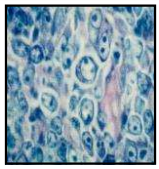

DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN-LYMPHOME*
German High Grade Non-Hodgkin's Lymphoma Study Group
*(supported by Deutsche Krebshilfe)

Randomised Study Comparing an Immuno-Chemotherapy with 6 Cycles of the Monoclonal anti-CD20 Antibody Rituximab in Combination with 6 Cycles of Chemotherapy with CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone)

at 21-day Intervals or 14-day Intervals

both with or without consolidating Radiotherapy of Large Tumour Masses (≥ 7.5 cm) and/or Extranodal involvement

in Patients with Aggressive CD20$^+$ B-Cell Lymphoma

Aged 18 to 60 years

with Age-adjusted IPI = 1 (all) or IPI=0 with Bulky Disease (≥ 7.5 cm)

Short Title: UNFOLDER 21/14 Study

Study number: DSHNHL 2004-3

Eudra CT-Nr: 2005-005218-19

Author: M. Pfreundschuh
With the support of M. Ziepert, C. Rübe, N. Schmitz and F. Hartmann
Translated from the German Original by A. Schmitz and M. Pfreundschuh

Version 4.0 of 22 Nov 2012 approved by the Ethics Committee of the Medical Council of Saarland on 25.02.2013

Version 3.2.2 on 06.02.2006 approved by the Ethics Committee of the Medical Council of Saarland on 02.03.2006

Version 3.2.1 approved by the Ethics Committee of the Medical Council of Saarland on 07.10.2005

Version 3.2 with amendment approved by the Ethics Committee of the Medical Council of Saarland on 18.08.2005

Version 3.1 approved by the Ethics Committee of the Medical Council of Saarland on 30.09.2004

Chairman DSHNHL 2004-3	DSHNHL Study Secretariat	DSHNHL Biometry & Data Centre
Prof. Dr. M. Pfreundschuh	Prof. Dr. M. Pfreundschuh, PD Dr. G. Held Dr. N. Murawski Dr. V. Pöschel	Prof. Dr. M. Löffler, Dr. M. Ziepert
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http://www.lymphome.de

List of contents

0 General Issues

0.1 Persons responsible for DSHNHL 2004-3

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Reference Pathology:	Prof. Dr. med. A. Rosenwald (Coordinator of the Panel) Institute of Pathology University of Würzburg, Josef-Schneider-Str. 2 97080 Würzburg Tel.: 0931/31-81199, Fax: 31-81224 E-Mail: Rosenwald@mail.uni-wuerzburg.de
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0.2 DSHNHL Study Management Committee

0.2.1 Board of the DSHNHL

- Prof. Dr. M. Pfreundschuh, Homburg
- Prof. Dr. N. Schmitz, Hamburg
- Prof. Dr. M. Loeffler, Leipzig
- Prof. Dr. L. Trümper, Göttingen

0.2.2 Other members of the Study Management Committee

- Prof. Dr. B. Glass, Hamburg
- PD. Dr. G. Held, Homburg
- Dr. M. Nickelsen, Hamburg
- V. Pöschel, Homburg
- Prof. Dr. G. Wulf, Göttingen
- Dr. S. Zeynalova, Leipzig
- Dr. M. Ziepert, Leipzig

0.2.3 Scientific Advisory Board

The Scientific Advisory Board decides on the support of scientific projects accompanying the study. In February 2011, the board has been composed of:

- 1 Member of the Study Management: Prof. Dr. L. Trümper (Göttingen)
- 1 Pathologist: Prof. Dr. A. Rosenwald (Würzburg)
- 1 Biometrician: Dr. M. Ziepert (Leipzig)
- External Experts: Prof. Dr. M. Kneba (Kiel), Prof. Dr. R. Siebert (Kiel)

0.3 Protocol Committee and Data and Safety Monitoring Committee (DSMC)

0.3.1 Protocol Committee

The following members constitute the Committee (as of February 2011):

- Prof. Dr. M. Bentz, Karlsruhe (7)
- PD Dr. P. Borchmann, Köln (7)
- PD Dr. A. Buck, München (4)
- Prof. Dr. A. Bücker, Homburg (5)
- Prof. Dr. M. Dreyling, München (7)
- Dr. M. Engelhard, Essen (3)
- Prof. Dr. N. Frickhofen, Wiesbaden (7)
- Prof. Dr. B. Glass, Hamburg (1)
- PD Dr. M. Hänel, Chemnitz (7)
- Prof. Dr. F. Hartmann, Lemgo (7)
- PD Dr. G. Held, Homburg (1)
- Prof. Dr. D. Hellwig, Homburg (4)
- Prof. Dr. U. Kaiser, Hildesheim (7)
- Prof. Dr. C.-M. Kirsch, Homburg (4)
- Prof. Dr. W. Knauf, Frankfurt/Main (6)
- Dr. P. Koch, Münster (7)
- PD Dr. E. Lengfelder, Mannheim (7)
- Dr. R. Liersch, Münster (7)
- Dr. W. Lindemann, Hagen (7)
- Prof. Dr. M. Löffler, Leipzig (1)
- Dr. B. Metzner, Oldenburg (7)
- Dr. M. Nickelsen, Hamburg (1)
- Dr. N. Peter, Cottbus (7)
- Prof. Dr. M. Pfreundschuh, Homburg (1)
- V. Pöschel, Homburg (1)
- Prof. Dr. A. Rosenwald, Würzburg (2)
- Dr. Ch. Rudolph, Berlin (7)
- Prof. Dr. Ch. Rübe, Homburg (3)
- PD Dr. H. Schmidberger, Mainz (3)
- PD Dr. R. Schmits, Saarbrücken (6)
- Prof. Dr. N. Schmitz, Hamburg (1)
- Prof. Dr. J. Schubert, Hamm (7)
- PD Dr. S. Stilgenbauer, Ulm (7)
- Prof. Dr. L. Trümper, Göttingen (1)
- PD Dr. U. Wedding, Jena (1)
- PD Dr. M. Witzens-Harig, Heidelberg (7)
- Prof. Dr. G. Wulf, Göttingen (1)
- Dr. S. Zeynalova, Leipzig (1)
- Dr. M. Ziepert, Leipzig (1)

(1) Representative of the DSHNHL Study Management Committee
(2) Representative of the Reference Pathology
(3) Representative of the Reference Radiotherapy
(4) Representative of the Reference Nuclear Medicine
(5) Representative of the Reference Diagnostic Radiology
(6) Representative of the Oncologists in Private Practice
(7) Elected Members and Managers of Substudies within the DSHNHL

The addresses of the members of the Protocol Committee are given in Appendix 13.5.

0.3.2 DSMC

The following independent experts are members of the Data and Safety Monitoring Committee:

- Prof. Dr. G. Brittinger, Essen
- Prof. Dr. V. Diehl, Cologne
- Prof. Dr. K. Havemann, Marburg
- Prof. Dr. R. Hermann, Basel

The DSMC receives information on the progress of the study at regular intervals and performs the following functions:

- Review of the study progress
- Review of safety
- Review of serious adverse events
- Review of the results of interim evaluations

The DSMC gives recommendations concerning the continuation, modification or early discontinuation of the study to the Study Management.

The addresses of the members of the DSMC are given in Appendix 13.5.

0.3.3 GCP Conformity

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

Signature of the Principal Investigator:

.....
Prof. Dr. med. M. Pfreundschuh

0.4 Preamble to the amendment

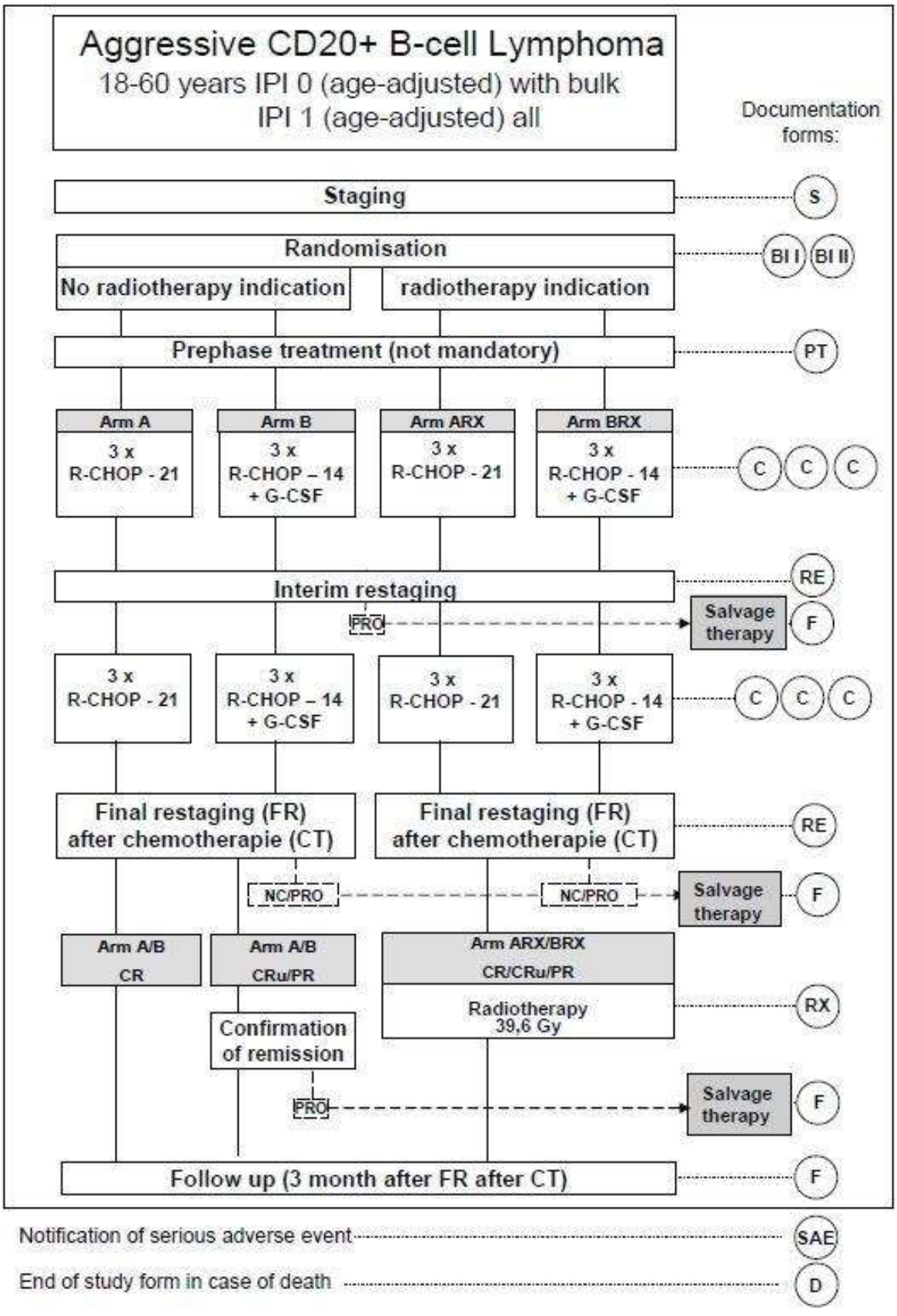
The planned interim analysis of the UNFOLDER trial as of 01 July 2012 with 443 patients evaluable for analysis, of whom 285 with bulky disease and/or extranodal involvement were randomized to receive radiotherapy to these localisations or observation, showed that the predefined formal criterion of discontinuation was fulfilled, because the event-free survival of the 139 patients randomised to receive radiotherapy was highly significantly better compared to those randomised into the observational arm, with a p-value of 0.004 in favour of the radiotherapy arm, thus meeting the „alpha spending function“ of p = 0.008. The Data and Safety Monitoring Committee (DSMC) was called to a meeting on 31 July 2012 and recommended to close the two treatment arms without radiotherapy for patients with bulky disease and/or extranodal involvement (R-CHOP-21 without radiotherapy; R-CHOP-14 without radiotherapy) and to continue both arms with radiotherapy (R-CHOP-21 with radiotherapy; R-CHOP-14 with radiotherapy) as planned. On 31 August 2012 the protocol committee assented to this recommendation. This decision made an amendment necessary. This amendment is restricted to those sections where changes in the practical procedures within the UNFOLDER protocol apply. Otherwise, there was no need to revise the scientific basics because no other data relevant for the further conduction of the UNFOLDER trial have been published since the original UNFOLDER protocol was written.

Homburg, November 2012

0.5 Synopsis of Protocol DSHNHL 2004-3

Study number	DSHNHL 2004-3
Short title of the study:	6 x rituximab plus CHOP-21 vs. 6 x rituximab plus CHOP-14 with or without consolidating radiotherapy of bulky disease and/or extranodal involvement (Unfavourable young low-risk densification of R-chemo regimens = UNFOLDER 21/14)
Therapeutic indication	Aggressive $CD20^+$ NHL in patients aged 18 to 60 years: all patients with IPI = 1 (according to age-adjusted IPI) and those with IPI = 0, in the concurrent presence of bulky disease only ($\geq$ 7.5cm)
Primary aim of the study	Improvement of treatment outcome respectively reduction in side effects of a combined immuno-chemotherapy with six cycles of the monoclonal anti-CD20 antibody rituximab by shortening therapy intervals from three to two weeks or else improvement by radiotherapy (39,6 Gy) of bulky disease.
Secondary aims of the study	Relevance of consolidating radiotherapy of qualifying extranodal involvements. Comparison of short and long-term side effects, quality of life and costs
Study design	2 x 2 arm (in analogy to factorial design), open-label, multicentre, prospective, randomised phase-III-study (therapy optimisation study)
Study population	Patients with untreated aggressive $CD20^+$ Non-Hodgkin's Lymphoma aged 18 to 60 years without major accompanying diseases with IPI = 1 (all) or IPI = 0 and bulky disease ($\geq$ 7.5cm)
Sample size	578 patients with bulky disease , 1072 patients in total
Therapy	Patients will be randomly assigned to receive six cycles of a combined immuno-chemotherapy with the monoclonal anti-CD20 antibody rituximab, together with 6 cycles of a chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone, at 21-day intervals (R-CHOP-21) or 14-day intervals (R-CHOP-14). Patients with initial bulky disease and/or qualifying extranodal involvement will subsequently receive additional consolidating radiotherapy with 39.6 Gy.
Primary endpoint	The main endpoint is the time to treatment failure (TTF), calculated from randomisation
Secondary endpoint	Secondary endpoints are CR rate, survival, tumour control, disease-free survival, toxicity, parameters of health costs and adherence to protocol, and analysis of relapse.
Evaluation	The time to treatment failure within the two treatment arms will be compared by using the log-rank test.
Time plan	Study to commence in October 2005. End of recruitment approx. in September 2014. Assuming a recruitment rate of 214 patients per year, 1072 patients are to be randomised during a recruitment period of 9 years. Each patient will be observed for 3 years within the study, starting from completion of treatment. Afterwards, beyond clinical investigation, livelong follow-up will be carried out.
Supported by	Deutsche Krebshilfe / Dr. Mildred-Scheel Foundation

0.6 Flow Chart of Study 2004-3



0.7 Therapy plan and examinations to be conducted

Phase	Staging	Prephase	Therapy			Interimen-staging	Therapy			Final resta-ging after therapy	Confirmation of remission (only arms with-out radio-therapy indica-tion in CRu/PR)	Radiotherapy in ARX/BRX	Follow-up exams
			Cycle 1	Cycle 2	Cycle 3		Cycle 4	Cycle 5	Cycle 6				
Day		-6 bis 0	**1**	**22/15**	**43/29**	**43/29 + ca. 14**	**64/43**	**85/57**	**106/71**	**106/71 + ca. 14**	**4 weeks after final restaging**	**2 to 6 weeks after final restaging**	**– 3 month after final restaging: 1. FU – in year 1 and 2: every 3 month – in year 3-5: every 6 month – then yearly**
Prephase therapy		X											
Arm A, ARX Arm B, BRX			X X	X X	X X		X X	X X	X X				
Radiotherapy (Arm ARX, BRX)												X[1]	
Patient's history	X		X	X	X	X	X	X	X	X	X	X	X
Clinical examination	X		X	X	X	X	X	X	X	X	X	X	X
Performance status (ECOG)	X[2a]	X[2b]	X[2c]	X[2c]	X[2c]	X	X[2c]	X[2c]	X[2c]	X	X	X	X
Laboratory analysis	X[3a]		X[3b]	X[3b]	X[3b]	X[3a]	X[3b]	X[3b]	X[3b]	X[3a]	X[3a]		X[3c]
Haemogram during therapy			X[4]	X[4]	X[4]		X[4]	X[4]	X[4]				
Chest X-ray	X[8]												X[6]
Abdominal ultrasound	X												X[6]
CT-neck / thorax / abdomen	X[8]					X[5]				X	X[9]		X
Bone marrow biopsy	X									X[5]	X[5]		X[6]
Lumbar puncture	X[7]												
CTC evaluation			X	X	X		X	X	X			X	
Adverse events			X	X	X		X	X	X			X	X
Secondary disease													X

1	In case of initial bulky diseasey/extranodal involvement and in case of testicular involvement (radiotherapy of contralateral testis)
2	a) at patient enrolment b) at end of prophase c) minimum value during chemotherapy
3	a) leukoc., lymphoc., monoc., bas., neut., eos., platelets, Hb, ESR, LDH, GPT (ALT), AP, γGT, bilirubin, total protein, albumin, paraprotein, IgG, IgA, IgM, β_2-microgl., creat., EF, pulmonary diffusing capacity b) leukoc., platelets, Hb, LDH, GPT, AP, bilirubin, creatinine, electrolytes immediately prior to cycle c) leukoc., lymphoc., monoc., bas., neut., eos., platelets, Hb, LDH, EF, pulmonary diffusing capacity

4	leukoc., platelets, Hb prior to cycle and at least 2 measurements in nadir range
5	if initially affected
6	if initially affected, check after end of therapy until no further signs
7	lumbar puncture with spinal fluid cytology in case of testicular involvement
8	Send complete diagnostic images to the study secretariat in Homburg, if possible in digital form (CD)
9	only in arms A and B without radiotherapy indication: contro of residual masses if response to immunochemotherapy is Cru/PRI

G-CSF: G-CSF should be administered in case of prolonged leukocytopenia (> 3d mit < 1 x 10^9/L) within arms A, ARX starting on day 4 of the following cycles; within arms B, BRX the administration of G-CSF is mandatory!

0.8 Physician's checklist

0.8.1 What is required prior to initiation of therapy?

1) Requirement: declaration of centre participation confirmation and ethics approval of the ethics committee responsible sent to study secretariat?
2) Diagnosis of the primary pathologist with result of CD20 immunohistology test available?
3) Risk factors determined using the IPI?
4) Bulky disease: yes / no?
5) Extranodal involvement: yes / no?
6) Pretherapeutic diagnostic images (CT, MRT – if possible on CD/electronic) sent to study secretariat Homburg for reference evaluation **(of every patient, independent from bulky disease and/or E-involvement!)**?
7) Study assignment decided?
8) All inclusion criteria met?
9) Any exclusion criteria applicable?
10) Information of patient, patient´s approval for randomisation and consent form sent to the study secretariat?
11) All staging examinations completed?
12) Staging-, Base Line Information I-, Base Line Information II- report forms and histology results submitted to the study secretariat? **Signature of radiotherapist on Staging report form (obligatory for all patients)?**
13) Randomisation performed by Study Secretariat?
14) If consolidating radiotherapy to bulky disease and/or to sites of qualifying extranodal involvement, or radiotherapy of contralateral testis (in case of testicular involvement) is planned: procedures discussed by internist with radiotherapist? Suggested radiotherapy schedule sent to reference radiotherapy?
15) Serum, blood and bone marrow samples forwarded?

0.8.2 Treatment procedures

1) Immuno-chemotherapy cycles 1-3
2) Interim restaging
3) Immuno-chemotherapy cycles 4-6
4) Final restaging after chemotherapy: 14 days after the last application of rituximab
5) In arms without radiotherapy indication: remission must be confirmed 4 weeks after final restaging after the end of chemotherapy, if treatment result CRu/PR
6) Radiotherapy to bulky disease and/or sites of qualifying extranodal involvement, or to contralateral testis (in case of testicular involvement) (arms ARX, BRX) should start 2 to 6 weeks after commencement of chemotherapy cycle 6.

0.8.3 What is required in connection with consolidating radiotherapy?

If radiotherapy of bulky disease and/or of sites of qualifying extranodal involvement, or of the contralateral testis (in case of testicular involvement) (arms ARX, BRX) (cf. 5.7.3) is planned:

1) Pretherapy consultation with the local radiotherapist with staging report and images
2) Determination ff the radiotherapy schedule
3) On completion of radiotherapy: completed radiotherapy report form, simulation and verification plates, with therapy plan of the radiotherapist to be sent to the study supervisory centre (documentation will be returned after evaluation!)

0.8.4 What is required on completion of therapy?

1) Restaging 14 days after the last application of rituximab
2) In arms without radiotherapy indication: confirmation of remission 4 weeks after final restaging after chemotherapy if result of therapy CRu/PR
3) In case of radiotherapy (arm ARX, BRX): 1st follow-up exam 3 months after final restaging on completion of chemotherapy
4) Regular follow-up exams: 1st follow-up exam by internist in all arms: 3 months after final restaging on completion of chemotherapy, then every 3 months in the first 2 years, every 6 months in years 3-5, subsequently on an annual basis

0.8.5 What is required in progression, NC and relapse?

Please contact the Study Secretariat and check if an alternative treatment protocol would be appropriate for the patient

0.8.6 What is required on early discontinuation of therapy?

Inform the Study Secretariat of the reasons for early discontinuation. If possible, conduct a restaging examination at the time of discontinuation and document therapy outcome at time of discontinuation on the restaging form. Document any subsequent follow-up examinations.

