number	Entity	WHO category number	Entity
9729	Precursor T-cell lymphoblastic leukaemia / lymphoma	9837/3	T lymphoblastic leukaemia / lymphoma
9834	T-cell prolymphocytic leukaemia	9834/3	T-cell prolymphocytic leukaemia
9831	T-cell granular lymphocytic leukaemia	9831/3	T-cell large granular lymphocytic leukaemia
9948	Aggressive NK-cell leukaemia	9948/3	Aggressive NK-cell leukaemia
9827	Adult T-cell leukaemia / lymphoma (HTLV1+)	9827/3	Adult T-cell leukemia / lymphoma
9719	♦ Extranodal NK / T-cell lymphoma, nasal-type	9719/3	♦ Extranodal NK / T-cell lymphoma, nasal-type
9717	♦ Enteropathy type T-cell lymphome	9717/3	♦ Enteropathy associated T-cell lymphoma
9716	♦ Hepatosplenic γ / δ T-cell lymphoma	9716/3	♦ Hepatosplenic T-cell lymphoma
9708	♦ Subcutaneous panniculitis-like T-cell lymphoma	9708/3	Subcutaneous panniculitis-like T-cell lymphoma
-	-	9726/3	♦ Primary cutaneous gamma-delta T-cell lymphoma
9700	Mycosis fungoides	9700/3	Mycosis fungoides
9701	Sézary syndrome	9701/3	Sézary syndrome
9714	Anaplastic large cell lymphoma, primary cutaneous type	9718/3	Primary cutaneous anaplastic large cell lymphoma
9702	♦ Peripheral T-cell lymphoma (not otherwise specified)	9702/3	♦ Peripheral T-cell lymphoma, NOS
9705	♦ Angioimmunoblastic T-cell lymphoma	9705/3	♦ Angioimmunoblastic T-cell lymphoma
9714	Anaplastic large cell lymphoma* (T- and null-cell types), primary systemic type	9702/3	Anaplastic large cell lymphoma, ALK negative
		9714/3	Anaplastic large cell lymphoma, ALK positive
9724	Unclassifiable	-	-

* only alk-negative cases included

D. 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

E. Ann Arbor staging classification

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 extralymphatic focus

II,N: nodal involvement in two or more regions on one side of the diaphragm
II,N,E: presence of one or more involvements in regions and one extralymphatic foci 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 involvements in regions and one extralymphatic foci on both sides of the diaphragm

IV,E: exclusive disseminated involvement of one or more extralymphatic foci, or extralymphatic foci at sites which cannot be treated using radiotherapy Involvement of the liver and / or the bone marrow is stage IV,E.
IV,N,E: IV,E with additional involvement of lymphatic regions

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

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

- skin and soft tissue e-foci count as E-manifestations each
- bone: 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.

F. International Prognostic Index

The age-adjusted international prognostic index (IPI) distinguishes 4 risk groups of patients according to their Ann Arbor stage, ECOG performance status and LDH[42].

Risk factors are:

- Age >60 years
- Ann Arbor stage III or IV
- ECOG performance status 2-4
- LDH > 1x Upper limit of normal (ULN)
- More than 1 extranodal site

The IPI:

- Low risk : 0 - 1 risk factors
- Low-intermediate risk : 2 risk factor
- High-intermediate risk : 3 risk factors
- High risk : 4 - 5 risk factors

G. Common Terminology Criteria for Adverse Events

The grading of toxicity and adverse events will be done using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 3.0, published June 10, 2003. A complete document (72 pages) may be downloaded from the following site:

http://ctep.cancer.gov

H. NYHA* scoring list

Grade 1	No breathlessness
Grade 2	Breathlessness on severe exertion
Grade 3	Breathlessness on mild exertion
Grade 4	Breathlessness at rest

The *New York Heart Association functional and therapeutic classification applied to dyspnoea

I. Response Criteria

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.

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.

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.

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 ended HDT 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.

2. 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.

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%).

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.

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.