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

Fax the SAE report to the Study Secretariat within 1 working day of the event, or within 10 days if the event occurs after completion of therapy.

0.8.8 What is required in the event of patient death?

Document exact time of death and the suspected cause of death on the final report form and supply the post-mortem report (if available) to the study secretariat.

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

Inform the study secretariat who will be responsible for treatment, follow-up and documentation and where treatment will be continued in case of change of centre.

0.9 Changes introduced into this protocol in comparison with the second study generation (High-CHOEP and MInT study)

Several definitions and procedures have been changed in this third study generation (after DSHNHL-1999-2 "High-CHOEP" and MInT) of DSHNHL studies. The main changes are:

- six cycles of immuno-chemotherapy are given instead of six cycles of chemotherapy
- etoposide is not given anymore (cf. 2.3)
- randomisation into immuno-chemotherapy given every three weeks versus every two weeks
- radiotherapy dose increased to 39,6 Gy (from 36 Gy)
- central review of primary diagnosic procedures of **all included patients** including staging and acknowledgement or exclusion of bulky disease/extranodal involvement according to consistent criteria by the central study secretariat in Homburg. This is necessary for quality control and preparation of radiotherapy schedules for randomised patients
- patients with CNS involvement (intracerebral, meningeal and intraspinal) are not eligible
- the first follow-up exam is performed by the internist in all arms: 3 months after final restaging on completion of chemotherapy
- an additional restaging after consolidating radiotherapist by the radiotherapist is not mandatory
- the performance status will be assessed in ECOG

The GCP principles are being adhered to throughout the study.

0.10 Changes in the amendment of 22 November 2012

- A confirmation of remission (4 weeks after final restaging after chemotherapy) will only be performed in the arms without radiotherapy if therapy result in this restaging was CRu/PR. A confirmation of remission is not mandatory in the arms with radiotherapy.
- Consolidating radiotherapy to bulky disease and/or qualified extranodal involvement will be performed in any case, it will not be randomised any more. Patients will only be randomised into the two therapy arms: 6xR-CHOP-21 +RX und 6xR-CHOP-14 +RX
- in case of testicular involvement the contralateral testis will be irradiated prophylactically

1 Aims of the study

1.1 Primary aim of the study

The aim of this study is to investigate the following questions in patients with untreated aggressive good-prognosis CD20$^+$ Lymphoma (i.e. with no or one risk factor according to age-adjusted IPI[1]), who have one risk factor and/or bulky disease, in a randomised, multicentre clinical study:

Does a shortening of therapy intervals from three to two weeks result in an improved efficacy of immuno-chemotherapy with 6 cycles of rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristin and prednisone), (6 x R-CHOP-21 vs. 6 x R-CHOP-14)?
Does addition of consolidating radiotherapy to bulky disease following the administration of immuno-chemotherapy result in an improved treatment outcome?

To be included in this clinical study are all patients with CD20-positive aggressive good-prognosis NHL (age-adjusted IPI = 0,1) aged 18 to 60 years [i.e. age-adjusted IPI[1] = 0 with bulky disease or IPI =1 with or without bulky disease (diameter of a single or conglomerate tumour measuring at least ≥ 7.5 cm)]. The primary endpoint is the time to treatment failure (TTF). The objective is to demonstrate a difference in the 3-year TTF rate of 10% (constant hazard ratio of 0.615) with an error probability of 5% (two-sided), at a power of 80%.

1.2 Secondary aims of the study

One secondary aim of the study is to investigate the relevance of consolidating radiotherapy of qualified extranodal involvement.
Other secondary aims are to collect further data in order to be able to evaluate:

1) Side effects:
   - rate of neutrocytopenia
   - rate of thrombocytopenia
   - rate of thrombocytopenia
   - rate of anaemia
   - rate of infection
   - rate of antibiotic therapy
   - rate of blood and platelet transfusion
   - rate of secondary neoplasia

2) Efficacy (cf. 7.2.2.1):
   - rate of complete remission
   - rate of progress under therapy
   - relapse-free survival
   - disease-free survival
   - survival
   - tumour control
   - rate of local control in bulky disease or extranodal involvement with or without consolidating radiotherapy

[1] International Prognostic Index

3) Relapse pattern -
   - relapse in regions treated with radiotherapy
   - relapse in primarily involved regions
   - relapse in not primarily involved regions

4) Safety (cf. 7.2.2.2)

5) Health-economic aspects (cf. 7.2.2.3)

6) Adherence to protocol (cf. 7.2.2.4)

2 Rationale of the study

2.1 Current state of the art

Aggressive non-Hodgkin´s lymphoma, as defined by the R.E.A.L. Classification[2;3] are aggressive malignant diseases of the lymphatic system which rapidly cause death if they remain untreated. Radiotherapy is only curative in cases of localised stages, with a marked decline of cure rates in patients over the age of 60 years[4]. Only with the development of polychemotherapy such as the CHOP protocol, in which the most effective cytotoxic drug, besides cyclophosphamide, vincristine and prednisone, is the anthracycline doxorubicin, has it become possible to achieve complete remissions and cures in patients with advanced stage lymphoma[5]. However, attempts to improve the outcome of chemotherapy treatment in high-grade non-Hodgkin lymphoma have failed since the introduction of the CHOP protocol almost 30 years ago[5], despite increases in the dosage of individual cytostatic drugs and the introduction of new cytostatic drugs into the second and third generation treatment protocols[6-11]. This was proven by the results of the intergroup SWOG and ECOG studies in which CHOP was compared with m-BACOD, ProMACE-CytaBOM and MACOP-B for the first time in a large scale randomised clinical study (in more than 1000 patients). It was established that the efficacy of the regimens of the so-called first, second and third generations was comparable: there were no significant differences in rates of disease-free survival after 4 years, which was approximately 40% for all treatment protocols[12]. Similarly, there were no differences in overall survival rates. This holds also true if the outcome is adjusted for patients with different risk profiles in accordance with the "International Prognostic Index" (IPI)[1]. In terms of the toxicity of the individual regimens, however, differences were observed: the treatment-related mortality rate after CHOP was 1%, after m-BACOD 5%, after ProMACE-CytaBOM 4% and after MACOP-B 6%[12].

There are five internationally accepted prognostic criteria in the "International Prognostic Index". These are based on pretherapeutic risk factors which had been found to be relevant to prognosis in a meta-analysis of the results obtained by 16 international research groups for 3373 patients: age > 60 years, stage III + IV, > 1 extranodal involvement, poor general status (ECOG 2,3,4) and elevated LDH[1]. It is thus possible to differentiate between four risk groups on the basis of the number of risk factors present (≤1, 2, 3, > 3); in the group with the best prognosis, the complete remission rate is 87%, with 79% of patients relapse-free after 2 years and a 73% 5-year survival rate: in the group with the poorest prognosis, the corresponding rates are 44%, 58% and 26%. This index has since been confirmed in independent study populations, e.g. in the patients of the "National High Priority Study"[12] where it was found to have a similarly good discriminatory function with respect to patient populations with different prognoses. The IPI is in particular scientifically valid when comparing the results of clinical studies including patients with aggressive lymphoma, and when data of subgroup analysis according to risk factor are available.

Only after adding a moderate dose of etoposide (CHOEP protocol) there was an improved outcome demonstrated for good-prognosis (aaIPI = 0,1) patients. This was shown by the NHL-B1 study which was supported by the Deutsche Krebshilfe / Mildred Scheel Foundation (figure 1)[13].

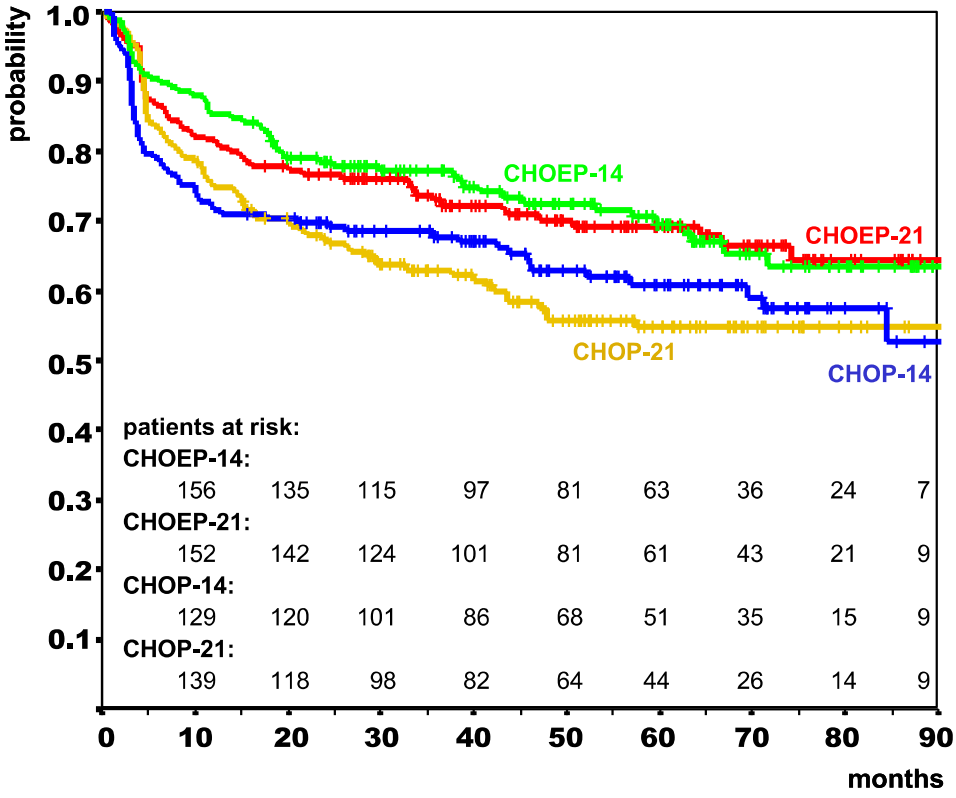


Figure 1A

Figure 1: **Time to treatment failure (TTF) in young patients with good-prognosis (aaIPI = 0,1; normal LDH) aggressive lymphoma within the NHL-B1 study[13].** There was a significant improvement of TTF achieved by CHOEP-21 when compared with CHOP-21. CHOEP-14 significantly improved the rate of complete remission, TTF, and overall survival when compared with CHOP-21.

Despite this progress, it is still necessary to further improve results of young good-prognosis (aaIPI = 0,1) patients with aggressive lymphoma. In the DSHNHL 1999-2 ("High-CHOEP") study of the second study generation of the DSHNHL we investigated whether by significantly increasing the doses of cyclophosphamide, doxorubicin, and etoposide the outcome of young good-prognosis (aaIPI = 0,1) patients can actually be improved. DSHNHL 1999-2 was designed under the impression of the concept of "effective dose"[14] which had predicted an additional 8% improvement of the TTF rate (time to treatment failure). The first interim results of the DSHNHL 1999-2 study that included more than 300 patients after a median observation period of 16 months, showed that both therapy arms are equal regarding TTF rate (time to treatment failure) and survival rate (figure 2). There would be a 2.1 % probability of a difference between the standard-CHOEP arm and the high-CHOEP arm if the clinical study were continued.

In view of equal efficacy and more adverse effects of High-CHOEP compared with the standard CHOEP arm, it was unanimously decided at the study meeting of the DSHNHL in Hamburg in June 2004 to prematurely terminate this DSHNHL study.

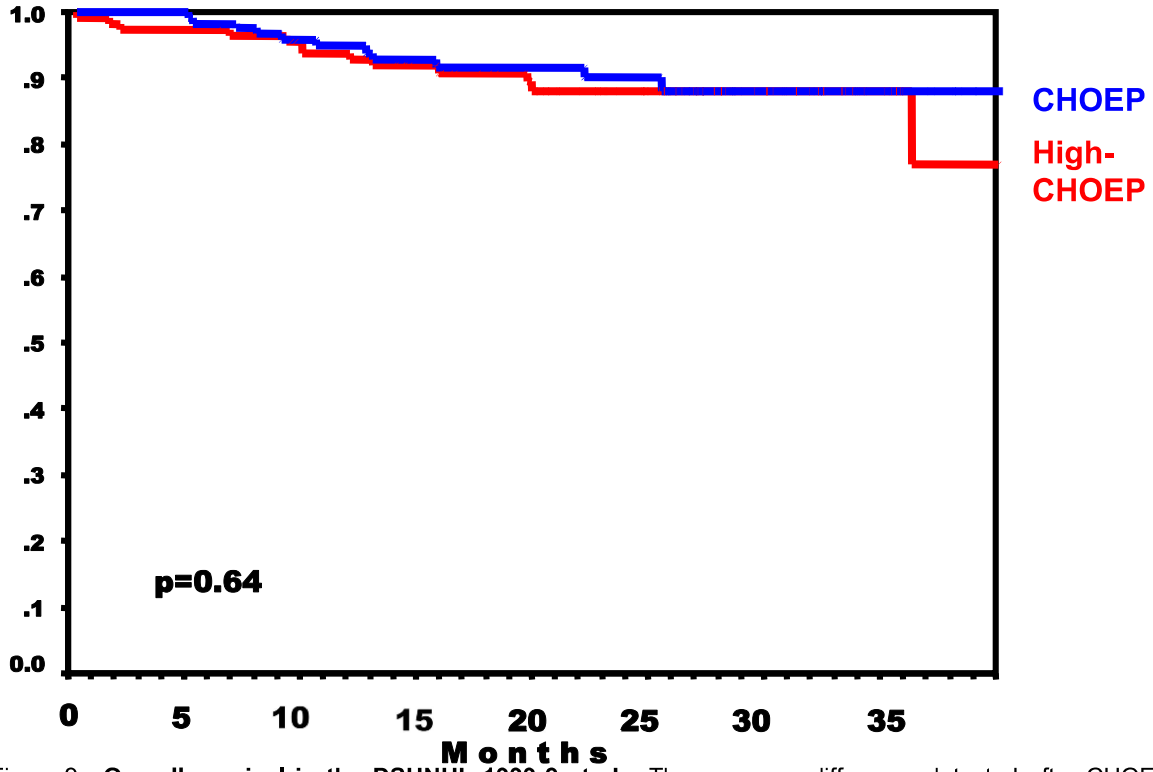


Figure 2: **Overall survival in the DSHNHL 1999-2 study.** There was no difference detected after CHOEP in standard dose and escalated dose (High-CHOEP) regarding overall survival (demonstrated here). The curves were also congruent for TTF.

Several centres of the DSHNHL participated in the "MInT" study in parallel to the DSHNHL 1999-2 study. The inclusion criteria of this study of the Mabthera International Group which compared 6 cycles of a CHOP-like chemotherapy with 6 cycles of the same chemotherapy plus 6 applications of the monoclonal anti-CD20 antibody rituximab corresponded to those of the DSHNHL 1999-2 study. Young good-prognosis patients were included (age-adjusted IPI = 0,1). In contrast to DSHNHL 1999-2, young good-prognosis patients in stage I without bulky disease were excluded from the MinT study. Just as in the high-CHOEP study, patients with "bulky disease" and/or extranodal involvement were given radiotherapy to the corresponding regions.
The first interim results that included 326 patients of the MInT study who fulfilled all inclusion criteria and for whom results of the first follow up, 3 months after final restaging, were available demonstrated a highly significant advantage of the combined chemo-immunotherapy compared with single chemotherapy. The significance level of $p = 0.000005$ was in favour of the combined approach. It was more than two log intervals below the critical α-value of 0.00105 which had been chosen for premature termination of study when using an alpha-spending function (figure 3)[15]. That was why the international data safetey monitoring board, comprising G. Brittinger, B. Coiffier and P. Carde, decided to prematurely terminate the study in December 2003 when there were still 50 patients under treatment. A follow-up analysis of patients who were part of the first interim analysis in May 2004 confirmed the results of the first interim analysis after a mean observation period of 2 years, as did an analysis of the corresponding intention-to-treat population which was performed at the same time[16]. During a mean observation period of 24 months, 58% of patients treated with 6 cycles of chemotherapy alone remain free of treatment failure whereas 81% of patients treated with a combination of chemotherapy and rituximab continue to be disease-free. This way, almost a quarter of patients can be saved from salvage therapy which is able to take 50% of patients into long lasting remission.

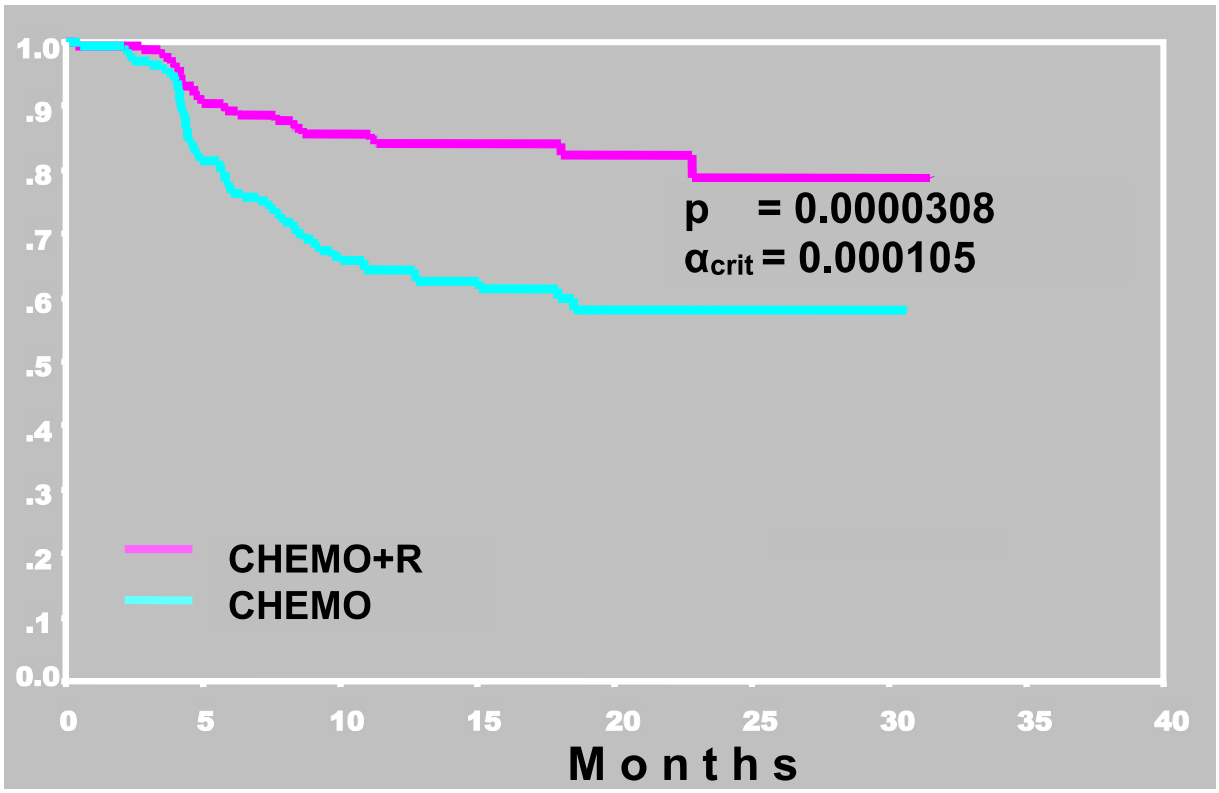


Figure 3: Time to treatment failure in the MInT trial after 6 cycles of CHOP-like chemotherapy (CHEMO) compared with 6 cycles CHOP-like chemotherapy in combination with 6 applications of the monoclonal CD20 antibody rituximab (R-CHEMO). Results of the first interim analysis including 326 patients (mean obsevation period of 16 months)

Although survival differences between the two arms are diminished by salvage therapy, there is a significant advantage after two years for those patients treated with a combination of chemotherapy and rituximab. There is an increase of overall survival from 85% to 95% after 2 years (figure 4). The same applies to those 50% of patients included in the interim analysis who were given CHOEP.

The addition of rituximab to a CHOP-like chemotherapy (R-CHEMO), unlike dose escalation ("High-CHOEP"), has resulted in a substantial improvement of all endpoints. Six Cycles of a CHOP-like chemotherapy in combination with rituximab must therefore be regarded as optimal treatment and reference arm of studies including young patients with CD 20^+ aggressive lymphoma and good prognosis risk profile.