J. Patient Information Sheet and Informed Consent Form ACT-1
(should be adapted to national guidelines)

Dear Patient,

We would like to ask you for your consent to participate in a clinical study. Clinical studies are designed to improve established treatment procedures with the aim of improving the outcome of treatment. The doctor treating you has informed you that you have T-cell non-Hodgkin's lymphoma, a malignant disease of the lymphoid system, which can be cured in many cases by treatment using cytotoxic drugs (cell poisons), followed by a consolidation with a high-dose chemotherapy and stem cell transplantation, and sometimes radiotherapy, if necessary. As many, but by no means all patients with this disease can be cured using these methods, investigations are currently being conducted to determine if it is possible to further improve treatment results. Possible ways of improving treatment results are to use a monoclonal antibody in addition to chemotherapy.

The purpose of this treatment optimisation study
As most T-cell lymphomas show an abundant expression of the antigen CD52, it may be of benefit in your case to conduct immunotherapy using alemtuzumab, a specific monoclonal antibody which has an affinity for the CD52 structure present on the surface of malignant cells of many lymphoma types. This antibody is able to recognise these cells, attach itself to them and thus trigger immune mechanisms which can lead to the destruction of the lymphoma cells. As it is not yet known whether concurrent administration of alemtuzumab with CHOP-14 chemotherapy is of benefit, we need to compare two different treatment arms (6 x CHOP-14, 6 x CHOP-14 with alemtuzumab) using a random design. This means that, should you consent to participate in this study, you will be randomly assigned to one of these two treatment arms. The doctor treating you will have no influence on this random assignment.

Study procedures
In the standard chemotherapy group, you will receive the chemotherapy combination treatment which is currently regarded as the most effective and is known as CHOP-14. This regimen involves the administration of the substances cyclophosphamide, doxorubicin, vincristine and prednisone. The chemotherapy is administered every 14 days. In the other treatment group, the patients will receive the same dose of these medications plus one dose of the antibody Alemtuzumab during each of the first four cycles of CHOP-14. The study will commence in September 2007 and, with the follow-up procedures, will continue to December 2013. A total of 308 patients are to participate in the study.

Prior to the commencement of treatment, you will be extensively examined, as is also standard practice in patients with lymphoma who are not taking part in clinical studies. During this examination, the exact extent of the disease will be determined. In addition to analysis of blood samples, analysis of bone marrow (biopsy), X-ray investigations, including computer tomography (CT) and/or ultrasound scans will be necessary. In some lymphoma types, it is also necessary to perform so-called lumbar puncture to investigate and provide treatment for the cerebrospinal fluid. During the initial examination, your heart and lung function will be tested and tests for viral infection (including HIV) will be performed. Other tests will be performed during the study in order to determine the effects of treatment on your disease. Weekly tests are planned for the treatment phase, but some of these can be performed by your GP. The consolidation treatment with infusion of your own stem cells (transplantation), previously harvested after chemotherapy, will be done secondarily after the chemotherapy but only in case your disease has been proven to be sensitive to the chemotherapy. It is now accepted by the medical community that this consolidation is more efficacious when it is using increase doses of chemotherapy (high-dose chemotherapy). These increased doses of cytotoxic drugs imply a re-infusion of your own stem cells in order to reduce the haematological disadvantages of the intensive treatment. In order to prepare the stem cell transplantation, the stem cells will be collected from the peripheral blood after the last cycle or one of the last cycles of chemotherapy. Peripheral stem cells are immature cells from the bone marrow which are appearing temporarily in the peripheral blood from where they can be easily collected. This mobilization from the bone marrow to the peripheral blood can be increased under the administration of a haematopoietic growth factor or G-CSF. You will therefore receive subcutaneous injections of this G-CSF. When a sufficient number of stem cells is appearing in the peripheral blood, the stem cells are collected during a procedure named cytapheresis. This means that after the blood is taken from a vein of an arm, as for a blood donation, it will go through a separator where only the stem cells will be taken away, the rest of the blood coming back through a vein in the other arm. Stem cells are

then frozen at -180°C. The cytapheresis procedure will last approximately 4 hours, until the needed number of stem cells is achieved. If not, the procedure can be repeated the following days. In case the blood vessels are too small or not in good conditions, a central venous catheter can be placed. One day after the end of the BEAM high-dose chemotherapy (consisting of the cytotoxic drugs BCNU, Etoposide, Cytosine Arabinoside and Melphalan), the stem cells will be defrosted and reinfused in your body like a transfusion. They will go the bone marrow and grow to rebuild hematopoietic cells. For this treatment, you will have to stay at the hospital 3 to 6 weeks. In the interval of time after the high-dose chemotherapy and the stem cell transplantation during which the white blood cells, the red blood cells and the platelets are destroyed and not yet reconstituted, there is a period named aplasia during which the risks of infection and of inflammation of the mucous membranes are higher than after the normal chemotherapy. In case of infection, you will be treated with antibiotics. Inflammation of the mucous localized to the intestines and the mouth could lead temporarily to an impossibility of a normal alimentation and the need for an intravenous nutrition. Additionally, transfusions of platelets and red blood cells could be necessary in order to avoid haemorrhagic complications. On completion of treatment, you will be examined in order to check how the disease has responded to the treatment and checked again every 3 months in the first 2 years, every 6 months during the next 2 years and annually thereafter until six years after the beginning of the whole trial. During these appointments, you will be asked to provide information on any side effects, on accompanying medication used and infections. There will be no further tests conducted in this study apart from the examinations and blood tests which would be required in any case. We will ask you to provide your consent so that part of the blood samples and lymph node samples obtained from you during routine and diagnostic procedures prior to initiation of treatment can be frozen and stored for subsequent scientific investigation (e.g. of chromosome alteration, overexpression of tumour growth-promoting genes and suppression of tumour growth-inhibiting genes, biological tumour markers). These investigations are to be performed so that the treatment of future patients can be better targeted. The results of these investigations will not be used for commercial purposes. We will ask you to transfer the right of utilisation of these materials to the Study Management Panel which is responsible for ensuring that the study is conducted correctly in accordance with scientific standards and which has the support of a scientific advisory board. On completion of the course of chemotherapy, radiotherapy may also be required in some cases to ensure that particularly large lymph nodes or atypically sited lymphomas (so-called extranodal involvement) are eliminated.

Responsibilities of patients

If you do decide to participate in this study you will be required to cooperate with the study physician and will be expected to comply with the following:

- You must always report regularly for examinations
- You must always follow the instructions of the study physician
- You must state which other medications you are using during the study
- You should report any accompanying illnesses you may have
- If you decide to early discontinue participation in the study, you must report for the final examination and follow-up examinations.

Risks

Both treatment arms are associated with medication-specific side effects. The possible side effects of the proposed treatments are:

After chemotherapy: nausea and vomiting, suppression of blood formation and reduced numbers of blood cells (thus increasing the risk of infection, bleeding and anaemia), loss of hair, damage to nerves, damage to the heart muscle, inflammation of the mucous membranes, tissue damage after inappropriate injection of chemotherapeutic substances, damage to the bladder, allergic reactions, and possible side effects of fertility. In rare cases, there may be inflammation of the bladder or the intestines after administration of cyclophosphamide. You should not consume alcoholic drinks during chemotherapy treatment and women of childbearing potential should use safe anticonception. All cytotoxic drugs used during chemotherapy can increase the risk of developing a second cancer.

In case of infection, you will have to be treated with antibiotics. In order to prevent infections, oral antibiotics are administered. The diminution of the white blood cells will be fought by the administration of G-CSF which is stimulating the production of white blood cells and reducing the duration of the aplasia.

After intrathecal treatment (puncture of the spinal canal and the introduction of chemotherapeutic agents) you may experience nausea and vomiting; inflammation of the meninges may occur in rare cases.

After G-CSF: you may experience temporary bone pains and/or fever. In this case, you will receive a treatment against pain or fever.