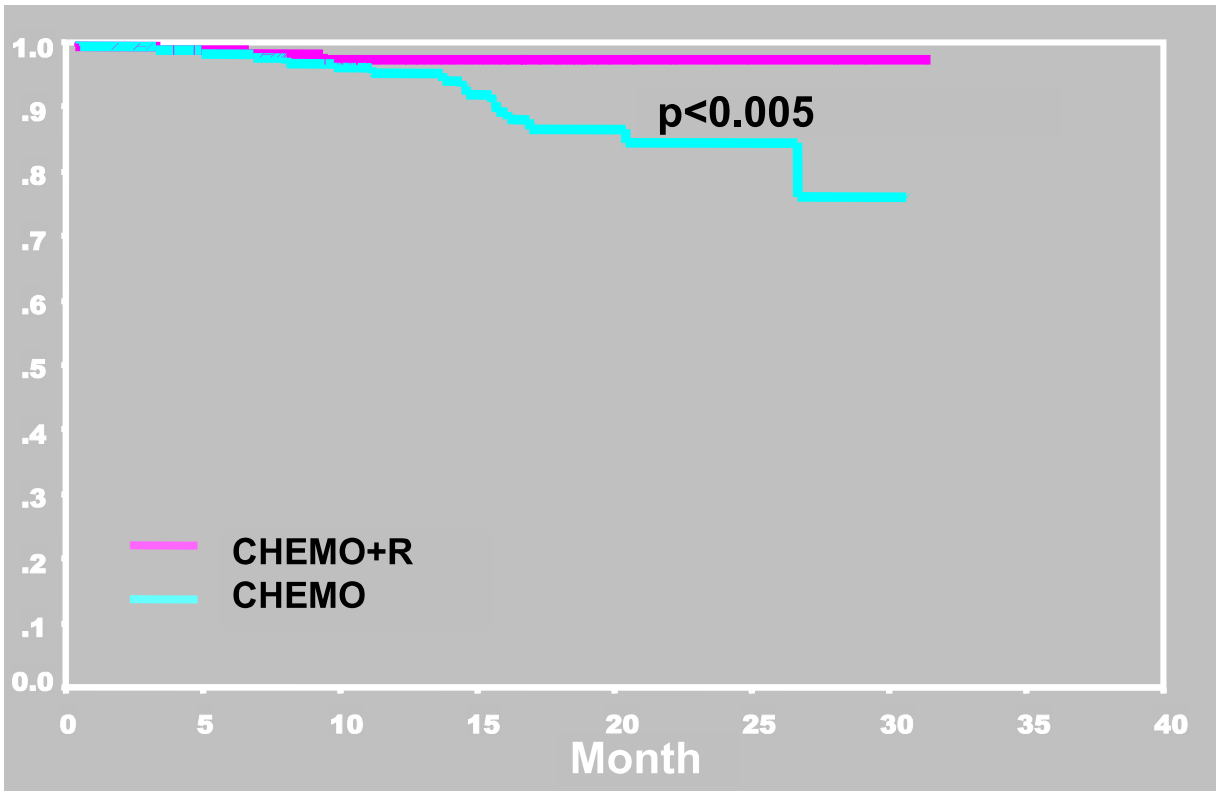


Figure 4: Overall survival in the MInT trial after 6 cycles of CHOP-like chemotherapy compared with 6 cycles of CHOP-like chemotherapie and 6 cycles of the monoclonal CD20-antibody rituximab. Results of the first interim analysis of 326 patients (mean observation period of 16 months)

A Cox regression adjusting for the stratification variables therapy arm, risk factor according to IPI and bulky disease demonstrated an association of events, relevant to TTF, with therapy arm and bulky disease, and to a lesser degree with IPI. There were marked differences regarding TTF and overall survival when patients of the MInT study without risk factor and bulky disease were compared with the other patients (figure 5).

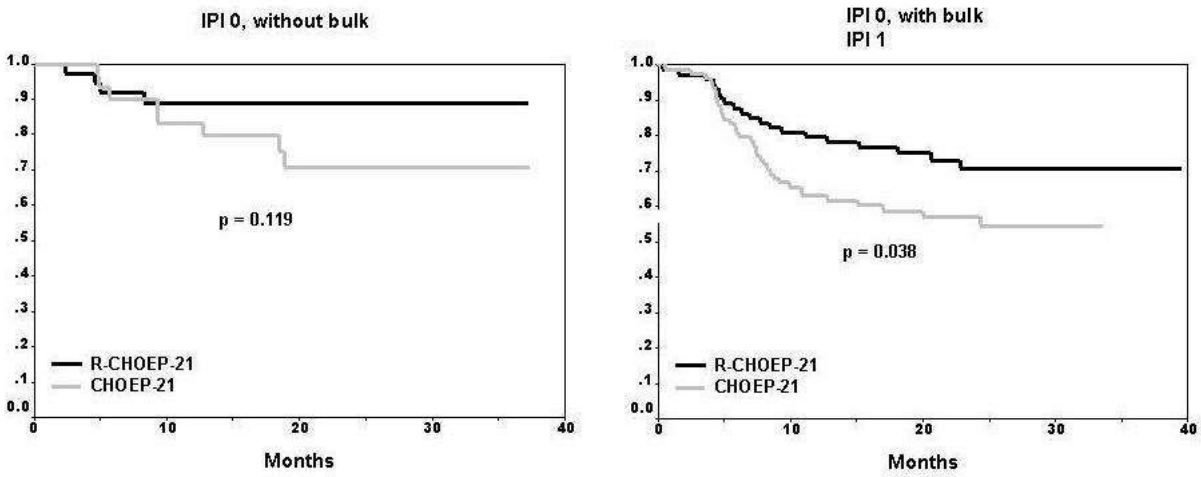


Figure 5: TTF of patients in the MInT study Patients with IPI = 0 and without bulky disease who were treated with chemotherapy alone (1) or chemotherapie plus rituximab (2). Other patients who were treated with chemotherapy alone (3) or chemotherapy plus rituximab (4).

The results of the MInT study demonstrated a difference between two prognostic groups within the population of young good-prognosis (aaIPI = 0,1) patients with aggressive lymphoma: young good-prognosis patients with favourable prognosis (young good-prognosis, favourable) and those with less favourable prognosis (young good-prognosis, less favourable). Therefore, these groups should be treated differentially according to new specific treatment strategies (figure 6).

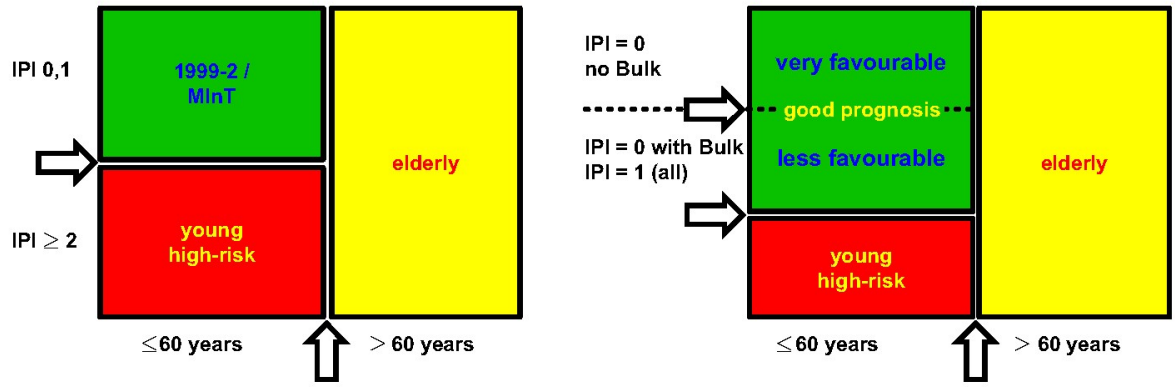


Figure 6: Classification of therapeutic groups of the second (left) and third study generation of the DSHNHL.

2.2 Rationale for the patient target group of DSHNHL 2004-3

The results of the MInT study demonstrate that young (i.e. aged 18 to 60) patients with aggressive lymphoma do have an unsatisfactory TTF rate after two years when they have one risk factor according to IPI, and/or lymphomas (single or conglomerate) with a diameter ≥ 7.5 cm. The treatment results of this group within the MInT study were as follows:

- Complete remissions: 75%
- Progression under therapy 10%
- TTF after 3 years 71%
- Survival after 2 years 82%

The results of this comparatively young patient collective are unsatisfactory and definitely need to be improved.

2.3 Standard regimen/control arm

There is no doubt, although direct comparisons are missing, that the results of patients who were treated within the MInT study with a combination of 6 cycles of CHOP-21-like chemotherapy together with 6 cycles of the chimeric monoclonal anti-CD20 antibody rituximab are the best which have been reported for this patient collective to date. This also holds true when the results of the MInT study are compared with the outcome after a shortened course of chemotherapy (three times CHOP) in combination with a fairly highly dosed "involved-field" radiotherapy[17], or with approaches of an intensified chemotherapy [compared to CHO(E)P] like "High-CHOEP" (see above), as well as with the intensified 2-week-CHOP variant ACVB of the French study group GELA[18]. In this study, three cycles of this treatment proved to be significantly superior to a shortened course of chemotherapy with four cycles of CHOP in combination with "involved-field" radiotherapy. Since the side effects after 6 cycles of R-CHEMO in the MInT study do not differ

from those after 6 cycles of the respective CHOP-like chemotherapy, 6 cycles of R-CHEMO can presently be considered as the optimum treatment for this patient collective.

The most recent subgroup analysis of the MinT study[19] has confirmed the superiority of CHOEP-21 over CHOP-21. However, in combination with rituximab, no advantage of R-CHOEP-21 over R-CHOP-21 has been shown. Since R-CHOEP-21 is associated with more severe (particularly haematological) side effects and R-CHOP-21 (a one day regimen) is much easier to give than R-CHOEP-21 (a three day regimen), the following does apply to the reference arm of the DSHNHL 2004-3 study:

1) 6 cycles of R-CHOP-21 in combination with radiotherapy of bulky disease have produced so far the best results in young good-prognosis patients (MInT study[16]).
2) 6 cycles of R-CHOP-21 in combination with radiotherapy of bulky disease are well tolerated by patients aged ≤60 years, with a very good feasibility (mean relative dose intensity: 99%).
3) In the MInT Study, the presence of bulky disease proved to be a highly significant prognostic factor ($p = 0.0003$) in the multivariate cox regression, despite radiotherapy. The efficacy of radiotherapy can therefore be questioned.
4) A further improvement in results of the collective of young good-prognosis patients with less favourable risk profile (IPI = 1 and/or bulky disease) is urgently indicated.
5) 6 cycles of R-CHOP-21 is therefore the appropriate reference arm for such a clinical study.

All these points justify the selection of 6 cycles of R-CHOP-21 as reference arm of the DSHNHL 2004-3 study.

2.4 Rationale for the treatment optimisation protocol

As shown above, the combination of 6 cycles of a CHOP-like chemotherapy with 6 cycles of the monoclonal antibody rituximab has produced the best results in the group of young good-prognosis patients that have ever been reported for this patient group. However, a subgroup analysis of the MInT study has demonstrated that the prognosis of young good-prognosis patients with one risk factor according to age-adjusted IPI and/or bulky disease prior to therapy is still unsatisfactory and urgently needs to be improved. There are several strategies that can be applied in order to achieve a better outcome. They will be addressed next.

2.4.1 Intensification of chemotherapy

The issue of the optimal number of CHOP-like chemotherapy cycles for the treatment of aggressive lymphoma is unresolved. It was first investigated by means of the DSHNHL study 1999-1 (RICOVER-60). In RICOVER-60, six vs. eight cycles of CHOP-14, with or without rituximab, were compared in a randomised fashion. Since those patients who qualify for 2004-3 do not have a large tumour burden, an increase in the number of cycles within the experimental arm appears little promising. The GELA also treats their patients with three cycles of ACVBP in early stages of aggressive lymphoma that is 3/4 of number of cycles that patients receive in advanced stages.

Just as the increase in the number of cycles from six to eight, it appears unlikely that an escalation of chemotherapy dose in this patient population will be crowned with success, considering the available data and interim analysis of the DSHNHL 1999-2 study ("High-CHOEP", see above). As explained above, the first planned interim analysis of the 1999-2 study demonstrated that the outcome in good-prognosis patients was not improved by High-CHOEP-21, even though High-CHOEP could be administered in a significantly higher dose than CHOEP-21, not only according to protocol, but also in reality.

In contrast to the increase in the number of cycles or escalation of chemotherapy dose, the shortening of therapy intervals from three to two weeks resulted in a significant prolongation of life, not only in the elderly patients of the NHL-B2 study, but also in the young good-prognosis patients (normal LDH) of the DSHNHL NHL-B1 study[13]. When CHOEP-21 and CHOEP-14 are compared with the previous standard CHOP-21, the introduction of etoposide (in CHOEP-21) only achieved a significant improvement in the primary endpoint TTF, whereas shortening of therapy intervals (CHOEP-14) resulted in an improvement of all endpoints, an increase of the rate of complete remission, a decrease of the rate of primary progress and a significant prolongation of overall survival, besides TTF[13]. The positive effect of shortening the interval was particularly marked in patients with elevated LDH[20] and in patients with bulky disease[13]. As we assume that approximately 40% of patients in this study will have an elevated LDH and approximately 60% will have bulky disease, it is expected that the positive effect of shortening the interval will be more marked in this study than in the NHL-B1 study[13]. It should come close to the one observed in the NHL-B2 study[20].

Recently published work of the French study group GOELAMS[21] does support the assumption, when carefully analysed, that dose density rather than high dose chemotherapy. Contrary to the suggestive title is responsible for the superiority of the intensified arm of that study compared to eight cycles of classic CHOP-21. Whereas patients of the experimental arm received two cycles of an intensified, i.e. dose-escalated CHOP variant every 15 days, followed by high dose methotrexate in combination with cytosinarabinoside, with termination of treatment including high dose BEAM on day 67, patients of the control arm received by that time only four of eight planned cycles of CHOP-21 that were to be given over 148 days.

In summary, the published data of the DSHNHL and other study groups, besides yet unpublished results of DSHNHL 1999-2, support the assumption that dose intensification by shortening of therapy intervals ("dose densification") instead of dose escalation is a promising approach to further improve the outcome in young good-prognosis (aaIPI = 0,1) patients with unfavourable risk profile. **The protocol committee of the DSHNHL and the study participants have unanimously decided at their meeting in Hamburg in June 2004 to investigate in a randomised fashion whether it is possible to improve the results of 6 cycles of R-CHOP-21 in this patient collective by shortening therapy intervals from three to two weeks (R-CHOP-14).**

2.4.2 Radiotherapy

In the absence of large randomised studies, the value of radiotherapy in the treatment of aggressive non-Hodgkin´s lymphoma has not clearly been defined and is mainly based on retrospective and relapse analyses. This also applies to the treatment of bulky disease and extranodal involvement.

The curative potential of radiotherapy given alone declines with increasing age. Elderly patients (> 70 years) in particular cannot be cured by radiotherapy alone, not even in stage I[4]. Radiotherapy alone is therefore an obsolete treatment of aggressive lymphoma, in particular in elderly patients.

Radiotherapy given alone by involved field therapy with 40 to 45 Gy can only achieve results comparable to chemotherapy or combined therapy if a by clinical means undetectable dissemination has been excluded by staging laparotomy, even in stage I[22;23]. Since this procedure is associated with significant morbidity and letality, this therapeutic strategy has been abandoned. The results of larger studies where radiotherapy alone was given to patients in stage I/IE are not satisfactory[23]. Only monocentric and, mostly retrospective, studies demonstrate disease-free survival rates of 70-80% in patients aged < 60 years with small lymphomas (< 2.5cm) [24;25].

As there is little convincing data that can scientifically justify the application of radiotherapy alone, the same applies to a combined therapeutic approach. In particular, the optimal number of reduced chemotherapy cycles and volume and dose of radiotherapy are not clearly defined within a combined approach. Some study groups, e.g. the French GELA, have totally abandoned radiotherapy as part of treatment of aggressive lymphoma in some collectives.

When a combination therapy of a few cycles of chemotherapy and involved field radiotherapy with 35 to 45 Gy was administered, disease-free survival rates of 75 to 80% and 5-year survival rates of 80 to 90% were reported[26;27]. However, during a longer follow-up period it appeared that there were considerable relapse rates, even after 5 years, when only a few chemotherapy cycles had been given. A short course of chemotherapy is obviously not capable of eliminating the malignant clone that is responsible for late relapses. It was proven by clonality analysis that these late relapses are not due to secondary tumours[28].

In the late nineties of the last century, a combined chemo-radiotherapy of locally limited aggressive lymphoma (stage I and II) appeared to be justified because of an early analysis of a randomised SWOG study[17] and an ECOG study [29-31]. In the ECOG study, patients in stage I with bulky disease or extranodal involvement and patients in stage II were randomly assigned to eight cycles of CHOP alone or with additional involved field radiotherapy with 40 Gy. The patients that were treated with the combined approach had a marginally significant advantage regarding DFS, but not OS. In the SWOG study, patients with extranodal lymphomas had been included whereas patients with stage II and bulky disease had been excluded. An early analysis of the SWOG study demonstrated an advantage of a combination of four cycles of CHOP chemotherapy and intensive (45 Gy) involved field therapy over eight cycles of CHOP alone. A follow-up analysis of this study that a priori could hardly be interpreted due to numerous methodical problems demonstrated a crossing-over of the curves after 7 years[32]. A recently published study of the GELA also demonstrated an advantage of a chemotherapy given in full over a shortened chemotherapy in combination with radiotherapy [18;33].

Consolidating radiotherapy, given as additive measure after a full course of chemotherapy in case of initial bulky disease, has been recommended by many study groups. This procedure has been suppoted by the results of a small randomised study from Mexico with 88 patients. An additional radiotherapy of initial bulky disease resulted in a prolongation of the relapse-free interval and overall survival in those patients[34]. In the DSHNHL NHL-B study, relapses in regions with initial bulky disease that had been treated with radiotherapy (36 Gy) were as rare as those in non-bulky disease regions[35]. However, bulky disease proved to be an independent risk factor in spite of the addition of radiotherapy. This was rather due to a negative impact of bulky disease on the rate of primary progress under chemotherapy than on the relapse rate.

A subgroup analysis of a large GELA study of patients aged > 60 years without IPI risk factor indicated that additive radiotherapy after chemotherapy can be even disadvantageous. An additive chemotherapy after four cycles of CHOP chemotherapy in patients aged > 70 years resulted here in a worse overall survival of these patients [36].

Additive radiotherapy to residual enlarged lymph nodes after chemotherapy should only be given within prospective studies as there are also no convincing results from prospective studies[37]. A differentiation between residual scarring and remaining vital tumour tissue has hardly been possible so far. It cannot be decided on the basis of the available data whether such differentiation can be safely, and with clinical relevance, achieved by a posttherapeutic FDG-PET (i.e. improved long-term results through earlier salvage therapy)[38].

Additive radiotherapy to extranodal involvement is also not supported by prospective studies. However, it is worth noticing that > 1 extranodal involvement that was considered an independent risk factor in IPI was no risk factor in those DSHNHL studies where extranodal involvement was treated with additive radiotherapy [13;20].

In summary, there has been much dispute worldwide over the value of radiotherapy in the treatment of high-grade non-Hodgkin's lymphoma. It is therefore of great importance to identify patient collectives who potentially do or do not benefit from radiotherapy[16;35;37].

It can be expected from the NHL-B1 study[13], the MInT study[16] and the DSHNHL 1999-2 study that approximately 60% of patients of the collective qualifying for DSHNHL 2004-3 will have bulky disease. This study is therefore, more than any other study, suitable for answering questions regarding the value of consolidating radiotherapy of initial bulky disease and/or bulky disease. At the meeting of the protocol committee and study participants in June 2004 in Frankfurt it was thus unanimously decided to address this question within a 2x2 factorial design within the DSHNHL study 2004-3.

2.4.3 Dose of radiotherapy

Aggressive Lymphoma are very sensitive to irradiation. Doses between 36 Gy and 45 Gy are obviously sufficient to eliminate the malignant clone. In combination with a full course of CHOP-like chemotherapy, a reduced dose is certainly sufficient. Within the SWOG study[17], ECOG study[30] and GELA study[18] that all compared a combined approach of a shortened course of chemotherapy with involved-field radiotherapy, doses between 36 Gy and 45 Gy were administered. Within the previous DSHNHL studies (NHL-B1, NHL-B2, DSHNHL 1999-1, DSHNHL-1999-2, MInT), 36 Gy were applied to bulky disease. Experiences from these studies do demonstrate that a dose of 36 Gy, given to a restricted volume, is very well tolerated, even when given after a full course of chemotherapy. It can be assumed that radiotherapy up to a dose of 40 Gy should also be very well tolerated after a full course of CHOP-like chemotherapy, whereas radiotherapy doses exceeding 45 Gy, depending on the location of bulky disease, after a full course of CHOP-like therapy are expected to result in marked side effects of radiotherapy.

Since the value of radiotherapy given to bulky regions is to be investigated in this study in a randomised fashion, the panel members and study participants have unanimously decided at their meeting in Hamburg in June 2004 to apply a radiotherapy dose of 39,6 Gy. On the one hand this dose appears sufficient to reject an allegation of underdosing in case of ineffectiveness of bulky disease radiotherapy. On the other hand an increase from 36 Gy to 39,6 Gy should not result in a significant increase in side effects.

2.4.4 Definition of bulky disease

The definition of bulky disease is not uniform. It varies in size from 5.0 to 12.5 cm. There are no data from retrospective or prospective investigations of large randomised studies stating which diameter is needed for a bulk to become a risk factor. Even in the MInT study, where bulky disease proved to be the most important prognostic factor besides therapy arm, the definition of bulky disease was country-specific and varied from 5 cm to 10 cm. However, a bulky disease definition of 7.5 cm applied to 75% of patients within the MInT study.

A bulk size of 7.5 cm has significantly contributed to the prognostic importance of this parameter within the MInT study. An a-priori definition of bulk size of 7.5 cm proved to be prognostically relevant in earlier DSHNHL studies. Both facts do support a cut-off point of 7.5 cm for bulky disease for a maximum diameter of a single lymph node or a lymph node conglomerate within this study. Both maximum transversal and longitudinal diameter of involved lymph nodes and lymph node conglomerates need to be determined.

2.4.5 Definition of qualifying extranodal involvement

The following extranodal localisations are principally excluded from radiotherapy due their pattern of spread and expected side effects (cf. 5.7.3.1):

- Bone marrow involvement
- Lung involvement (localised or disseminated or both)
- Pleura involvement/ pleural effusion (disseminated/ malignant)
- Kidney involvement (also one-sided)
- Small bowel involvement (disseminated)
- Large bowel involvement (disseminated)
- Liver involvement (localised or disseminated or both)
- Spleen involvement (localised or disseminated or both)
- Peritoneal involvement (Ascites)

All other extranodal involvements are principally treatable with radiotherapy and therefore designated as qualifying extranodal involvement. In isolated cases, radiotherapy can be contraindicated due to localisation and extent of the extranodal involvement.