After radiotherapy the following can occur: nausea, retching, problems with swallowing, headache, fatigue, leukopenia, anaemia, alterations to skin and loss of hair in the irradiated region, also possible are radiation-

related reactions of lung tissue (laboured breathing), of the intestines (diarrhoea) and of the pericardium (effusion).
After the administration of alemtuzumab the following side effects are possible: fever, muscle and joint pain, low blood pressure and, occasionally, chills and skin rash. In theory, severe allergic reactions involving life-threatening effects (so-called "anaphylactic shock") are possible. After chemotherapy or radiotherapy, there may be temporary impairment of the ability to drive which can be further exacerbated by the administration of medications to prevent nausea. You should avoid driving a vehicle yourself during the period in question. In order to prevent and alleviate side effects and complications which can occur in association with the rapid destruction of cells, particularly at the start of chemotherapy, a so-called prephase treatment will precede the actual CHOP chemotherapy cycles. During prephase treatment, which is an obligatory part of the therapeutic schedule, you will be given an intravenous injection of the chemotherapeutic agent vincristine on the first day and cortisone tablets over a period of 7 days. If your lymphoma is of a type which affects a particular body region (the bones of the face, a high site on the neck, bone marrow or testes) for which we know that it is associated with an increased risk of (subsequent) involvement of the meninges and the central nervous system, you will also receive concurrent intrathecal treatment. This means that, in addition to intravenous and oral chemotherapy, a combination of chemotherapeutic agents (methotrexate, cytosine arabinoside and dexamethasone) will be injected into your cerebrospinal fluid. Over the whole period in which you are receiving chemotherapy there is an increased risk that you may develop an infection. This is particularly the case for the time between days 6 and 12 after commencement of a chemotherapy cycle when there is a temporary fall in numbers of leukocytes. You should ensure that you maintain a good standard of hygiene, particularly oral hygiene, during the whole treatment period. If there is an excessive fall in the number of leukocytes in your case, your doctor may prescribe antibiotics to prevent the risk of infection. You should take these in accordance with instructions. If signs of infection, particularly fever or chills, develop in this period, please contact the treating doctor or a hospital so that the symptoms can be assessed and antibiotic treatment initiated if necessary. It is possible that administration of blood products may be necessary during treatment, particularly red blood cells, more rarely, blood platelets. Although products are carefully checked prior to use, there is still a slight risk of transmission of infection during these procedures.

Possible benefits of the study treatment
If the additional administration of alemtuzumab antibody results in an improved response to treatment and a prolongation of the remission period, this may be of benefit to you. It is not possible to predict at present whether, and to what extent, this effect may occur in each individual case. An additional possible benefit for patients in general would be the improvement of treatment efficacy with acceptable side effects. The only way to determine if this can be achieved is to compare the treatment, which is currently held to be optimal with the modified treatment regimen

Other alternative treatments
If you decide not to participate in this study, you will be given the standard chemotherapy. The standard of medical care you receive in future will in no way be influenced by your decision not to participate in this clinical study.

Further information
The protocol for this clinical study was submitted for review by the Ethics Committee of….(fill in as appropriate)….Participation in this clinical study is completely voluntary. The doctor will ask you to sign a consent form and thus confirm that you have been informed in detail about the study and that you understand its purpose. The treating physician will answer any questions you may have concerning the study in detail, and you can contact him/her in this connection at any time during the study. You retain the right to withdraw your given consent to participate in the study at any time and without giving reasons for doing so; this will not influence your relationship with the treating doctor in any way. However, for reasons of precaution, it is advisable for you to receive a final examination if you do decide to prematurely withdraw from the study. You will continue to receive all medical procedures required for the treatment of the disease even if you prematurely withdraw from the study. You will, of course, be notified immediately should any information come to light which could be relevant to your participation in the study.

Insurance cover
In accordance with the requirements of the laws of your country, a patient insurance policy has been taken out for your benefit with the …..(fill in as appropriate)……

To ensure that you retain insurance cover, you must comply with the following:
1. You should receive other medical treatment (except in emergencies) only with the approval of the study physician.
2. If you experience damage to your health or suspect that such damage has occurred as a result of your participation in this clinical study, you must notify the insurer of this immediately: you must report all physical injury which may have occurred in association with the use of the preparation under investigation or with procedures conducted as part of the clinical study.