2.4.6 Summary of the rationale

The points discussed in sections 2.4.1 to 2.4.4 demonstrate that according to current knowledge a shortening of therapy intervals from three (R-CHOP-21) to two weeks (R-CHOP-14) of six cycles of immuno-chemotherapy with rituximab in combination with the CHOP protocol is the most likely approach to result in the urgently required improvement in outcome of patients aged 18 to 60 years with good-prognosis (aaIPI = 0,1) $CD20^+$ aggressive Lymphoma and a less favourable risk profile [IPI = 1 (all) and IPI = 0 with bulky disease]. Since the value of additional consolidating radiotherapy is controversial and urgently needs clarification, six cycles of R-CHOP-14 will be compared with six cycles of R-CHOP-21, both combined with or without radiotherapy of bulky disease and/or extranodal involvement in this study, in a 2x2 factorial design, in a prospective and randomised fashion. The aim is to demonstrate that a shortening of therapy intervals from three to two weeks or radiotherapy of bulky disease will result in a 10% improvement of TTF rate after three years. We assume that at a recruitment rate of 214 patients per year over a 5-year period the questions asked in this study can be answered with sufficient power.

3 Study Protocol

3.1 Study design

The DSHNHL 2004-3 study is a prospective randomised treatment optimisation study or so-called quality assurance protocol. Its aim is to investigate whether results achieved by combination of 6 cycles of rituximab and CHOP can be further improved by shortening the treatment intervals from 3 weeks (R-CHOP-21) to 2 weeks (R-CHOP-14). At the same time, the study will investigate whether radiotherapy of bulky disease or qualifying extranodal involvement will improve the outcome. These questions will be addressed in an open-label multicentre clinical study.

3.2 Participating institutions and number of patients

All institutions (currently 297) which cooperate within the DSHNHL will participate in the DSHNHL 2004-3 study. We assume that these centres will be able to enroll 1072 patients during the approximate 9-year recruitment phase from October 2005 to September 2014.

3.3 Duration of the study

The treatment duration of immuno-chemotherapy in the standard arm will be 18 weeks (6 x R-CHOP-21). It will be 12 weeks in the experimental arm (6 x R-CHOP-14). The treatment duration will be approximately prolonged by another 10 weeks in arms that receive additional radiotherapy of bulky disease and/or qualifying extranodal involvement or, respectively, prophylactic radiotherapy of the contralateral testis in case of involvement of testis including therapy pauses.

3.4 Study discontinuation

3.4.1 Discontinuation of the study by individual patients

3.4.1.1 Post-randomisation non-qualification

Since this study will be analysed according to internationally accepted criteria[39] and the intention-to-treat principle, no patient will be excluded. **The only reason for exclusion is withdrawal of consent by the patient.** A patient will not be withdrawn from the study if, after inclusion in the study, an exclusion criterion is found to apply or if it subsequently becomes apparent that an exclusion criterion had applied at the time of inclusion (this applies to all exclusion criteria listed in Section 4.2 and, in particular, to any change in histological diagnosis by the reference pathology). **The treating physician will be informed of post-randomisation non-qualification of the patient by the study coordinators. Further documentation of patients who are not qualified is the same as those of qualified patients.**

3.4.1.2 Early termination of therapy

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

- lack of response to treatment as defined in the protocol
- serious deviation from the protocol
- non-compliance on the part of the patient
- excessive toxicity
- in response to the wish of the patient
- decision of the treating physician
- contact broken off by the patient

The reason for early termination of therapy must be documented in written form and notified to the Study Coordinators. After early termination of therapy, documentation of patients must continue (remission status, survival with and without lymphoma).

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

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

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

Should any of the above occur, the Study Management Committee will notify the Protocol Committee, which will then decide within 1 month whether to terminate the study or not. If no unanimous decision can be reached by the Protocol Committee, the recommendation of an independent committee which will consist of international experts in the field of research into the treatment of lymphoma (Data and Safety Monitoring Committee, cf. 0.3.2) will be obtained. If it is still not possible to reach a consensus in the Protocol Committee, the Study Management Committee shall decide whether or not to terminate the study after obtaining the opinion of the Ethics Committee.

4 Eligibility

4.1 Inclusion criteria

1) Age:
18 to 60 years

2) Risk group:
good-prognosis, less favourable
- (age-adjusted) IPI = 1: all patients
- (age-adjusted) IPI = 0: only patients with bulky disease (for definitions see Appendix 13.9, largest single or conglomerate tumour must be ≥ 7.5 cm in diameter)

3) Histology:
Diagnosis of a untreated CD20-positive aggressive B-cell lymphoma, confirmed by excisional biopsy of a lymph node or by a sufficiently extensive biopsy of extranodal manifestation if there is no lymph node involvement. It will be possible to treat the following entities in this study:

- **B-NHL:**
  - follicular lymphoma stage III°b
  - follicular lymphoma stage III° and diffuse large B-cell lymphoma
  - diffuse large B-cell lymphoma
    - centroblastic
    - immunoblastic
    - plasmoblastic
    - anaplastic large cell
    - T-cell-rich B-cell lymphoma
  - primary effusion lymphoma
  - intravasal B-cell lymphoma
  - primary mediastinal B-cell lymphoma
  - Burkitt-like lymphoma
  - Burkitt lymphoma
  - aggressive marginal zone lymphoma (monocytoid)
  - Mantle-cell lymphoma (blastoid)

- **T-NHL:**
  T-NHL cannot be included in this study!
  The respective patients should be included in phase-II studies of the DSHNHL instead which have been specially designed for this patient cohort (please contact the study secretariat).

4) Performance status:
Performance status ECOG 0-2 at the time of randomisation; definitions see Appendix 13.10.

5) Declaration of participation provided by the study centre and the written consent by the patient

4.2 Exclusion criteria

1) Already initiated lymphoma treatment (except for prephase treatment according to this protocol)
2) Serious accompanying disorder or impaired organ function (in particular impaired left ventricular function or severe cardiac arrhythmias)
3) Platelets < 100 000/mm^3, leukocytes < 2 500/mm^3
4) Known hypersensitivity to the medications to be used
5) Known HIV-positivity
6) Active hepatitis infection
7) Suspected poor patient compliance
8) Simultaneous participation in other treatment studies
9) Prior chemo- or radiotherapy for previous disorder
10) Prior immunosuppressive treatment with cytostatics
11) Other concomitant tumour disease and/or tumour disease in the past 5 years (except carcinoma in situ and basalioma of the skin)
12) Pregnancy and lactation period
13) > 1 Risk factor according to age-adjusted IPI (LDH > UNV, stage III/IV, ECOG > 1)
14) CNS involvement of lymphoma (intracerebral, meningeal, intraspinal)
15) MALT lymphoma
16) Non-application of inclusion criteria.

Patients with primary CNS involvement or MALT lymphoma should not be included in this study. We would recommend the inclusion of the respective patients in one of the studies of the German Study Group GIT-NHL (Prof. Dr. Berdel, Dr. Koch, Münster) and the German Study Group PCNSL (Prof. Dr. Thiel, Berlin; Prof. Dr. Weller, Tübingen) respectively. Patients with lymphoblastic lymphoma should be referred to the multicentre ALL study (Prof. Dr. Hoelzer, Frankfurt).

5 Study procedures for individual patients

5.1 Staging examination

5.1.1 Obligatory examinations

1) Patient history (onset of symptoms, B symptoms, performance status - ECOG)
2) Clinical examination
3) Laboratory tests:
   - Haematogram with differential blood cell count
   - LDH
   - GPT (ALT)
   - GOT (AST)
   - Alkaline phosphatase (serum)
   - γ-GT
   - Bilirubin
   - Creatinine
   - Electrolytes (Na, K, Cl, Ca) only in case of increased creatinine
   - HIV serology (after separate informed consent)
   - Hepatitis serology
   - Pregnancy test
4) CT scan of the neck/thorax/abdomen
5) Bone marrow biopsy (histology und cytology)
6) Lumbar puncture with CSF cytology in cases of involvement of the testes
7) Electrocardiogram
8) Echocardiography (alternatively: determination of the ejection fraction by radionuclide ventriculography) prior to initiation of treatment (recommended by the Medical Council of North Rhine)
9) Determination of pulmonary diffusing capacity (only in patients with pre-existing pulmonary disease)

5.1.2 Optional tests

1) Laboratory tests:
   - ESR
   - total potein + albumin with protein elektrophoresis and immunoelektrophoresis (paraprotein)
   - immunoglobulins IgG, IgA, IgM
   - β2-microglobulin
2) Total body bone scan
3) Chest X-ray in two planes in upright position
4) Abdominal ultrasound
5) Gastroscopy (obligatory in case of tonsil involvement)
6) Examination by an ENT specialist (obligatory in cervical involvement)
7) Haemoccult test
8) Lumbar puncture with CSF cytology, if not obligatory (cf. 5.1)
9) Gallium scintigraphy
10) positron emission tomography
11) NMR tomography
12) cervical sonography

13) Liver biopsy
14) Examination of fertility, if applicable sperm asservation

5.2 Evaluation of disease stage and risk group allocation

The results of the staging examination are used to classify the stage of the disease in accordance with the criteria of the Ann Arbor Conference (cf. Appendix 13.8.1) and Cotswolds[40]. In addition, on the basis of the number of risk factors determined during examination, the patient will be allocated to one of the four risk groups according to the "International Prognostic (age-adjusted) Index" (IPI) as follows:

1) low risk group,
2) low-intermediate risk group
3) high-intermediate risk group
4) high risk group

The criteria of the age-adjusted IPI and the definitions of "bulky disease" and "E involvement" can be found in Appendix 13.8 to 0 of the study protocol. **All patients aged 18 to 60 years with age-adjusted IPI = 1 and patients with IPI = 0 in case of bulky disease can participate in this study.**

5.3 Central evaluation of pretherapeutic diagnostic imaging

All pretherapeutic diagnostic imaging (CT or MRT) of **all patients included in the study, independent of randomisation or disease extent** needs to be evaluated in cooperation with the radiologist of the reference radiotherapy centre in order to obtain standardised definitions of bulky disease and extranodal involvement. All pretherapeutic imaging including reports must therefore be sent to the Study Secretariat in Homburg. They will be copied and returned to the treating centre.
A radiotherapy schedule will only be prepared for patients in arms ARX and BRX by the reference centre and sent to the treating physician.

5.4 Patient information

The treating physician will provide the patient with information on the study prior to the commencement of any Lymphoma-specific therapy.
Treating physicians will provide patients with information (in the presence of a witness where appropriate) in comprehensible terms on the diagnosis of aggressive Lymphoma and the current status of knowledge about the diagnosis and treatment of this disease and on the aims of the study. Patients will also be informed about the expected and possible effects and adverse effects of treatment and about the insurance cover which they will have as study participants. It must be ensured that patients are fully aware that they are free to decide whether to participate or not, that they can cancel their decision to participate at any time and that there will be no disadvantages for them if they do not participate. Patients will also be informed that, if they consent to participate in the study, their treatment records will be viewed for documentation purposes, and that personal data required for the scientific monitoring of the disease will be collected and assessed. The aim and purpose of the collection of data will be explained to the patient. In addition, the patient is to be asked to immediately report all impairments to his/her health which may occur during or after treatment and which could be associated with the

treatment (e.g. later alterations to blood counts) to the treating physician. The patients will also be informed that regular follow-up examinations, which will be in their own interest, are to be conducted over a period of some years and that the results of these examinations will be notified to the Study Management Centre.
Patients have to confirm their consent to participate in written form and the consent form must also be signed by the physician providing the patient with information. The form will explicitly specify consent to the collection of patient data, its transfer to the Study Management Centre, evaluation in anonymous form and consent to the accompanying scientific investigations. In addition, patients must consent to being directly contacted by the Study Management Centre if the Study Management Centre is no longer able to obtain the required information from the treating physician. The Patient Information and Informed Consent Form must be signed by the patient, physician and any witness present.
The Patient Information and Informed Consent Forms are provided in Appendix 13.2 to 13.4 of this protocol. The originals of the Informed Consent Form and the protocol of the patient information are to be retained by the treating physician. The patients will be given the copies of these forms together with a copy of the Patient Information Leaflet. In addition, the patients will receive a copy of the insurance policy.

5.5 Notification of the inclusion of the patient in the study

The treating physician must notify the Study Management Centre in Homburg of patient inclusion so that randomisation can be performed. This should be done immediately on completion of the staging examination, information of the patient and obtaining written consent, prior to the commencement of any Lymphoma-specific treatment (for exceptions see below, though definitely before starting immuno-chemotherapy).

Randomisation by the studysecretariat of the DSHNHL

Telefon: 06841/16-23084
Fax: 06841/16-23004
E-mail: dshnhl@uks.eu

For the randomisation procedure, please send the completed Baseline Information I, Baseline Information II, Staging Report Form, Informed Consent Form and a copy of the initial histology report by fax to the Study Management Centre *(Fax: +49-6841-16-23004)*.
The Study Management Centre will make a phone call if there are further inquiries necessary.
The following information is required for randomisation:

- name of institution and treating physician
- name of pathologist
- name of radiotherapist if radiotherapy planned
- identification of the patient
- age
- gender
- histopathologic subtype (WHO classification) and determination whether $CD20^+$ B-cell Lymphoma
- confimation that patient conforms to eligibility criteria
- confirmation that no exclusion criteria apply

- IPI criteria: -
  - LDH and upper normal limit of LDH in the respective laboratory
  - performance status (ECOG score)
  - Ann Arbor stage
  - presence of extranodal involvement (number, site)
- presence of bulky disease (site)
- sites of lymhoma involvement
- haematological status

Note:

As the randomised study allocations and stratifications of the DSHNHL studies are based on the (age-adjusted) International Prognostic Index score[1], stage, performance status, number of extranodal involvements and LDH value must be known at the time of randomisation and this information must be documented! The LDH value given at randomisation must be the value measured prior to any treatment. Care must be taken to ensure that the result is not influenced by haemolysis. The reference values used by the laboratory in question must also be stated. Bulky disease is a charteristic for stratification and must therefore be determined prior to randomisation.

5.6 Inclusion of the patient in the study

After the central Study Secretariat has been notified of the inclusion of a patient, the patients will be randomised. The results of the randomisation will be reported to the recruiting physician immediately by phone. **In addition, the treating institution will receive *a written confirmation* of randomisation *by fax and by surface mail.***
The pretherapeutic diagnostic imaging of all patients, independent of randomisation into radiotherapy arms, should be sent in electronic form (CD) to the study secretariat in Homburg/Saar in order to ensure quality control.
The primary pathologist will be written to by the Head of the Reference Panel with a request to forward tissue samples for reference pathological analysis. The Study Management Centre will inform the reference pathologist on a monthly basis of new patients included in the study.
The Radiotherapy Reference Panel will determine the extent of disease on the basis of the pretherapeutic imaging and will send a radiotherapy schedule for patients randomised into radiotherapy arms to the treatment centre.
Within the context of the randomisation procedure, the recruiting physician will be informed about the requirement of patient material for accompanying investigations conducted under the supervision of the Scientific Advisory Board. The physician will receive logistic support from the Study Management Panel for the submission of this material. In the Patient Information and Informed Consent Form, patients are requested to consent to these scientific procedures and to allow primary lymph node material to be made available to the Study Management Centre for this purpose.
On the day of randomisation, the documentation dossier will be sent from the Central Study Secretariat to the recruiting physician.

5.7 Execution of treatment according to protocol

Prephase treatment can be commenced prior to randomisation in exceptional circumstances. The main treatment phase must not be initiated before randomisation and must directly follow the prephase treatment. Randomisation must be performed prior to the commencement of study treatment with R-CHOP-21 / R-CHOP-14 at the latest. Thus, commencement of the prephase treatment in cases of emergency, e.g. in cases of extensive tumour size or poor performance status, is permitted prior to notification of the Study Management Centre. Prephase treatment is not obligatory and does precede the main treatment phase with R-CHOP-21/14, which consists of six cycles in any study arm. After the third cycle there will be an interim restaging. Salvage therapy will be recommended to all patients who do not show a response to treatment at this point in time (PRO). Salvage therapy should also be given within a prospective study. This will be regulated in a separate study protocol for salvage therapy (available on request). There will be a final restaging after six cycles. A confirmation of remission must be carried out after further four weeks in all arms in case of CRu/PR treatment results for definite determination of treatment result. **Patients with radiotherapy indication in CR/CRu/PR after completion of chemotherapy will receive consolidating radiotherapy to initial bulky lesions and/or qualifying extranodal involvements, and/or to the contralateral testis in case of testicular involvement with a dose of 39.6 Gy (ARX and BRX)! Patients with radiotherapy indication who are not in CR, CRu or PR in the restaging after chemotherapy, principally have progressive disease and require further treatment (salvage therapy; for peculiarities concerning PR, please refer to paragraph 5.9.3).** As a rule, salvage therapy will consist of a different type of chemotherapy, but may consist of radiotherapy if the treating physician considers this to be appropriate.
In patients without radiotherapy indication who are in PR/CRu after completion of chemotherapy, a confirmation of the remission status must be obtained by a control CT of the suspect residual lesions 4 weeks after the final restaging after immuno-chemotherapy. Because of the growth dynamics of aggressive lymphomas all patients who do not have a PRO in the confirmation of remission are assumed to be in CR/CRu, because progressive disease would manifest itself during the time elapsed between the two controls! Patients without radiotherapy indication who are not in CR or CRru in this confirmation of remission, have principally progressive disease and require further treatment (salvage therapy; please refer to paragraph 5.9.3 for the peculiarities of PR). As a rule, salvage therapy will consist of a different type of chemotherapy, but may consist of radiotherapy if the treating physician considers this to be appropriate.
The first follow-up examination is done by the internist: **three months after final restaging on completion of chemotherapy <u>in all arms.</u>**
In view of the treatment intensity of this study, very close clinical monitoring is recommended. Patients should be examined on a weekly basis by an experienced physician so that any side effects from chemotherapy (e.g. mucositis, polyneuropathy, deterioation of general status) are recognised at an early point in time and appropriate treatment can be provided.

5.7.1 Prephase treatment

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

Vincristine	1 mg	i.v.	day* -6	single dose
Prednisone	100 mg	p.o.	Tag* -6 bis Tag 0	7 days

*day 1 = day 1 of 1st R-CHOP-21/14 cycle

The purpose of the prephase treatment is to prevent tumour lysis syndrome in patients with Bulky Disease, to improve the performance status of the patient and to reduce the toxicity of

the first chemotherapy cycle. **Although prephase treatment is not obligatory, though it is recommended and can also be given in abbreviated form!** Sufficient fluid intake and appropriate supportive measures (see below) are to be provided.

5.7.2 Chemotherapy

The dosage of R-CHOP does not differ in arms A (R-CHOP-21) und B (R-CHOP-14):

- Arm A: 6 x R-CHOP-21
- Arm B: 6 x R-CHOP-14

R-CHOP schedule:

Cyclophosphamide	750 mg/m^2	i.v.	d1
Doxorubicin	50 mg/m^2	i.v.	d1
Vincristine	1,4 mg/m^2, max 2 mg	i.v.	d1
Prednisone	100 mg (absolut)	p.o.	d1-5
Rituximab	375 mg/m^2	i.v.	d0 oder d1

To be repeated on: day 22 (R-CHOP-21) or day 15 (R-CHOP-14) 6 cycles in total

G-CSF

G-CSF (Lenograstim®) is to be given after CHOP-14 from day 4 to day 13 or until recovery of leucocyte count > 2.5 x 10^9/l.
G-CSF (Lenograstim®) should be given after R-CHOP-21 if the following therapy cycle was delayed due to leukocytopenia and in case of prolonged leukocytopenia (i.e. leukocytopenia lasting > 3 days with leukocyte count < 1 x 10^9/l). In that case G-CSF (Lenograstim®) should be given during the following cycles starting from day 4.

Tapering of prednisone:

Prompt discontinuation of prednisone can result in marked fatigue. We therefore recommend a gradual reduction of the prednisone dose, with administration of 50 mg on day 6, 25 mg on day 7 and 12.5 mg on day 8.
R-CHOP-21 is to be repeated on day 22, R-CHOP-14 on day 15. Prerequisites for the continuation of therapy are:

1) Patient has passed the leukocyte and platelet nadir
2) Leukocyte count > 2500/mm^3 on day 22 or day 15 after discontinuation of G-CSF (Lenograstim®) and
3) Platelet count > 80 000/mm^3 on day 22 or day 15
4) No active infection

5) No thrombocytopenia < 20.000/mm³ during the entire preceding cycle
6) Duration of leukocytopenia < 1000/mm³ not longer than four days during entire preceding cycle
7) No severe organ toxicity or other toxicity

If the threshold counts for leukocytes and platelets on day 22 or day 15 are not reached, the commencement of the next cycle will be postponed for 3 days. If the threshold counts are still not reached by that time, the next chemotherapy cycle will be postponed for a further 3 - 4 days. Such delays are an indication for the administration of G-CSF (Lenograstim®), just as prolonged leukocytopenia. In these cases, administration of G-CSF is to be continued until the necessary leukocyte count is achieved (see above) and is to be repeatedly given during the following cycles starting from day 4. If a postponement exceeding 1 week is required, dose reduction will be necessary (s. 5.7.2.1.).

5.7.2.1 Dose reduction

If the requirements regarding continuation (s.5.7.2) are not met after a delay of 1 week, i.e. on day 22 after the administration of CHOP-14 or day 29 after the administration of CHOP-21, further treatment should be postponed with checks of blood counts every three days until these values are reached. The next cycle should then be given in a reduced dose.

	Cyclo-phosphamide	**Doxorubicin**	**Vincristine**	**Prednisone**	**Rituximab**
Postponement of therapy 0-7 days:	no reduction				
Postponement of therapy 8-14 days	75%	75%	100%	100%	100%
Postponement of therapy > 14 days	50%	50%	100%	100%	100%

Dose reduction due to overweight:

According to the "ASCO-Guideline on Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer" from April 2012 we recommend that full weight-based chemotherapy doses be used in the treatment of the obese patient (with the exception of conventional vincristine which will be capped at 2mg absolute). Physicians should respond to all treatment-related toxicities in the same way they do for non-obese patients. If a dose reduction is is done because of toxicity, resumption of full weight-based doses should be considered for subsequent cycles, especially if a possible cause of toxicity (e.g., impaired renal, hepatic function) has been resolved. There is no evidence to support the need for greater dose reductions for obese patients compared with non-obese patients [41].

In addition, dose reduction of individual medications can be considered if other toxicities (e.g. polyneuropathy, severe mucositis) occur. In such cases, prior consultation with the Study Management Centre is recommended.

5.7.2.2 Administration of rituximab

Rituximab: 375 mg/m² iv., to be commenced 48 to 2 hours prior to initiation of CHOP-21/14
Repeat: **every 3 or 2 weeks, six applications in total, synchronised with CHOP-21/14.**

The antibody solution is to be diluted 1:10 with 0.9% NaCl (maximum antibody concentration: 1 mg/ml). Excessive agitation of the solution should be avoided to prevent precipitation of the antibody.
As side effects of rituximab are particularly frequent and pronounced during and after the first administration, the first dose must be administered while patients are hospitalised and at least 24 hours prior to the commencement of CHOP chemotherapy, so that any side effects of the antibody can be clearly distinguished from the side effects of chemotherapy! Adequate hydration of patients should be ensured and patients should be given allopurinol prior to the administration of the first dose. Although the risk of a tumour lysis syndrome is very low after prephase treatment, these precautionary measures are still advisable.
Rituximab must not be given by bolus injection!
Prior to the initial administration of rituximab, patients are to be given paracetamol (1000 mg) and 5 ml clemastinfumarat i.v.. Rituximab must be administered via a peripheral or central venous catheter. Prior to the first infusion, it should be ensured that epinephrine and clemastinfumarat are available in case an allergic reaction occurs. All necessary equipment for the treatment of anaphylactic shock should be readily available.
During the first hour of the rituximab infusion, blood pressure, pulse rate and respiratory rate are to be measured every 15 minutes. If there are no side effects during the first hour, the infusion rate can be increased from 50 mg/h to 300 mg/h: from the second infusion onwards, the rate can be increased to up to 400 mg/h. Patients may develop fever and chills during the infusion of rituximab. If these symptoms are observed, the administration of the antibody should be discontinued. When the symptoms have regressed, the infusion can be recommenced at half the previous rate. On completion of the infusion, the venous access should be left *in situ* for a further hour.
Rituximab is principally to be given synchronized with chemotherapy. In rare cases, where there is an unforeseen delay of chemotherapy after the administration of rituximab, the next application of rituximab is to be given at the chemotherapy cycle thereafter.

5.7.2.3 CNS prophylaxis/radiotherapy in case of testicular involvement

The CNS prophylaxis has been abandoned. This also applies for cases with testicular involvement as it was shown not to be effective when CHOP therapy is combined with rituximab.[42]
However, in case of testicular involvement a lumbar puncture should be performed in order to exclude latent CNS involvement. Additional radiotherapy to the contralateral testis is recommended as it has been shown that this reduces the incidence of lymphoma of the contralateral testes. Radiotherapy to the contralateral testis should be given with 1.8 Gy, 5x/week up to a total dose of 30.6Gy.

5.7.2.4 G-CSF therapy

Patients in treatment arms A1 and ARX (R-CHOP-21) will not receive G-CSF unless there is prolonged leukocytopenia or treatment delay due to leukocytopenia. Patients in treatment arms B and BRX (R-CHOP-14) will principally receive G-CSF (Lenograstim®)from day 4 to day 13 or recovery of the leukocyte count > 2.5 x 10^9/l.

G-CSF (Lenograstim®): 263 µg once daily s.c.

5.7.2.5 Side effects of the treatment modalities applied

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

- **Doxorubicin:**
  myelosuppression, nausea/vomiting, alopecia, cardiomyo-pathy (max. cumu-lative dose: 550 mg/m^2), necrosis after paravasal injection

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

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

- **Rituximab:**
  allergic reactions, with anaphylactic shock in rare cases; particularly during the first application: nausea/vomiting, impaired swallowing, headache, tiredness. During and after treatment with rituximab there is a slightly increased incidence of viral infections (HSV stomatitis, herpes zoster)

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

- **Radiotherapy:**
  nausea, vomiting, impaired swallowing, headache, tiredness, leukocytopenia, thrombocytopenia, anaemia, skin alterations and alopecia in the irradiated area. Also possible are reactions to irradiation of the lungs (dyspnoea), of the intestine (diarrhoea), of the pericardium (effusion).

- **Intrathecal treatment:**
  Headache, nausea/vomiting after prophylactic administration of MTX

5.7.2.6 Supportive measures

- **Selective intestinal decontamination:**
  generally **not required** as a rule; however, prophylactic oral administration of an antibiotic [e.g. ciprofloxacin (Ciprobay®) 500 mg twice daily] is recommended during leukocytopenia < 1000/mm^3.

- **Pneumocystis carinii prophylaxis:**
  not required

- **Cystitis prophylaxis:**
  ensure adequate fluid intake particularly on day 1 of therapy or provide fluids by infusion under cardiopulmonary monitoring. Urometixan (Mesna®) prophylaxis in accordance with local standards.

- **Antiemesis:**
  metoclopramide (Paspertin®) or alizapride (Vergentan®), 10 and 50 mg i.v. respectively, given at 0, 4 and 8 hours, may be sufficient. The use of serotonin antagonists (e.g. Ondansetron®, Granisetron®) is recommended however.

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

5.7.2.7 Control monitoring during therapy

- **On a regular basis twice weekly:**

  blood counts (leukocytes, platelets, Hb) with differential blood counts [note: the experience from the NHL-B1 and DSHNHL 1999-2 studies shows that the leukocyte nadir will be reached on days 10-12 after CHOP-21 or days 8-10 after CHOP-14.

- **Prior to each cycle:**

  clinical examination (in particular: lymph node status, exclusion of polyneuropathy, mucositis), blood counts (leukocytes, platelets, Hb), LDH, GPT (ALT), AP, bilirubin, creatinine, electrolytes

- **Additional:**

  echocardiography after 200 mg/m^2 doxorubicin (recommended by the Ethics Committee of the Medical Council of North Rhine)

5.7.3 Consolidating Radiotherapy

5.7.3.1 Indications for consolidating radiotherapy

Involved-field radiotherapy will be given to all patients with radiotherapy indication. The presence of at least one bulky disease that has not been surgically removed and/or E-involvement amenable to radiotherapy are an indication for radiotherapy

Consolidating radiotherapy is administered to the following regions:

1) Bulky Disease:
- regions with initial bulky disease (lymph node conglomerate or extranodal involvement ≥7,5 cm, see Appendix 13.9.
- The total dose is 39.6 Gy; the single dose is 1.8 Gy, 5x/week

2) Extranodal involvement:
In general no radiotherapy will be given if there is extranodal involvement of the following locations:

- bone marrow involvement
- lung involvement (localised or disseminated or both)
- pleural involvement/pleural effusion (disseminated/malignant)
- kidney involvement (also if one-sided)
- small bowel involvement (disseminated)
- large bowel involvement (disseminated)
- liver involvement (localised or disseminated or both)
- spleen involvement (localised or disseminated or both)
- peritoneal involvement (ascites)

All other locations with qualifying extranodal involvement will be treated with radiotherapy. The total dose is 39.6 Gy; the single dose is 1.8 Gy, 5x/week. The daily dose can be reduced 1.6 Gy if the area that needs to be treated with radiotherapy is too large.

3) Radiotherapy in case of testicular involvement:

Patients with testicular involvement receive prophylactic radiotherapy of the contralateral testis and scrotum with a total dose of 30.6 Gy, with a single dose of 1.8 Gy, 5x/week.

4) Treatment strategy after surgical removal of bulky disease or E involvement:

Surgical removal of lymphoma involvement is an exception; there is no radiotherapy planned afterwards. In case of additional bulky disease or extranodal involvement that has not been surgically removed, but is amenable to radiotherapy, radiotherapy will be given to this localisation.

5.7.3.2 Initiation of consolidating radiotherapy

Consolidating radiotherapy should be commenced 2 - 6 weeks after the last immuno-chemotherapy cycle following complete recovery of bone marrow (leukocytes > 3 000/mm^3, platelets > 100 000/mm^3) and complete remission of any mucositis.

5.7.3.3 Requirements of equipment to ensure per protocol-conformable consolidating radiotherapy

- Use of linear accelerators. Radiotherapy with Co-60 should be avoided. Appropriate moulage must be used for photon energy limit > 8 MeV in case of superficial lymphoma localisation.
- 3-D Computer-based radiotherapy planning on the basis of CT scans.
- Preparation of individual shields or use of multileaf collimators must be possible.
- Availability of individual positioning aids (mask techniques)
- Preparation for radiotherapy and documentation in a therapy simulator
- Preparation of verification images / portal imaging

5.7.3.4 Radiotherapy doses

The pretreatment images and staging report form must be sent to the Study Management Centre in order to control a consistent definition of bulky disease and extranodal involvement.
Once the pretreatment images and the staging report form are available, the reference radiotherapist in case of randomisation into a radiotherapy arm will prepare an individual radiotherapy proposal which will be sent to the primary radiotherapist.

1) Consolidating radiotherapy of bulky disease:

The applied volume does not necessarily extend to all affected lymph node regions. It is given as involved-field radiotherapy corresponding to the lymphoma involvement as ascertained by pretherapeutic imaging.
The target volume should only contain the initial lymphoma with a 1.5 cm safety margin. The target volume is determined after the initial imaging. If there is certain evidence for displacing growth without infiltration (particularly at the lateral field borders), the target volume is to be reduced to the postchemotherapeutic volume. This is to be documented in the radiotherapy documentation.

Conformal 3-D radiotherapy techniques are applied with optimal protection of all initially non-involved normal tissues.
The dose specification is performed according to ICRU 50.
Principally, the simultaneous radiotherapy of all regions with bulky disease or extranodal involvement is to be aimed at. In cases of bulky disease on both sides of the diaphragm, radiotherapy of the region with the larger initial tumour mass should be performed first if simultaneous radiotherapy of all regions does not appear feasible because of the large volume to be applied.

2) Consolidating radiotherapy of qualifying extranodal involvement

Consolidating radiotherapy of extranodal involvement is performed according to randomisation (exceptions see above). A specific radiotherapeutic technique cannot be recommended because of the great variety of possible localisations and patterns. The definition of the target volume is analogous to the treatment guideline for bulky disease. The clinical target volume corresponds to the initial extent of lymphoma with a safety margin of 1.5 cm. Conformal 3-D radiotherapy techniques are applied, with optimum protection of initially non-involved normal tissue.

In case of any questions, please consult with Reference Radiotherapy in Homburg

Dr. Berdel, Dr. Fleckenstein, Prof. Dr. Rübe

Tel. +49 06841/16-24606
E-Mail: radonk@uks.eu

5.7.3.5 Documentation of radiotherapy

On completion of consolidating radiotherapy, the completed Radiotherapy Reports (RX form), radiotherapy plan, simulation images, verification images and computertomograms of the final restaging should be sent to the Study Management Centre. These documents will be assessed by the panel of reference radiotherapists and will then be returned to the treatment centre.

5.8 Restaging and follow-up procedures

5.8.1 Interim restaging

Approximately two weeks after commencement of the third cycle (assuming that treatment can be continued on time) an interim restaging will be performed, including the following:

- patient history
- clinical examination (lymph node regions!)
- laboratory parameters as during the staging examination (cf. 5.1)
- electrocardiogram
- CT scan of thorax/abdomen (in case of primary involvement)
- evaluation and documentation of success of therapy (cf. 5.9) and adverse effects (cf. 6).

5.8.2 Final restaging on completion of chemotherapy

Approximately two weeks after commencement of the sixth cycle the final restaging is performed. It consists of the same examinations that are performed for the other staging procedures:

- patient history
- clinical examination (lymph node regions!)
- laboratory parameters as for the primary staging examination (cf. 5.1)
- electrocardiogram
- CT scan of thorax/abdomen (in case of primary involvement)
- appropriate evaluation of other primary manifestations (e.g. bone marrow biopsy)
- evaluation and documentation of results of therapy (cf. 5.9) and side effects (cf.6).

This is the definitive final restaging of all patients of all arms.

5.8.3 Confirmation of remission

Patients without radiotherapy indication in CRu/PR as demonstrated by the final restaging on completion of immuno-chemotherapy will receive a confirmation of their remission status by a control CT of all residual lesions **Patients in CR/CRu at this stage will proceed according to protocol. All other patients will be given salvage treatment (for pecularities of PR please refer to paragraph 5.9.3).**

This confirmation of remission is not necessary in patienta with radiotherapy indication.

5.8.4 Additional restaging after radiotherapy by radiotherapist (not mandatory)

Since the first follow-up examination is already performed three weeks after the final restaging on completion of chemotherapy by the internist, no additional restaging by the radiotherapist is planned. An additional restaging by the radiotherapist is optional.

5.8.5 Restaging in case of early discontinuation of therapy

In cases of early discontinuation of therapy (e.g. at the wish of the patient or because of excessive toxicity), a restaging examination should be conducted **as soon as possible** to determine the success of treatment at the time of discontinuation: procedures should include the same as those for the final restaging on completion of chemotherapy (cf. 5.8.2).

5.8.6 Follow-up examinations

Follow-up of all patients will continue until the completion of the study and the planned observation period, i.e. al least until June 2017. **The first follow-up examination will be performed three months after the final restaging on completion of chemotherapy in all arms.** After that, follow-up examinations will be performed during the initial 2 years every 3 months, in years 3-5 years every 6 months and then subsequently on an annual basis. Follow-up examinations consisting of a clinical examination, laboratory analysis, imaging techniques and documentation of remission status and of therapy-induced disorders including secondary neoplasias are to be conducted as described in detail in the therapy plan (cf. 0.7) and are to be recorded on the follow-up documentation forms (CRFs).

5.9 Documentation of endpoints

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 to the interim restaging, control restaging and follow-up examinations, too. The remission criteria have been defined on the basis of the recommendations of the recently published International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas[39] and have been appropriately modified for application within a large-scale multicentre trial for aggressive lymphomas.

Remember:
As a rule, if a case is classified as PR, NC or PRO, it is assumed that further treatment is required.

Notes:

- Patients classified as CR/CRu, PR or NC during interim restaging after three cycles of chemotherapy will receive three additional cycles of R-CHOP-21 (arms A/ARX) or R-CHOP-14 (arms B/BRX).
- Patients with initial bulky disease and/or extranodal involvement in CR/CRu receive consolidating radiotherapy with 39.6 Gy onto these localisations
- Patients with testicular involvement receive prophylactic radiotherapy to contralateral testis and scrotum with 30.6 Gy.
- Patients without radiotherapy indication not in CR/CRu in confirmation of remission four weeks after final restaging on completion of chemotherapy will receive salvage treatment.
- Non-responders (PRO) will be given salvage treatment.

5.9.1 Complete remision (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). Any enlargement 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 *light microscopy* must confirm that bone marrow is free of signs of lymphoma. Blood counts must have normalised, with granulocytes > 1,500/µl, Hb >12 g/dl, and platelets > 100.000/µl. **On completion of therapy, the patient must be in CR from the time point of the final restaging examination for at least 2 months.**

5.9.2 Complete remission with remaining uncertainty (CRu)

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

5.9.3 Partial remission (PR)

The following criteria must be met in partial remission:

- Lymphoma tissue still present (histological confirmation in all doubtful cases), but a
- definitive reduction at all involved sites and reduction of the total lymphoma volume by at least 50%;
- no new lymphoma manifestations;
- 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, this implies that the treating physician considers that additional treatment (assuming that there are no contraindications) extending beyond that of the protocol is indicated (e.g. salvage therapy). **An operational 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 a supposed CRu/PR in which active tumour tissue is still present in the residual lesions, renewed tumour growth as shown by an increase in size of the residual lesions in the control CT would manifest itself within 2 months after a therapy-free interval, so that the actual outcome of a putative PR would be unmasked as PRO.** This will be taken into account in the evaluation and final definition of the effects of therapy by the Study Management Committee (cf. 7.5.1). **In any case of doubt or uncertainty, particularly with respect to the differentiation between CRu and PR, it is advisable to contact the Study Management Centre.**

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.

5.9.4 No Change (NC)

Continuing presence of lymphoma manifestation with only a slight reduction in size or slight increase in size of involved lymph nodes or organs (exclusion of PRO 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. the reduction is less than 50%).

5.9.5 Progress (PRO)

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.

5.9.6 Relapse

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

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

If the interval is shorter, the case is to be classified as progress. **In any case of relapse, a new histological confirmation should be obtained; the experiences obtained in the first and second study generations of the DSHNHL have shown that completely unexpected consequences for treatment may emerge as a result!**

5.9.7 Evaluation of unmeasurable tumour or bone involvement

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

6 Evaluation of safety / adverse events

6.1 Evaluation of safety

During staging examinations, all laboratory parameters (cf. 5.1) relevant for therapy will be documented. These will be documented during the interim restaging examination after three cycles of chemotherapy (cf. 5.8.1), during the final restaging examination on completion of systemic therapy (cf. 5.8.2) and, if applicable, during the control restaging examination (cf. 5.8.3).
Blood counts will be monitored on initiation of chemotherapy cycles and at least twice during each cycle, particularly during the nadir phase. The performance status of the patient (ECOG) will be determined prior to therapy and before every treatment cycle.

6.2 Adverse events (AEs)

6.2.1 Definition of expected/unexpected adverse events

An adverse event is every unfavourable alteration of the health status of a patient during and/or after therapy, compared with the health status prior to the commencement of therapy, irrespective of whether this alteration is associated with therapy. Adverse events are to be classified in accordance with the NCI Common Toxicity Criteria (CTC) (cf. Appendix 13.13, German version prepared by the Deutsche Krebsgesellschaft [German Cancer Society]).
Any adverse events that are not explicitly included in the CTC list should be classified as "Other" and evaluated, in analogy with the other AEs, using the following four point system:

Grade 0	"none"
Grade 1	"mild"/"slight"
Grade 2	"moderate"/"clear"
Grade 3	"severe"/"marked"
Grade 4	"severe"/"marked"

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

- myelosuppression
- nausea/vomiting
- alopecia
- infections, particularly during phases of leukocytopenia
- peripheral polyneuropathy
- radiation damage to the lungs, pericardium or intestines

In addition, unexpected adverse events may occur. All expected and unexpected adverse events must be carefully documented (cf. 6.2.2).

6.2.2 Documentation of expected/unexpected adverse events

The grade of severity of the adverse events classified in accordance with the CTC criteria should be documented in the respective fields provided on all chemotherapy and radiotherapy CRFs. If side effects occur which are not explicitly mentioned on the documentation forms, the relevant CTC number of the adverse event and the grade of severity should be classified as specified in Protocol Appendix 13.13 and recorded on the CRFs with the relevant CTC number. Adverse events which do not appear on the CTC list should be described in detail and the grade of severity should be documented in analogy with the CTC criteria as defined in 6.2.1.
Relevant fields are provided on the basis of a diagnosis key (cf. Appendix 13.13) on the follow-up CRFs for the documentation of complications which occur after the completion of therapy. Intercurrent disorders which do not conform to CTC criteria should be specified in written detail.

6.3 Serious adverse events (SAEs)

6.3.1 Definition of serious adverse event

An adverse event is to be classified as "serious" if the event represents a particular "risk" to the patient.
The following events are to be classified as serious adverse events (SAEs):

- persistent (i.e. continuing for more than 3 months after completion of therapy) anaemia and thrombocytopenia requiring transfusion therapy
- life-threatening infection
- therapy-associated mortality
- severe cardiomyopathy (NYHA stage III/IV)
- therapy-induced myelodysplasia
- therapy-induced secondary neoplasia (particularly leukaemia)
- unscheduled hospital admission for medical reasons (emergency)

Consultation with the Study Management Centre is necessary if other events occur which are not listed above and which the treating physician evaluates as serious. Any events which are solely attributable to tumour progression are not to be classified as SAEs. The reporting of SAEs is obligatory (cf. 6.3.2).

6.3.2 Documentation of serious adverse events

All serious adverse events must be documented on the SAE report forms and must be faxed to the Study Management Centre within one working day if the event occurs during therapy or within 10 working days if the event occurs during the follow-up phase.
If there is an excessive frequency of SAEs in one of the two therapy arms or the frequency of SAEs appears excessive in comparison with the NHL-B study, it may be necessary to terminate the study early (cf. 3.4.2).