Notification of your GP
Assuming that you have no objections, your GP will be informed that you are participating in this clinical study.

Confidentiality of documents
All data collected on individual patients during the study will be sent via the trial office in Aarhus, Denmark to the Data Management Centre in Leipzig (Institute for Medical Informatics, Statistics and Epidemiology) in Germany for confidential evaluation. The requirements of the professional code of conduct for doctors and the law on data protection will be complied with in full. Full data protection will be maintained in the case of publication in specialist journals. All persons who have authorised access to stored data are obligated to observe the requirements of the law on data protection. These persons will be permitted to access stored information on your disease at any time.

Thank you for your cooperation.

……..
Date and signature of the doctor providing information

Name of the patient:
Surname:……. Forename(s):……. Date of birth…….
DD MM YYYY

The patient was provided with information on:
1. The nature of the disease
2. The prognosis for the disease if protocol-conformable treatment is provided.
3. The current scientific knowledge, the purpose of the study
4. Therapeutic effects and side effects
Therapeutic effects: possibility of complete remission of all symptoms and recovery.
Side effects: After chemotherapy and high-dose chemotherapy: nausea and vomiting, suppression of blood cell formation and reduced numbers of blood cells (thus increasing the risk of infection, bleeding and anaemia), loss of hair, damage to nerves, damage to the heart muscle, tissue damage after inappropriate injection of chemotherapeutic substances, damage to the bladder, allergic reactions, second cancer. After radiotherapy: nausea, retching, problems with swallowing, headache, fatigue, leukopenia (reduction of numbers of white blood cells with increased risk of infection), anaemia, alterations to skin and loss of hair in the irradiated region, also possible are radiation-related reactions of lung tissue (laboured breathing), of the intestines (diarrhoea) and of the pericardium (effusion). After administration of the haematopoietic growth factor (G-CSF): bone pain, high body temperature. After administration of the alemtuzumab antibody: fever, chills, muscle and joint pain, fall in blood pressure, skin rash, in rare cases allergic reactions with shock in extreme cases.
5. Data transfer
The patient agrees to the documentation of disease/study-related data during the clinical study and to its release for evaluation by the Study Group and for verification by the Regulatory Authority or Federal Authority. The patient also consents to allow persons authorised by the Study Group and/or the stated authorities access to their original case records and original study data, and to allow personal data and information to be transferred to third parties for the purpose of scientific evaluation of the study. The patient also consents to be directly contacted by the Study Management Centre if no information on their case is received for a period of 1 year.
6. Patient's freedom of choice
This patient has freedom to decide whether to participate in the study or not.
7. Patient's decision:
□ wishes to participate
□ does not wish to participate