7 Biometrical aspects of the study

7.1 Randomisation algorithm

All patients to whom exclusion criteria do not apply and who conform to all eligibility criteria on completion of staging examinations can be recruited and randomised. A minimisation method will be used for randomisation[43]. The randomisation algorithm will be applied using the ORACLE database. The minimisation method allows therapy arms and strata to be balanced. Patients with indication for consolidating radiotherapy - initial bulky disease that has not been surgically removed, E-involvement that can be treated with radiotherapy, or both - will be randomly allocated to one of the four therapy arms R-CHOP-21 + RX, R-CHOP-21 – RX, R-CHOP-14 + RX and R-CHOP-14 - RX at a ratio of 1:1:1:1.
In the planned interim analysis of 01 July 2012 the formal criterion for stopping the 2 arms without radiotherapy contrast was fulfilled. The therapy arms with radiotherapy were significantly better. The DSMC recommended to close the two treatment arms without radiotherapy and therefore randomisation into these arms was stoppend on 13 July 2012.
Patients without indication for consolidating radiotherapy will be randomised into the treatment arms R-CHOP-21 - RX and R-CHOP-14 – RX at a ratio of 1:1. In both randomisations, patients will be stratified according to the following criteria:

- Centre
- Value of serum LDH (LDH ≤UNV vs. LDH > UNV)
- Stage (I, II vs. III, IV)
- General status of patient (ECOG = 0,1 vs. ECOG = 2,3)
- Bulky disease
- Extranodal involvement

In addition to stratification by treatment centre, patients will also be stratified by the prognostic factors of the age-adjusted international prognostic index (LDH, stage and ECOG).
The presence of bulky disease and extranodal involvement are two more stratification criteria. Stratification by to those characteristics does enable a seperate evaluation of consolidating radiotherapy in patients with bulky disease as well as radiotherapy. Moreover, in two-armed randomisation, surgically removed bulky disease and E-involvement that can not be treated with radiotherapy for technical reasons will be balanced.
All patients where - after inclusion of the patient in the study – it is found that eligibility criteria were not met at the time of randomisation although it was assumed that the patient was eligible at that time – will not subsequently be withdrawn from the study. Patients will only be withdrawn if they subsequently withdraw their written consent. When patients are withdrawn from the study, the balances will be appropriately adjusted in the randomisation program.

7.2 Study endpoints

7.2.1 Primary endpoint

The main endpoint of this study is the time to treatment failure (TTF). The Kaplan-Meier method will be used to assess TTF. The time to treatment failure is the time from the time of randomisation (or first day of prephase treatment in case of prephase treatment prior to randomisation) until one of the following events occurs:

- Disease progression during therapy (PRO)
- Early discontinuation of therapy because of excessive toxicity and patient not in CR/CRu at this point in time
- No CR/CRu on completion of therapy
- Relapse after achievement of CR/CRu
- Change to salvage therapy/additional therapy which is not according to protocol
- Death due to any cause.

The first occurrence of one of the above events is the endpoint. If no such event occurs, the endpoint is the time of the last available information on the patient. The evaluation of protocol deviations, discontinuation of therapy at the request of the patient, discontinuation of therapy by the physician or other issues must be conducted separately for each case within the framework of the evaluation criteria (cf. 7.5.1).

7.2.2 Secondary endpoints

7.2.2.1 Secondary endpoints of efficacy

Secondary endpoints of efficacy are CR rate, rate of progression under therapy (PRO), survival, tumour control and relapse-free / disease-free survival. Tumour control allows the evaluation of the biological efficacy excluding the influence of toxicity. Evaluation of disease-free survival makes it possible to compare the time course of the occurrence of relapse.

- **CR rate:**
  Number of complete remissions (including CR in patients after early discontinuation) divided by the number of all patients

- **Progress rate:**
  Number of progressions during therapy divided by the number of all patients

- **Survival:**
  Time from randomisation (or first day of prephase treatment in case of prephase treatment prior to randomisation) to death due to any cause; in the case of surviving patients, time to last available information on the patient

- **Tumour control:**
  similar to TTF, but events which are not tumour-related are censored

- **Disease-free survival:**
  similar to TTF, but events occurring during and immediately after therapy are assigned to timepoint $\varepsilon = 0.01$ month

- **Relapse-free survival:**
  analogous to TTF, though only of patients in CR/CRu after complete immuno-chemotherapy

7.2.2.2 Secondary endpoints of safety

Secondary endpoints of safety are:

- adverse events (AEs) (cf. 6.2)
- serious adverse events (SAEs) (cf. 6.3)
- selected laboratory parameters (cf. 5.1, 5.7)
- rate of secondary neoplasias

7.2.2.3 Secondary endpoints of health economic analysis

In order to evaluate the differences in direct costs between the therapy arms, the following health economic parameters will be documented:

- cumulative dose of cytostatics
- cumulative dose of rituximab
- cumulative dose of G-CSF in each patient
- days in hospital
- total number of days on which antibiotics were administered
- total number of erythrocyte and platelet concentrates
- measures provided to treat SAEs.

7.2.2.4 Secondary endpoints of adherence to protocol

- duration of cycles
- cumulative dose and dose intensity
- G-CSF dose and duration of G-CSF administration.

7.2.2.5 Secondary endpoints of consolidating radiotherapy

Relapse profile of patients with bulky disease and/or qualifying extranodal involvement that have been or not been treated with radiotherapy seperated by relapse in relapse within or without irradiated areas, or primary involvement.

7.3 Statistical phrasing of the questions to be investigated in the study and sample size calculation

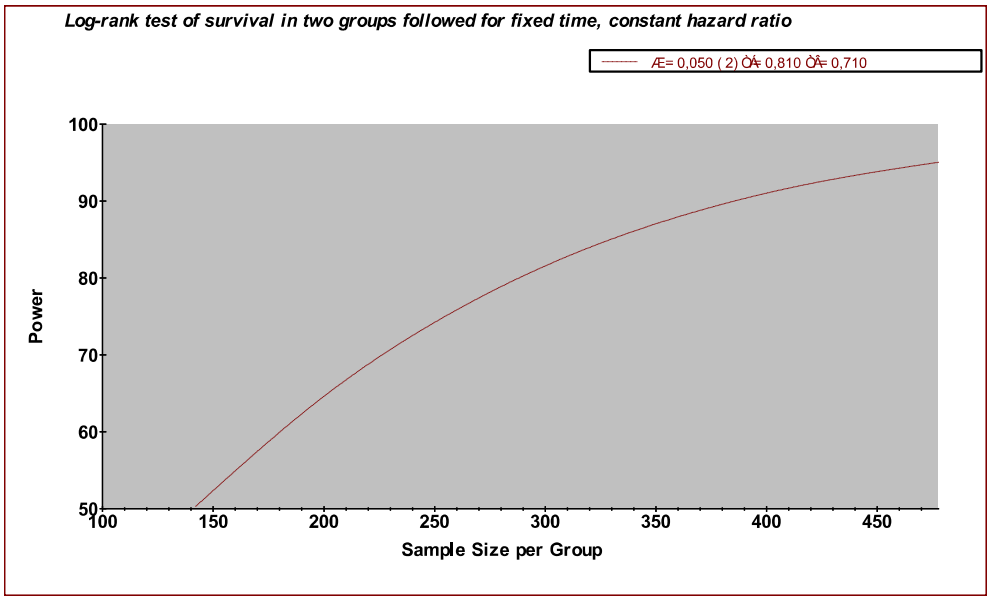
The following questions are to be investigated in this study:

1) Can the efficacy of an immuno-chemotherapy with six cycles of rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) be improved by shortening the therapy intervals from three to two weeks (6 x R-CHOP-21 vs. 6 x R-CHOP-14)?
2) Does consolidating radiotherapy of bulky disease after immuno-chemotherapy result in an improved treatment outcome?

Since it cannot be excluded that the increase in dose intensity or the administration of bulky disease radiotherapy will result in more toxicity which could compromise treatment outcome, both questions are to be investigated by using a two-sided test. In order to answer the study questions, the following statistical hypotheses will be tested:

To 1.) H_0: TTF (R-CHOP-21) = TTF (R-CHOP-14)
H_A: TTF (R-CHOP-21) ≠ TTF (R-CHOP-14)
To 2.) H_0: TTF (R-CHOP-21/14 - RX) = TTF (R-CHOP-21/14 + RX)
H_A: TTF (R-CHOP-21/14 - RX) ≠ TTF (R-CHOP-21/14 + RX)

Any detectable difference will result from failure under therapy and relapse profiles. On the basis of observed hazard rates in other study groups, estimation of tumour latency periods and of theoretical models, it is assumed that the differences between the therapy arms with respect to TTF rate should mainly become apparent in the period up to 3 years after the commencement of therapy.
From the interim analysis of the MInT study in May 2004 we know that the 3-year TTF rate in the population of ≤ 60 year-old patients as defined by this protocol in the R-CHOP-21 arm is 71%. R-CHOP-21 without RX is below that, provided that radiotherapy has a positive effect. However, if R-CHOP-14 has a positive effect, the contrast of all arms without RX will be greater. The assumption of 71% does therefore appear plausible for planning of the case number. Previous experience indicates that the demonstration of a 10% improvement in TTF rate can be seen as relevant success.
It is the aim of this study to demonstrate an improvement of the TTF rate from 71% to 81% (i.e. a constant hazard ratio of 0,615). The two-sided test will be answered with an error probability of α = 5% and a power of 80%.
In order to calculate the required sample size, a procedure developed by Freedman has been used. Calculations were performed using the software program nQuery Advisor, Version 2.0. The calculations came up with a necessary case number of 578 informative patients with bulky disease, i.e. 289 patients per contrast (-RX, +RX). The calculation of the case number is based on the assumption that there will be no drop outs for the duration of three years. If patients cannot be evaluated at the end of the study due to missing documentation, the power will be accordingly less (see figure).



From the results of the High/CHOEP study we know that the percentage of patients with bulky disease is approximately 56% of the study population. With 68% in the MInT study, it was probably estimated too high due to the exclusion of stage I non-bulky disease. So, 60% more patients should be randomised in order to answer the question regarding radiotherapy with sufficient power. 964 patients are therefore to be included in this study. There should be 10% more patients randomised in order to carry out the "per protocol" analysis (patients with confirmed reference pathology and conformity to entry criteria) with sufficient power in addition to the intention-to-treat analysis. This results in a total case number of 1072 patients.
Since the entire population of 964 patients is available for answering the question of immuno-chemotherapy of the "per protocol" analysis, this question will be answered with a power of 95%. An alpha adjustment for multiple testing of the second question will therefore be possible.

The calculation of the required sample size was based on patients with radiotherapy indication who were to be randomised into four arms i. e. patients with initial bulky disease (if not surgically removed), and/or extranodal involvement or both. Using a 2x2 factorial design it was intended to answer for these patients two study questions regarding the role of radiotherapy (RX +/-) and regarding the role of the duration of the chemotherapy cycles (14/21). The formal criterion of discontinuation regarding the radiotherapy contrast was fulfilled in this interim analysis. The two treatment arms with radiotherapy (6xR-CHOP-21+RX, 6xR-CHOP-14+RX) were significantly better compared to the two therapy arms without radiotherapy (6xR-CHOP-21-RX, 6xR-CHOP-14-RX). In a 2x2 factorial design, if a contrast is closed prematurely, the two other therapy arms will be continued and there will not be changes regarding the calculation of the required sample size unless the former base level assumption (3-year EFS) were not appropriate any more. Based on the data available at the last interim analysis, this assumption was reassessed and it was found that it still applies.

7.4 Interim analysis and criteria for early discontinuation of the study

Events occurring during the study will be continuously monitored by the investigators and the biometricians. If the criteria specified in section 3.4 are met, the Study Management Committee will decide whether to discontinue the study or not. A formal criterion of early discontinuation will be defined using the so-called "alpha spending function"[44]. In contrast to standard group sequential designs, this design allows for an adjustment to be made for the time point of the interim analysis. The method suggested by O'Brien and Fleming will be used to calculate the

"stopping boundary"[45]. This method requires almost conventional p values for the final analysis, but makes it difficult to terminate the study early for unjustified reasons.
[With 133 expected events in all, the following O'Brien-Fleming boundaries would result after $\tau_1 = 25$, $\tau_2 = 50$, $\tau_3 = 75$, $\tau_4 = 100$, $\tau_5 = 125$ events:
$\alpha(\tau_1) < 0.0000061$, $\alpha(\tau_2) = 0.0013903$, $\alpha(\tau_3) = 0.0090525$, $\alpha(\tau_4) = 0.0237975$, $\alpha(\tau_5) = 0.0432024$]
The premature discontinuation of the study will require a complex consideration of different factors. The proposed criterion of early discontinuation can therefore only initiate a decision-making process.
A conclusive interim analysis enabling an assessment of efficacy is not expected within the first two years. For that reason, the first planned interim analysis of efficacy is to take place in year 3 after the commencement of recruitment when it is assumed that approximately 40% of the expected events will have already occurred (probably in 2008). Since at the time of the first formal interim analysis 650 patients will be recruited (approximately 60% of the total collective), it is planned to conduct a further interim analysis during the recruitment phase in year 4 after commencement of recruitment. As the proposed alpha spending function is flexible with respect to the number of interim analyses conducted, the Study Management Committee can decide when to conduct further interim analyses during the ongoing study. In the first 3 years, there will only be interim analyses of therapy feasibility and protocol adherence conducted on an annual basis.
A final analysis can be performed as soon as the planned number of events that occurred has been sufficiently documented. A report on each analysis will be prepared by the responsible biometrician. The results of the final analysis will be presented in a final report. This will provide a description of the patient population for each treatment therapy arm, the feasibility of the treatment, the safety of therapy (particularly in respect of the occurrence of adverse and serious adverse events), adherence to protocol and cases of early discontinuation. The results of the analysis of efficacy and safety will also be presented. The results of the respective analyses will be presented at regular meetings of the participating investigators.

7.5 Methods to be used for analysis

7.5.1 Definition of the evaluable study population

Prior to each analysis, the data for each study subject will be evaluated by a Review Panel consisting of a physician-member of the Study Managing Committee, a biometrician and a documentation manager. The following criteria will be applied for the evaluation:

- compliance with the eligibility criteria
- confirmation of the primary diagnosis (Reference Pathology)
- adequate classification and randomisation
- complete documentation of therapy
- observation period at least 2 months after final restaging on completion of chemotherapy and availability of the completed 1st follow-up CRF
- protocol-conform treatment
- known reasons for early discontinuation.

The course of therapy, the final outcome of therapy and the time of completion of protocol-conform treatment will be documented in the Confirmation of Evaluability and signed and dated by the Review Panel. Patients for whom there is a Confirmation of Evaluability can be included in the interim evaluations of efficacy. All patients who have completed at least one documented

chemotherapy cycle (including prephase treatment) can be included in the analyses of safety and of other secondary endpoints.
All analyses will be conducted according to the intention-to-treat principle; i.e. all patients will be evaluated within the therapy arm to which they were randomly assigned. If adherence to protocol, contrary to all expectations, is worse than in the MInT study and if there is a frequent change of therapy arms, additional "per protocol" analyses and "treatment given" must be performed in order to improve the estimation of the observed therapeutic effect.
We only expect a small loss of evaluable patients due to inadequate documentation. If the loss due to inadequate documentation exceeds 10%, a sensitivity analysis will be conducted to assess the structural similarity of the evaluable and non-evaluable collectives.

7.5.2 Analysis of efficacy and safety

7.5.2.1 Primary endpoint

In a primary analysis, the log-rank test will be used to compare the two treatment strategies regarding time to treatment failure. With regard to immuno-chemotherapy, the log-rank test refers to the whole study population and patients with initial bulky disease respectively and with regard to radiotherapy it refers to the patients with initial bulky disease. Kaplan curves will be used for description of the different treatment arms. In addition, the 3-year TTF rates will be shown including a 95% confidence interval.
In a secondary analysis, a Cox multivariate regression model will be used to test if the therapy effect that emerged from the univariate analysis remains stable after adjustment for prognostic factors. In addition, interactions between therapy effect and prognostic factors (Shipp criteria and variables with prognostic relevance within this study) will be analysed in order to establish whether the treatment effect is homogeneous in the different prognostic subpopulations.It is planned to perform subgroup analyses within the IPI-groups. Moreover, gender specific analyses will be performed because the role of gender in rituximab containing regimens has come into focus while this trial was ongoing.[46]
The estimates are given in the form of a hazard ratio with a 95% confidence interval and a corresponding p value. If the assumed proportional hazard estimate proves inaccurate, more suitable methods of analysis will be considered.
During the analysis of efficacy, an overview will be prepared of the number of randomised patients and number of cases for whom the primary and secondary endpoint can be analysed. Details of the numbers of patients completing therapy, numbers of early discontinuations and of the time point of early discontinuation will be provided. The intention-to-treat population and "per protocol" population (patients who fulfil the eligibility criteria and who do have a reference pathology report) will be evaluated regarding the primary endpoint. The final analysis will be conducted in accordance with a clearly defined evaluation policy to be defined in advance.

7.5.2.2 Secondary endpoints

The consolidating radiotherapy of extranodal involvement will be evaluated analogous to the radiotherapy of bulky disease.
The CR rates and rates of primary progression will be documented, together with the corresponding 95% confidence intervals. The secondary endpoints (data on survival time) will be analysed on the analogy of the primary endpoint (cf. 7.5.2.1). For qualitative secondary endpoints, such as adverse events and serious adverse events, frequency tables will be prepared. The percentage of patients with serious adverse events will be stated. Quantitative secondary endpoints, such as laboratory parameters, cumulative doses of cytotoxics/rituximab and G-CSF, days in hospital, total number of days of administration of antibiotics, total number of transfusion of erythrocyte and platelet concentrates, duration of chemotherapy cycles and

relative dose intensity will be described in terms of location (arithmetical mean and median) and distribution (distribution and lower and upper quartile). Error bar graphs or box plots will be used for graphic representations. Secondary endpoints will also be analysed separately by therapy arm.

8 Documentation and Monitoring

8.1 Structure of the documentation dossier

The participating institutions commit themselves to ensure thorough and complete documentation of the course of the disease of each patient. After inclusion of a patient into the study, the treating physician will immediately receive a documentation dossier with the clinical report forms (CRF) from the Study Secretariat in Homburg.
The documentation dossier contains:

- certificate of randomisation
- forms for the procurement of patient´s material for accompanying research projects
- a flowchart for the study
- a list of contact persons
- instructions for completing the documentation forms
- address labels for the forwarding of the completed forms
- case report forms (excluding the Staging Report which must be submitted prior to patient randomisation) (cf. Appendix 13.14)
- forms for reporting serious adverse events
- forms for the documentation of radiotherapy where appropriate (arms ARX and BRX)

8.2 The processing of the completed documentation forms

The completed documentation forms are to be sent to the Central Study Secretariat:

Study Secretariat of the DSHNHL
Prof. Dr. M. Pfreundschuh
Medical Clinic and Outpatient Clinic
Internal Medicine I, Bldg. 40
D-66421 Homburg/Saar

The submitted documentation forms will be processed in several steps in accordance with the methods specified in the SOPs (standard operation procedures):

Step 1 (pre-checking and first monitoring):

All documentation forms will be subject to initial medical assessment by the study physician at the Study Management Centre in Homburg who will consider the following:

- deviations from study protocol
- occurrence of adverse events
- occurrence of serious adverse events (faxed SAE reports).

This will allow any medical problems to be identified at an early stage so that appropriate queries can be initiated. In addition, forms will be checked for plausibility and completeness. Whenever medical aspects are unclear, the study physician will contact the treating physician

for clarification or to obtain missing information. Any necessary corrections of the data will be made directly in the documentation forms and signed and dated by the study physician.

Step 2 (second monitoring):

All documentation forms will be registered upon arrival at the Study Management Centre in Homburg and reported events and protocol deviations will be entered into the database. Forms will be checked for completeness, plausibility and accuracy by the monitor. If necessary, requests for missing data or further information will be made in writing or by telephone to the participating institutions. Reminders will be sent out regularly for any missing documentation. The main purpose of monitoring is to ensure continuous follow-up of patients and, if necessary, patients will be requested to report to physicians of their choice. It will also be ensured that the opinions of the Reference Pathology and the Reference Radiotherapy Panels and the relevant data from the accompanying projects are obtained.

Step 3 (database, data entry):

The data provided in the pre-checked documentation forms will be entered using the prepared templates in the ORACLE database. Data quality will be controlled by means of constraints and triggers. To ensure a high level of data integrity, a "second look" verification procedure will be performed by another data manager.

Step 4 (evaluability):

When the complete documentation of therapy and the reference pathology report are available, study physician, monitor and biometrician will convene to decide on the evaluability of each individual patient and will assess the significance of any protocol violation.
Pre-checking and first monitoring of the documentation forms (step 1) will take place at the NHL Study Secretariat in Homburg (Prof. Pfreundschuh). Steps 2 and 3 will also take place at the NHL Study Secretariat in Homburg (Prof. Pfreundschuh). Step 4 (confirmation of evaluability) will be executed during the 6-monthly meetings of study physician, biometrician and data manager.

8.3 One-site monitoring

It is the duty of the Study Management Committee to verify documentation quality by random on-site checks of participating institutions ("*on-site monitoring for data source verification"*). The participating institutions commit themselves to allow "on-site monitors" access to original patient documentation (case records, laboratory sheets, original images etc.).