Doctor:
……
Function Date Signature

Patient
……..
Date Signature

I, surname…….forename(s)……born on……
have been informed by the treating doctors in a detailed discussion that I have T-cell non-Hodgkin's lymphoma, a malignant disease of the lymphoid system, which can be cured in many cases by treatment using cytotoxic drugs (cell poisons), and additional radiotherapy if necessary. I have been informed that a clinical study is currently being conducted with the aim of improving the efficacy of chemotherapy by the additional use of the antibody alemtuzumab. The addition of alemtuzumab to the chemotherapy may theoretically increase the efficacy of the treatment. However, it is also possible that there may be more severe side effects. As it is not known at present which of the two treatment variants is the best, it is necessary to assign patients to one of the two treatment arms using a random procedure ("randomisation"). The medications used in the treatment are all approved by the National Health Authorities of primary and/or relapsing non-Hodgkins lymphoma or of relapsed or refractory chronic lymphatic leukaemia. I have been informed of the purpose of the study and voluntarily declare, with this knowledge, that I am willing to participate in this study. I consent to the documentation of case/study data during this study and to the release of this data in anonymous form for verification by the relevant Regulatory Authority or Federal Authority. I also consent to allow persons obligated to maintain confidentiality and authorised by the Study Group or the authorities access to my case records for the purposes of documentation and to collect and evaluate my personal data required for the monitoring of my disease and for documentation purposes in non-anonymous form. I have the right to be provided with information on the aim, purpose and site of storage of this collected data. The purpose of the processing of this data (storage, transfer, modification, deletion) at the Study Management Center is for the medical documentation of treatment and follow-up at the numerous collaborating study centres. All persons who have authorisation to access these data are obligated to maintain confidentiality. Data
will be used in anonymous form only in any publications. I consent to my personal data being released
to the GP named by me and to the doctors involved in my treatment. I herewith undertake to report all impairments to my health which may occur during treatment, or later, and which may be associated with treatment (e.g. subsequent effects on blood counts) without delay to the doctor treating me.
I consent to being assigned, to treatment with either six cycles chemotherapy in accordance with the CHOP regimen at 2-weekly intervals and to the random assignment to additional treatment with six doses of the antibody alemtuzumab or not. I will be voluntarily participating in this study and am aware that I can withdraw my consent at any time without giving reasons for doing so. I am free to choose an appropriate therapy if I choose not to participate in this study. If any of the therapies proves to be less effective during one of the regular intermediate analyses to be conducted during the study, any further randomisation will be abandoned. I also consent to allow tissue samples obtained from me to be sent to a specially qualified pathologist (Reference Pathologist) so that the diagnosis can be confirmed.

I also confirm that I consent to allow portions of the blood, bone marrow and tissue samples obtained from me for diagnostic purposes to be analysed for scientific, non-commercial purposes and herewith transfer the right of utilisation of this material to the Study Management Panel. The right of entitlement to this material shall remain with me. No additional tissue or blood tests will be conducted beyond those required by the medical indication.I have been informed that the regular monitoring examinations, which will be in my interest and particularly in the interest of future patients, will be conducted over a period of many years. The results
of follow-up analysis will be reported to the Study Management Centre. I have understood all information which has been provided to me in connection with this study. I have been given sufficient opportunity to discuss details of the treatments, their purpose and possible side effects with the treating doctors. With this information in mind, I consent to the planned procedures and to other reasonable procedures which may be necessary in connection with treatment. I confirm that a copy of the Patient Information Leaflet and Consent Form and a copy of the patient insurance conditions *(national/regional/local differences may apply)* have been given to me.

Doctor:……..Post……Date…….
DD MM YYYY

Stamp of the institution: Signature…….

Witness:……Date:……. Signature:……..
DD MM YYYY

Patient:
Name:……..Forename:…… Date of birth:……DD MM YYYY

Address of the patient: ……

Post code/town:……
(please print)

Date:…… Signature:……
DD MM YYYY

K. List of Participating Groups or Countries

One principal investigator will be designed within each country or group and will correspond with the sponsor regarding the organization of the trial.

Country	**Study Group / Centers**	**Principal Investigator**	**Study Participation**
Scandinavia	NLG	Prof. F. d´Amore	ACT-1 + ACT-2
Germany	DSHNHL	Prof. L. Trümper	ACT-2
Germany	Frankfurt	Dr Weidmann	ACT-1 + ACT-2
Netherlands	EORTC HOVON	Prof. H. Kluin-Nelemans Dr. G. van Imhoff	ACT-1 + ACT-2 ACT-1 + ACT-2
France	GELA GOELAMS	Prof. C. Gisselbrecht Dr. O. Tournilhac	ACT-2 ACT-2
Belgium	GELA, EORTC, HOVON	Dr. E. Van den Neste	ACT-1 + ACT-2
Austria	Vienna	Prof. G. Hopfinger	ACT-1 + ACT-2
Portugal	Lissabon and Porto	Prof. M. G. Silva	ACT-1 + ACT-2
Poland	Polish Lymphoma Group	Prof. J Walewsky	ACT-1 + ACT-2
Israel	Tel Aviv	Prof. O. Shpielberg	ACT-1 + ACT-2
Australia	ALLG	Prof. J. Seymour	ACT-1 + ACT-2
Czech Republic	Czech Lymphoma Group	Prof. M. Trneny	ACT-1 + ACT-2