9 Reference evaluations

9.1 Reference Pathology Report

The members of the DSHNHL Reference Pathology Panel are:

- Prof. Rosenwald, Würzburg (Secretary of the Reference Panel)
- Prof. Hansmann, Frankfurt
- Prof. Möller, Ulm
- Prof. Müller-Hermelink, Würzburg
- Prof. Klapper, Kiel
- Prof. Stein, Berlin

The primary histological diagnosis will be made by a local pathologist on the basis of the examination of a biopsy from a completely excised lymph node. Alternatively, in cases of no nodal involvement, the diagnosis can be based on the histologic examination of the biopsy of an appropriate sample of another involved organ. The diagnosis of "aggressive Lymphoma, $CD20^{+}$" by the local pathologist justifies reporting and randomisation into the study.
Whenever possible, fresh biopsy material or least fresh (wet) material fixed in formalin should be reserved for immunological and molecular biological analysis or sent directly to the Reference Pathologist. Fresh material should be shock-frozen (liquid nitrogen) in plastic tubes filled with normal saline. Material, deep-frozen for immediate intraoperative diagnosis, can also be used for molecular biological and, to some extent, immunohistochemical analyses.
After inclusion of the patient into the study, the local pathologist who made the primary diagnosis will receive a letter from the Reference Pathologist requesting that the paraffin tissue blocks and any remaining material together with a copy of the original pathology report to be sent to one of the Reference Pathologists. The local pathologist will also be asked to fax a report sheet to the Data Centre in Leipzig containing information on which reference centre has received the material. The forwarding of the material and the coding of the diagnosis will be monitored by the Data Centre.
Without a reference-pathological diagnosis, on the basis of paraffin tissue blocks, the patient will only be evaluated according to intention-to-treat.
The submitted material will be processed in two steps by the reference pathologist:

Step 1:

On receipt of the samples, the Reference Pathologist will either confirm or disprove the diagnosis of aggressive non-Hodgkin's lymphoma. If a therapy-relevant revision of the original diagnosis is necessary, the Reference Pathologist must immediately notify the treating haematologist, the local pathologist and the Study Management Centre. The aim of this first step is to confirm the diagnosis.

Step 2:

The tissue sections selected for reference evaluation will be assessed at meetings of the members of the Reference Pathology Panel. SOPs have been prepared which stipulate the procedures for sample selection and the requirements for diagnostic consensus. The classification agreed on by the Reference Pathology Panel will be notified to the Study Management Centre and the primary pathologist.

9.2 Reference Radiotherapy Report

The members of the DSHNHL Reference Radiologist Panel are:

- Prof. Dr. Ch. Rübe, Homburg (Chairman and Coordinator)
- Dr. M. Engelhard, Essen
- Prof. Dr. H. Schmidberger, Mainz

On completion of radiotherapy, the completed Radiotherapy Report Form with the radiotherapy plan and the verification images are to be submitted to the Study Management Centre. They will be evaluated by the chairman of the Reference Radiotherapy Panel. If there is any reason to assume on the basis of the documentation that violations of the radiotherapy protocol have occurred during radiotherapy, the Reference Radiologist will contact the treating radiologist. The Reference Radiotherapy Panel will also assess all cases of relapse in order to provide a quality control.

10 Ethical aspects

This clinical study will be conducted in accordance with ICH-GCP guidelines. All participating institutions are obliged to comply with the requirements of the Declaration of Helsinki.
This protocol is subject to the 11th AMG novella since it has been submitted to the ethics committee of the medical council of Saarland on 16th of July 2004.
The draft of this study protocol was approved by the Protocol Committee of the DSHNHL and the participating institutions at the study meeting held on 18th of June 2004. The study protocol has been submitted for evaluation to the local ethics committee and the Ethics Committee of the Medical Council of Saarland (Ärztekammer des Saarlandes). The Ethics Committee will be notified immediately of any changes or amendments to this protocol (changes of dosage, prolongation of treatment duration, prolongation of the study, changes in eligibility criteria, increase in sample size, etc.). These changes or amendments shall come into force only after they have received the positive approval of the Ethics Committee. In case of accumulating severe adverse events (SAEs), the ethics committee will be notified. It will decide whether to object the continuation of a study arm or the entire study.
Participating institutions in other regions should note that they must notify their local Ethics Committee of the study and establish whether they require a separate approval. If this is the case, patients may only be included in the study if the approval of the local Ethics Committee has been obtained!

11 Administrative aspects

11.1 Data processing and archiving of data

The data provided in CRF will be entered in an Oracle database using data entry templates. During entry, data will be checked by a multiphase concept involving triggers and constraints for accuracy and consistency. The study database will be checked for errors and validated by the data base programmer in cooperation with the biometrician and the data manager and then released for use. A back-up of all data will be made on a daily basis. Grades of access authorisation will be allocated on the basis of hierarchical roles to completely prevent unauthorised access to patient data. The system in place will ensure that the anonymity of the data is maintained during the analysis. The documentation forms will be retained for at least 10 years at the Study Secretariat in Homburg. The electronically stored data will be retained for at least 20 years by the Data Centre in Leipzig. The interim and final analysis reports will be retained at the Study Secretariat in Homburg for 20 years.
The treating physicians at the participating centres should retain the study documentation (Patient Consent Forms, Patient Information Confirmation Form, completed and submitted documentation forms) until the final analysis report for the study will be prepared.

11.2 Subsequent amendments to the protocol

Any subsequent amendments to the protocol must be approved by the Protocol Committee. The Protocol Committee shall also decide when such amendments are to come into force. If major amendments to the protocol are required, i.e. modification of a therapy arm, eligibility or exclusion criteria, numbers to be recruited and duration of the recruitment phase, or should it be necessary to discontinue a therapy arm or the study as a whole, the approval of the DMSC must be obtained. The General Study Supervisory Board of the Oncology group of the German Cancer Society (Studienleitkommission im Studienhaus Onkologie der Deutschen Krebsgesellschaft) will be informed. The Ethics Committee in charge must also approve any subsequent protocol amendments. If there is no objection to proposed amendments, the participating institutions will be informed in writing. In addition, the date of approval of the amendment by the Protocol Committee, the decision of the Ethics Committee, notification of the participating institutions and the date on which the amendment came into force will be documented in the study register. The amendment will also be incorporated in the study protocol.

11.3 Finances and insurance

An application for financial support of this clinical study has been approved by the Deutsche Krebshilfe/Mildred Scheel Foundation.
All participating patients will be covered by a study subject insurance policy taken out with the Gerling-Konzern (Köln). A copy of the insurance conditions is to be handed out to the patients (cf. Appendix 0).

11.4 Publication agreements

The results of this study are to be published in internationally recognised scientific journals. The Protocol Committee shall decide on authorship. To be taken into account are the contribution with respect to study planning and the active participation in the study (to be assessed on the basis of numbers of recruited patients). Manuscripts may only be submitted for publication when all authors have approved the contents. The main author will assume that contents have been approved by the co-authors if no requests for alteration have been received from the co-authors within 2 weeks after receipt of the draft manuscript.

12 References

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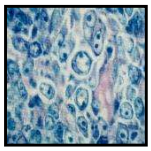
13 Appendix

13.1 Form for the declaration of participating institutions



DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN-LYMPHOME*
German High Grade Non-Hodgkin's Lymphoma Study Group

***(supported by Deutsche Krebshilfe)**

Study Secretariat of the DSHNHL Prof. Dr. M. Pfreundschuh Medical Clinic and Outpatient Department Internal Medicine I University Hospital of Saarland D-66421 HOMBURG/SAAR Tel: +49-6841-16-23084 Fax: +49-6841-16-23004	**Declaration of participating institution – I** **DSHNHL 2004-3**

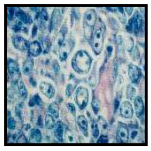
FORMAL DECLARATION OF PARTICIPATION
IN THE
THERAPY OPTIMISATION STUDY DSHNHL 2004-3
(6 x R-CHOP-21 vs. 6 x R-CHOP-14, both with or without radiotherapy)
IN AGGRESSIVE NON-HODGKIN'S LYMPHOMA

By signing this form, I herewith declare that I am willing to participate with my institution in the above-mentioned study. I confirm that I will notify the Study Management Centre, Prof. Pfreundschuh in Homburg, of all patients with the diagnosis "aggressive non-Hodgkin's lymphoma" who conform with the eligibility criteria for inclusion in the study. I will provide patients with information on the study and, assuming they consent to participate, will treat them in accordance with the study protocol and provide controlled patient follow-up.

The institution at which I am employed can provide medical oncology/chemotherapeutic treatment to patients and radiotherapy in accordance with the requirements specified in the protocol. I shall provide the appropriate collaborating personnel at my institution (pathologists, radiologists) with information on the study.

I will provide the Study Management Centre with the names of the clinical and/or documenting personnel who will act as contact persons for the Study Management Centre and who have been authorised and are obligated to coordinate all matters concerning notification of patient recruitment, documentation and follow-up at my institution. If physicians or patients should leave this institution, the Study Management Panel will be informed of who shall be responsible for the further treatment and documentation of the study subjects. The Study Management Centre will be informed of any cases of early discontinuation of therapy. We undertake to provide support for the accompanying scientific projects by supplying the respective patient materials. I consent to random on-site monitoring by the Study Management Panel in order to verify that my institution is conducting the study in accordance with protocol and will allow the required source data verification to be performed.

See Part II →



DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN-LYMPHOME*
German High Grade Non-Hodgkin's Lymphoma Study Group

***(supported by Deutsche Krebshilfe)**

Study Secretariat of the DSHNHL
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Declaration of participating institution – II
DSHNHL 2004-3

I further undertake to attend the regular meetings of the DSHNHL ("Study Meetings"), either personally or by sending a colleague of my institution as a representative, and will ensure that documentation forms are completed comprehensively and conscientiously and are forwarded to the Study Management Centre without delay.

Date:

.....
D D M M Y Y Y Y

Head of Institution:.....
(please print)

Signature .....

Institutional stamp:

Tel.: (.....).....-..... Fax: (.....).....-.....

Contact persons for study matters/Documentation supervisor(s):

Name: .....
(please print)

E-mail: .....

Tel.: (.....).....-..... Fax: (.....).....-.....

For money transfers (e.g. documentation fees):

Bank: .....

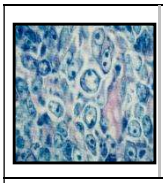
Bank code:..... Account No.:.....

A/C holder: .....

Purpose: .....

13.2 Patient Information and consent

13.2.1 Patient information on the study DSHNHL 2004-3 (UNFOLDER)



DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN-LYMPHOME*
German High Grade Non-Hodgkin's Lymphoma Study Group

***(supported by Deutsche Krebshilfe)**

Study Secretariat of the DSHNHL Prof. Dr. M. Pfreundschuh Tel in emergencies: +49-6841-16-23084 +49-6841-16-23000 (switchboard)	**Patient information - I** **DSHNHL 2004-3** **(Copy for the patient)**

Dear Patient,

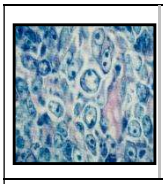
we would like to ask you for your consent to participate in a clinical study. Clinical studies are designed to improve established treatment procedures with the aim of improving the outcome of treatment.

If you suffer from certain accompanying disorders in particular from chronic viral infections (eg HIV, hepatitis), diseases of the heart, lung or kidney with significant functional impairment or tumour disease in the past, you will not be elligible to participate in this study as there might be a deterioation of your accompanying disorder or increased side effects from chemotherapy.

Your treating physician has informed you that you have aggressive 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), sometimes in combination with radiotherapy. 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 shorten the interval between the courses of chemotherapy which is known to be effective. As your lymphoma cells have the CD20 structure on their surface, they are amenable to immunotherapy with rituximab, a specific antibody, which is directed against the CD20 structure on the surface of many malignant lymphoma cells. The antibody is capable of recognizing and attaching to those cells and thus activating mechanisms of the immune system which can lead to the destruction of the target cells. Rituximab probably enhances the effectiveness of chemotherapy without increasing side effects.

In this trial it was also investigated whether subsequent radiotherapy – at the end of chemotherapy- in cases of bulky disease (above 7.5 cm, so called "bulk") and/or extranodal lymphoma involvement results in a further improvement of treatment outcome. A planned interim analysis in July 2012 showed that this additional radiotherapy improves treatment results highly significantly. Therefore, since July 2012, all patients with bulky disease and/or extranodal involvement receive additional radiotherapy to these sites of involvement.

See Part II ➔



DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN-LYMPHOME*
German High Grade Non-Hodgkin's Lymphoma Study Group

***(supported by Deutsche Krebshilfe)**

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Patient information - II
DSHNHL 2004-3

(Copy for the patient)

The purpose of this treatment optimisation study

In recent years the cure rates of patients with aggressive lymphoma have been improved through an intensification of chemotherapy. A further increase in chemotherapy does not seem possible as such increase will result in an increase in the number and severity of side effects. The German High-Grade Non-Hodgkin's Lymphoma Group and their partners have designed a scientific study in order to investigate whether the shortening of treatment intervals from three to two weeks using a CHOP chemotherapy, which is currently being considered the standard treatment, results in an improved treatment outcome. Sufficient experience from previous investigations (NHL-B1 study of the DSHNHL) is available showing that the shortening of treatment intervals of CHOP is safe and does not increase side effects.

Since it is not known whether the shortening of treatment intervals is advantageous, two treatment arms (6 x R-CHOP-21 and 6 x R-CHOP-14 (shortened interval) each with additional radiotherapy to bulky disease and/or extranodal involvement, must by randomly compared.

In case of your consent to this study, you will be randomly assigned to one of the two treatment arms. Your doctor will have no influence on this random selection.

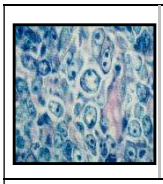
Study procedures

You will receive a combination of cytotoxic immunochemotherapy that is currently considered the most effective from a scientific point of view (6x R-CHOP). In case of bulky disese and/or extranodal involvement with additional radiotherapy to the respective sites will be given. Depending on the result of randomisation you will receive this therapy either every 3 weeks (R-CHOP-21) or every 2 weeks (R-CHOP-14). This R-CHOP regimen involves the administration of the substances cyclophosphamide, doxorubicin, vincristine and prednisone, as well as the monoclonal anti-CD20 antibody rituximab. If the size of your lymphoma is lager than 7.5 cm and/or if there is an extralymphatic involvement you will receive additional radiotherapy on these localisations after chemotherapy.

If a testis is involved a prophylactic radiotherapy to the contralateral testis should be given.

The immunochemotherapy is administered every 21 or 14 days. The study will commence in October 2005 and, with the follow-up procedures, will continue at least until September 2017. A total of 1027 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.

See Part III →



DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN-LYMPHOME*
German High Grade Non-Hodgkin's Lymphoma Study Group

***(supported by Deutsche Krebshilfe)**

Study Secretariat of the DSHNHL
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Patient information - III
DSHNHL 2004-3

(Copy for the patient)

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 case of testicular involvement, it is also necessary to perform so-called lumbar punctures to investigate. 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. During the treatment phase, weekly full blood counts (haemoglobin, leukocytes, platelets) are necessary. This is mandatory for any chemotherapy of lymphoma and can be performed by your general practitioner. On completion of treatment, you will be examined every 3 months in the first 2 years and every 6 months in years 3 to 5. The observation period within the study will last for 3 years starting from the time of final restaging on completion of chemotherapy. Afterwards, livelong follow-up will be provided on a voluntary basis. 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.

If indicated, radiotherapy will be administered on completion of chemotherapy.

Responsibilities of patients

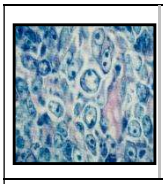
If you do decide to participate in this study you will be required to cooperate with the study physician and will be expected to comply with the following:

- 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.

Pregnancy

In view of the teratogenic properties of chemotherapy and missing data regarding the teratogenic effect of rituximab, a pregnancy must be excluded in younger women. Reliable contraception must be carried out during treatment and until 12 months afterwards. This applies to female and male patients. If you or your partner become pregnant in the course of the study or up to 12 months thereafter you must inform your doctor immediately.

See Part IV →



DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN-LYMPHOME*
German High Grade Non-Hodgkin's Lymphoma Study Group

***(supported by Deutsche Krebshilfe)**

Study Secretariat of the DSHNHL
Prof. Dr. M. Pfreundschuh

Tel in emergencies: +49-6841-16-23084
+49-6841-16-23000 (switchboard)

Patient information - IV
DSHNHL 2004-3

(Copy for the patient)

Risks

The treatment is associated with drug-specific side effects. The possible side effects of the proposed treatments are:

Cyclophosphamide: nausea and vomiting, suppression of blood cell production resulting in reduced numbers of blood cells (thus increasing the risk of infection, bleeding and anaemia), loss of hair, inflammation of the mucous membranes, bladder, and intestines; allergic reactions..

Doxorubicin: nausea and vomiting, suppression of blood cell production resulting in reduced numbers of blood cells (thus increasing the risk of infection, bleeding and anaemia), loss of hair, damage to the heart muscle, tissue damage (ulcers, necrosis) at sites of inappropriate injection (extravasation) of chemotherapeutic substances, inflammation of the mucous membranes, allergic reactions.

Vincristine: nausea and vomiting, damage to nerves, loss of hair, damage after inappropriate injection (extravasation) of chemotherapeutic substances, allergic reactions.

After *Prednisone*: agitation, gastric disorders, increase of appetite, osteoporosis, myopathy, steroid-induced diabetes mellitus.

You should not consume alcoholic drinks during chemotherapy treatment.

Radiotherapy: infertility, dysfunction of the Leydig cells of the testes, nausea, retching, problems with swallowing, headache, fatigue, low white blood or platelet count, anaemia, alterations to skin and loss of hair in the irradiated region. Also possible are radiation-related reactions of the lungs (laboured breathing), of the intestines (diarrhoea) and of the pericardium (effusion).

Rituximab 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.

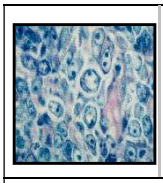
It is necessary to administer the growth factor G-CSF in order to enable the recovery of leukocytes, particularly under R-CHOP-14, so that the next chemotherapy cycle can be given on time. Bone pain, elevated temperature and an elevated LDH can happen *under G-CSF*.

After immuno-chemotherapy or radiotherapy there may be temporary impairment of the ability to drive a car 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 which preceeds the actual R-CHOP chemotherapy cycles is recommended.

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.

See Part V ➔



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Patient information - V
DSHNHL 2004-3

(Copy for the patient)

At the beginning of chemotherapy, rapid destruction of bulky disease can result in elevated blood levels of uric acid. You will therefore receive a tablet of allopurinol (300 mg) daily already before the beginning of therapy. Depending on the level of uric acid, it may be indicated to continue this treatment during subsequent chemotherapy cycles. 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. In case of a drop in leukocytes below 1000/µl, oral care (e.g. Hexetidin, Amphothericin B) after each meal is recommended. In case of a big drop in leukocytes, your doctor will prescribe you antibiotics (e.g. ciprofloxacin 500 mg twice daily) in order to prevent an 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 erythrocytes (red blood cells), more rarely platelets. Although products are carefully checked prior to use, there is still a slight risk of transmission of infection through these procedures.

Possible benefits of the study treatment

If the shortening of cycle duration from 21 to 14 days results in an improved response to treatment and prolongation of disease-free period, this may be of benefit to you. It is not possible to predict 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. This can only be achieved by comparing it with the treatment which is currently held to be optimal.

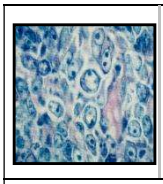
Alternative treatments

If you decide not to participate in this study, you will receive a standard immunochemotherapy (six cycles R-CHOP-21), but you are also free to choose your treatment. The medical care you receive in the future will in no way be influenced by your decision not to participate in this clinical study.

Additional information

The protocol of this clinical study has been approved by the Ethics Committee of the Medical Council of Saarland regarding ethical and professional legal issues on 30.09.2004. 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.

See Part VI →



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Patient information - VI
DSHNHL 2004-3

(Copy for the patient)

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 physician 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 German Drug Law (AMG), a patient insurance policy has been taken out for your benefit with the

Gerling-Konzern, Theodor Heuss-Allee 108, 60486 Frankfurt, tel: +49-69-7567-466 (policy no 70-005868405-2)

for 3 years after final restaging on completion of chemotherapy.

To ensure that you retain insurance cover, you must comply with the following:

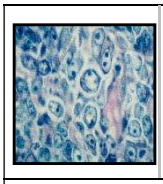
You should receive other medical treatment (except in emergencies) only with the approval of the study physician.

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 immediately, if possible the study physician (i.e. the doctor who is responsible for your treatment) and the Study Management Committee as well. You need to 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 General Practitioner

Assuming that you have no objections, your general practitioner will be informed that you are participating in this clinical study. If you wish the necessary blood tests are performed by your general practitioner, he will be informed of the recommended tests (haemoglobin, leukocytes, platelets- how often) by the study physician.

See Part VII ➔



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Patient information - VII
DSHNHL 2004-3

(Copy for the patient)

Discontinuation of the trial

Your local investigator, the principal investigator, the independent ethics committee located at this facility or other health authorities are at any time allowed to discontinue this study or your participation in this study due to any reason and without your consent.

Reasons for discontinuation of the study could be:

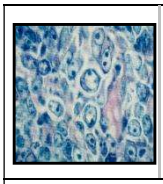
- by the patient: withdrawing his/her informed consent to participate in the trial
- by the local investigator (your treating physician): if he/she diagnoses your further participation is medically inacceptable
- by the principal investigator: if due to new results ermerging during the regularily performed interim analyses a continuation of the clinical study is not justified any more. In this case you will be informed about the results.

Confidentiality of documents

All data collected on individual patients during the study will be sent to the Data Centre in Leipzig (Institute for Medical Informatics, Statistics and Epidemiology). 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 obliged 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.

Please fill out the form: 'Data of the informing physician' ➔

13.2.2 Data of the informing physician



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German High Grade Non-Hodgkin's Lymphoma Study Group

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Study Secretariat of the DSHNHL Prof. Dr. M. Pfreundschuh Tel in emergencies: +49-6841-16-23084 +49-6841-16-23000 (switchboard)	**Patient information** **Informing doctor** **DSHNHL 2004-3** **(Copy for the patient)**

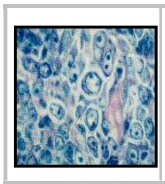
Doctor	
Surname:	
First Name:	
Practice / Institution	
Street + No.	
Post Code + Town:	
Telephone:	
Fax:	

Stamp of practice / institution:

Thank you for your cooperation.

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

13.3 Protocol of patient information and consent



DEUTSCHE STUDIENGRUPPE HOCHMALIGNE NON-HODGKIN-LYMPHOME*
German High Grade Non-Hodgkin's Lymphoma Study Group

***(supported by Deutsche Krebshilfe)**

-to keep-	**Protocol of patient information and consent (Prof. Dr. M. Pfreundschuh)** **DSHNHL 2004-3**

Patient's Name:

Surname: First Name: Date of Birth: _____

D D M M Y Y Y Y

The patient was provided with information on:

1. The nature of the disease
2. The prognosis of the disease if treatment is provided in conformity with protocol
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:* 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, side effects due to corticosteroids.
   After radiotherapy: nausea, retching, problems with swallowing, headache, fatigue, leukoctopenia (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, elevated body temperature.
   After administration of the rituximab antibody: fever, chills, muscle and joint pain, fall in blood pressure, skin rash, in rare cases allergic reactions with shock in extreme cases.
5. Reliable contraception during treatment and for 12 months afterwards including female and male patients
6. Data transfer (data protection)
   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 his/her case is received for a period of 1 year.
7. Patient's freedom of choice
   This patient has freedom to decide whether to participate in the study or not.
8. Patient's decision: ○ wishes to participate ○ does not wish to participate

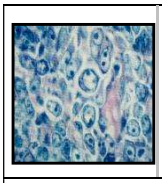
Doctor:

....
Function Date Signature

Patient:

....
Date Signature

13.4 Patient informed consent form



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German High Grade Non-Hodgkin's Lymphoma Study Group

***(supported by Deutsche Krebshilfe)**

Study Secretariat of the DSHNHL Prof. Dr. M. Pfreundschuh Dept. of Internal Medicine I University of Saarland Medical School D-66421 HOMBURG/SAAR Tel: +49-6841-16-23084 Fax: +49-6841-16-23004	**Patient informed consent form – I** **DSHNHL 2004-3** **(Original for the doctor)** **(Copy for the patient)** **(Copy to the Study Secretariat)**

I, surname: ---------- first name: ----------

born on: ----------

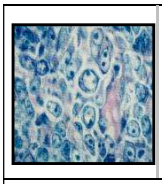
have been informed by the treating doctors in a detailed discussion that I have aggressive non-Hodgkin's lymphoma, a malignant disease of the lymphoid system, which can be cured in many cases with cytotoxic drugs (cell poisons) + immunotherapy, and if applicable radiotherapy. I have been informed that a clinical study is currently being conducted with the aim of improving the efficacy of chemotherapy with six cycles of R-CHOP-21 by shortening the duration of cycles. There is a theoretical possibility that the efficacy of treatment is higher when the cycles are shortend from 21 to 14 days. It cannot be excluded that there will be more severe effects. All medications to be administered have been approved by the BfArM/EMEA for use in the treatment of non-Hodgkin's lymphoma.

I have been informed of the purpose of this 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, obliged 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 Centre 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 general practitioner 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.

See Part II ➔



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Dept. of Internal Medicine I
University of Saarland Medical School
D-66421 HOMBURG/SAAR
Tel: +49-6841-16-23084
Fax: +49-6841-16-23004

Patient informed consent form – II
DSHNHL 2004-3

(Original for the doctor)
(Copy for the patient)
(Copy to the Study Secretariat)

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. 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 and this data to be stored for scientific evaluation.

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 material obtained will remain at my disposal. No additional tissue or blood tests will be conducted beyond those required for medical reasons.

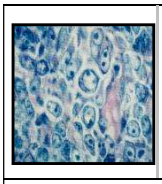
I further agree to the storing of personal data obtained in connection with tissue samples by the pathology register of the lymphoma joint project.

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 have been given to me.

I consent to being contacted directly by the Study Management Centre if no monitoring examination is performed in my case for the period of 1 year. The Study Management Centre may request that I attend an examination to be conducted by a doctor of my choice.

See Part III ➔



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University of Saarland Medical School
D-66421 HOMBURG/SAAR
Tel: +49-6841-16-23084
Fax: +49-6841-16-23004

Patient informed consent form – III
DSHNHL 2004-3

(Original for the doctor)
(Copy for the patient)
(Copy to the Study Secretariat)

Doctor: Post: .....

Date: _____ Signature: .....
D D / M M / Y Y Y Y

Stamp of practice / institution:

Witness: .....

Date: _____ Signature: .....
D D / M M / Y Y Y Y

Patient:

Surname: ..... First Name: .....
(please print)

Date of Birth: _____
D D / M M / Y Y Y Y

Adress of Patient:

Street: .....

Post Code: _____ Town: _____

Date: _____ Signature: .....
D D / M M / Y Y Y Y

13.5 Addresses of the members of the Protocol Committee and the DSMC

Name	Institution	Adresse
Prof. Dr. M. Bentz	Städtisches Klinikum Karlsruhe Medizinische Klinik II	Moltkestr. 90 76133 Karlsruhe
Prof. Dr. G. Brittinger	Universitätsklinikum Essen Zentrum für Innere Medizin	Hufelandstr. 55 45147 Essen
Prof. Dr. G. Borchmann	Klinik I für Innere Medizin Hämato-Onkol. Ambulanz	Kerpener Str. 62 50937 Köln
PD Dr. A. Buck	Klinikum rechts d. Isar	Ismaninger Str. 22 81675 München
Prof. Dr. A. Bücker	Universitätsklinikum des Saarlandes Klinik für Radiologie	66421 Homburg
Prof. Dr. V. Diehl	Universitätsklinik Köln Klinik I für Innere Medizin	Joseph-Stelzmannstr. 9 50924 Köln
PD Dr. M. Dreyling	LMU München Klinikum Großhadern Medizinische Klinik 3	Marchioninistr. 15 81377 München
Dr. M. Engelhard	Universitätsklinikum Essen Strahlentherapie	Hufelandstr. 55 45147 Essen
PD Dr. N. Frickhofen	Zentrum Innere Medizin, Innere Medizin III Hämatologie/Onkologie Dr. Horst-Schmidt-Kliniken GmbH	Ludwig-Erhard-Str. 100 65199 Wiesbaden
Prof. Dr. B. Glass	Allgemeines Krankenhaus St. Georg Abteilung Hämatologie	Lohmühlenstraße 5 20099 Hamburg
PD Dr. M. Hänel	Klinikum Chemnitz gGmbH Krankenhaus Küchwald Klini f. Innere Med. III	Bürgerstr. 2 09009 Chemnitz
Prof. Dr. F. Hartmann	Klinikum Lippe-Lemgo Medizinische Klinik II	Rintelnerstr. 85 32657 Lemgo
Prof. Dr. K. Havemann	Universitätsklinikum Marburg Abteilung für Hämatologie	Baldingerstr./ Lahneberge 35043 Marburg
Prof. Dr. R. Herrmann	Abteilung für Onkologie Kantonsspital	CH 4023 Basel
PD Dr. G. Held	Universitätsklinikum d. Saarlandes Med. Klinik u. Poliklinik Innere Med. I	66421 Homburg
Prof. Dr. D. Hellwig	Universitätsklinikum d. Saarlandes Klinik für Nuklearmedizin	66421 Homburg
Prof. Dr. U. Kaiser	II. Medizinische Klinik St. Bernward Krankenhaus	Treibestr.9 31132 Hildesheim
Prof. Dr. C.-M. Kirsch	Universitätsklinikum d. Saarlandes Klinik für Nuklearmedizin	66421 Homburg

Name	Institution	Adresse
Prof. Dr. W. Knauf	Gemeinschaftspraxis Dres.Klippstein/Grunewald/ Tesch/Knauf	Im Prüfling 17-19 60389 Frankfurt/Main
Dr. P. Koch	Med. Klinik A der Universitätsklinik Münster	Albert-Schweitzer-Str. 33 48149 Münster
PD Dr. E. Lengfelder	Universitätsmedizin Mannheim III. Med. Universitätsklinik	Theodor-Kutzer-Ufer 1-3 68167 Mannheim
Dr. R. Liersch	Universitätsklinikum Münster Med. Klinik u. Poliklinik A Hämatologie/Onkologie	Albert-Schweitzer-Str. 33 48129 Münster
Dr. W. Lindemann	Kath. Krankenhaus Hagen St.-Josefs/St.-Marien-Hospital	Bergstr. 56 58095 Hagen
Prof. Dr. M. Löffler	Institut für Medizinische Informatik, Statistik und Epidemiologie	Härtelstr. 16-18 04107 Leipzig
Dr. B. Metzner	Klinikum Oldenburg Abt. Hämatologie/Onkologie	Rahel-Straus-Str. 10 26133 Oldenburg
Dr. M. Nickelsen	Allgemeines Krankenhaus St. Georg Abteilung Hämatologie	Lohmühlenstraße 5 20099 Hamburg
Dr. N. Peter	Carl-Thiem-Klinikum Cottbus Med. Klinik II Hämatologie/Onkologie	Thiemstr. 111 03048 Cottbus
Prof. Dr. M. Pfreundschuh	Universitätsklinikum des Saarlandes Medizinische Klinik und Poliklinik Innere Medizin I	Kirrberger Str. 66424 Homburg
Viola Pöschel	Universitätsklinikum des Saarlandes Med. Klinik u. Poliklinik Innere Med. I	66421 Homburg
Prof. Dr. A. Rosenwald	Universität Würzburg Institut f. Pathologie	Josef-Schneider-Str. 2 97080 Würzburg
Dr. Ch. Rudolph	DRK Kliniken Berlin Köpenick Medizinische Klinik II Schwerpunkt Gastroenterologie	Salvator-Allende-Straße 2 12559 Berlin
Prof. Dr. Ch. Rübe	Klinik für Strahlentherapie und Radioonkologie der Radiologischen Universitätsklinik Gebäude 49	66421 Homburg/Saar
Prof. Dr. H. Schmidberger	Universitätsklinikum Mainz Klinik und Poliklinik für Radioonkologie	Langenbeckstr.1 55131 Mainz
PD Dr. R. Schmits	Praxis für Onkologie	Am Ludwigsberg 86 66113 Saarbrücken
Prof. Dr. N. Schmitz	Allgemeines Krankenhaus St. Georg Abteilung Hämatologie	Lohmühlenstraße 5 20099 Hamburg
Prof. Dr. J. Schubert	Evangelisches Krankenhaus Med. Klinik	Werler Str. 110 59063 Hamm

Name	Institution	Adresse
PD Dr. S. Stilgenbauer	Universitätsklinikum Ulm Innere Med. III	Albert-Einstein-Allee 23 89081 Ulm
Prof. Dr. L. Trümper	Zentrum Innere Medizin Abt. Hämatologie/Onkologie Universitätsklinik Göttingen	Robert-Koch-Str. 40 37075 Göttingen
PD Dr. U. Wedding	Universitätsklinikum Jena Klinik u. Poliklinik für Innere Med. II	07740 Jena
PD Dr. M. Witzens-Harig	Ruprecht-Karls-Universität Heidelberg Med. Klinik Abt. Innere Medizin	Im Neuenheimer Feld 410 69120 Heidelberg
Prof. Dr. G. Wulf	Zentrum Innere Medizin Abt. Hämatologie/Onkologie Universitätsklinik Göttingen	Robert-Koch-Str. 40 37075 Göttingen
Dr. rer.-nat. S. Zeynalova	Institut für Med. Informatik, Statistik u. Epidemiologie	Härtelstr. 16-18 04107 Leipzig
Dr. rer.-nat. M. Ziepert	Institut für Med. Informatik, Statistik u. Epidemiologie	Härtelstr. 16-18 04107 Leipzig

13.8 Definitions – stage and extranodal involvement

13.8.1 Staging

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

Stages:[41]

Stage I	N	nodal involvement in one region
	E	presence of one localised extralymphatic focus
Stage II	N	nodal involvement in two or more regions on one side of the diaphragm
	N, E	presence of one or more nodal involvements in regions and one localised extralymphatic focus on one side of the diaphragm
Stage III	N	nodal involvement in two or more regions on both sides of the diaphragm
	N, E	presence of one or more nodal involvements in regions and one localised extralymphatic focus on both sides of the diaphragm
Stage IV	E	• exclusive disseminated involvement of one or more extralymphatic foci (several involvements in one E-location also count as disseminated) • or disseminated E-involvement (more than one E-involvement) • or several lokalised extralymphatic foci at sites which cannot be treated using radiotherapy. • Involvement of the liver and/or bone marrow is always stage IV,E
	N, E	IV,E with additional involvement in lymphatic regions

Paired Organs count as one E-involvement (age-adjusted IPI).

13.8.2 Extranodal involvement (E)

Involvement of extralymphatic tissue, due to direct growth of an involved lymph node or because of close anatomical association.

Each of the following count as one E-involvement within the age-adjusted IPI: bone marrow, spleen, lung, liver, bone, pleura, pericard, CNS, stomach, small bowel, large bowel and further E-involvements (see code):

Exception:
- Skin and soft tissue involvement: each involvement counts
- bone involvement: involvements supra- and infradiaphramatic count as two involvements

Codes for extranodal 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
ST	soft tissues (including muscles, connective tissue and fat tissue)
ASC	ascites
WR	Waldeyer ring including tonsils
OTH	other, please write out

13.8.3 Definitions of general symptoms

Stages I to IV should be suffixed

- suffix B, if one or more of the following general symptoms are present, and suffixed
- suffix 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.

13.9 Definition of bulky disease

Bulky disease is present if:

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

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

13.10 Definition – Performance status according to the ECOG scale

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

13.11 International Prognostic Index

The International Prognostic Index (IPI) designed by [Shipp 1993] is based on five prognostic factors. These include:

age	≤ 60 years vs. > 60 years
LDH value	≤ upper reference value vs. > upper reference value
stage	I,II vs. III,IV
number of extranodal involvements	≤ 1 vs. > 1
performance status	ECOG 0,1 vs. ECOG 2-4

The age-adjusted IPI for patients aged ≤ 60 years includes:

- the LDH value
- stage
- performance status.

13.12 List of reference centres for the pathology of lymphnodes for the study DSHNHL 2004-3 (UNFOLDER)

Prof. Dr. med. A. C. Feller Institut für Pathologie, Universitätsklinikum Schleswig-Holstein, Campus Lübeck Ratzeburger Allee 160 D-23538 Lübeck	Tel: 0451/500 2705 Fax: 0451/500 3328 E-Mail: feller@patho.uni-luebeck.de
Prof. Dr. med. M.-L. Hansmann Senckenbergisches Institut für Pathologie, Universität Frankfurt Theodor-Stern-Kai 7 D-60596 Frankfurt	Tel: 069/6301 5364 Fax: 069/6301 5241 E-Mail: m.l.hansmann@em.uni-frankfurt.de
Prof. Dr. med. W. Klapper Institut für Pathologie Sektion Hämatopathologie und Lymphknotenregister der Universität Kiel Michaelisstraße 11 D-24105 Kiel	Tel: 0431/597 3399 Fax: 0431/597 3426 E-Mail: w.klapper@path.uni-kiel.de
Prof. Dr. med. P. Möller Pathologisches Institut, Universität Ulm Albert-Einstein-Allee 11 D-89081 Ulm	Tel: 0731/502 3321 Fax: 0731/502 3884 E-Mail: peter.moeller@medizin.uni-ulm.de
Prof. Dr. med. A. Rosenwald Pathologisches Institut, Universität Würzburg Josef-Schneider-Str. 2 D-97080 Würzburg	Tel: 0931/201 47424 Fax: 0931201 47440 E-Mail: rosenwald@mail.uni-wuerzburg.de
Prof. Dr. med. H. Stein Pathodiagnostik Berlin Komturstraße 58-62 D-12099 Berlin	Tel: 030/2360 842 10 Fax: 030/2360 842 19 E-Mail: h.stein@pathodiagnostik.de

13.13 Definitions – NCI-CTC Toxicity criteria

Key: V: Common Toxicity Criteria (CTC): Classification of acute side effects of chemotherapy and radiotherapy
C: Definition applicable to side effects of chemotherapy only
R: Definition applicable to side effects of radiotherapy only
■: Modification of phase I/II study group of the AIO ♦: Modification of the ARO

	Toxicity/Degree	0 = "None"	1 = "Slight"	2 = "Moderate"	3 = "Severe"	4 = "Life-threatening"
[1]	Laboratory values	N	N = Normal range			
	Haematology					
01.01	Haemoglobin (g/100 ml)	≥ 11.0	10.0 - 10.9	8.0 - 9.9	6.5 - 7.9	< 6.5
01.02	Leukocytes (x 10^9/l)	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
01.03	Granulocytes (x 10^9/1)	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
01.04	Platelets (x 10^9/1)	> 100.0	75.0 - 99.9	50.0 - 74.9	25.0 - 49.9	< 25
01.05	Lymphocytes (x 10^9/1)	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
	Blood coagulation					
01.06		N	0.99 x N - 0.75 x N	0.74 x N - 0.50 x N	0.49 x N - 0.25 x N	≤ 0.24 x N
01.07	Fibrinogen	N	1.01 x N - 1.25 x N	1.26 x N - 1.50 x N	1.51 x N - 2.00 x N	> 2.00 x N
01.08	Prothrombin time Partial thromboplastin time	N	1.01 x N - 1.66 x N	1.67 x N - 2.33 x N	2.34 x N - 3.00 x N	> 3.00 x N
	Kidney/bladder					
01.09	Creatinine	N	N - 1.5 x N	1.6 x N - 3.0 x N	3.1 x N - 6.0 x N	> 6.0 x N
01.10	Proteinuria (g/l)	None	< 3	3 - 10	> 10	Nephrotic Syndrome
01.11	Urea (mg %)	< 20	21 - 30	31 - 50	> 50	- -
	Liver					
01.12	Bilirubin	N	- - -	N - 1.5 x N	> 1.5 x N - 3.0 x N	> 3.0 x N
01.13	Transaminases (SGOT/PT)	N	N - 2.5 x N	2.6 x N - 5.0 x N	5.1 x N - 20.0 x N	> 20.0 x N
01.14	Alkaline phosphatase	N	N - 2.5 x N	2.6 x N - 5.0 x N	5.1 x N - 20.0 x N	> 20.0 x N
	Metabolism					
01.15	Hyperglycaemia (mg/dl)	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
01.16	Hypoglycaemia (mg/dl)	> 64	55 - 64	40 - 54	30 - 39	< 30 or hypoglycaemia shock
01.17	Amylase	N	N - 1.5 x N	1.6 x N - 2.0 x N	2.1 x N - 5.0 x N	> 5.0 x N
01.18	Hypercalcaemia (mmol/l)	< 2.65	2.65 - 2.87	2.88 - 3.12	3.13 - 3.37	> 3.37
01.19	Hypocalcaemia (mmol/l)	> 2.1	2.1 - 1.95	1.94 - 1.75	1.74 - 1.51	≤ 1.50
01.20	Hypomagnesaemia (mmol/l)	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤ 0.5
01.21	■ Hyponatraemia (mmol/l)	> 135	131 – 135	126 – 130	121 – 125	≤ 120
01.22	■ Hypokalaemia (mmol/l)	> 3.5	3.1 – 3.5	2.6 - 3.0	2.1 – 2.5	≤ 2.0

	Toxicity/Degree	0 = "None"	1 = "Slight"	2 = "Moderate"	3 = "Severe"	4 = "Life-threatening"
[2]	Gastrointestinal tract					
02.01	Nausea	None	Slight; normal food intake possible	Moderate; food intake reduced	Severe; no food intake possible	
02.02	Vomiting	None	Mild (1 times/day)	Moderate (2 - 5 times/day)	Severe (6 - 10 times/day)	Life-threatening (>10 times/day) or parenteral nutrition
02.03	Diarrhoea	None	Slightly elevated in comparison to usual (2 - 3 stools /day)	Moderately elevated (4 - 6 stools/day) or night stools or moderate spasms	Highly elevated (7 - 9 stools/day) or incontinence or severe spasms	Life-threatening (≥10 stools/day) or bloody diarrhoea
02.04	Stomatitis	None	Mild inflammation, erythema or painless erosions	Moderately painful erythema, oedema or erosions; solid nutrition possible	Very painful erythema, oedema or ulceration; liquid nutrition required	Enteral or parenteral nutrition required
02.05	■ Oesophagitis/Dysphagia	None	Mild inflammation, erythema or painless erosions	Moderately painful erythema, oedema or erosions or moderate dysphagia; no analgesics required	Very painful dysphagia, oedema or ulceration; none solid food intake possible or analgesics required	Complete obstruction or perforation; enteral or parenteral nutrition
02.06	■ Gastritis/ulcer	None	Mild; treatable with antacids	Moderate; forced or conservative therapy required	Severe, resistant to therapy; requires surgical procedures	Perforation or bleeding
02.07	■Obstruction of small intestine	None	-	Intermittent; no therapy required	Non-surgical intervention required	Operation required
02.08	■ Intestinal fistula	None	-	Present; no therapy required	Non-surgical intervention required	Operation required
02.09	■ Constipation	None	Mild constipation	Moderate constipation	Severe constipation, onset of subileus	Ileus > 96 h
2.10C 2.10R	■ Mucous membranes / ♦ Mucositis (RTOG)	N	Mild erythema, coating or pain; no therapy required	Patchy, serosanguineous mucositis or pain without narcotic requirement	Confluent fibrinous mucositis, ulcerations or narcotics for pain treatment required	Necrosis, deep ulceration or bleeding; parenteral nutrition

	Toxicity/Degree	0 = "None"	1 = "Slight"	2 = "Moderate"	3 = "Severe"	4 = "Life-threatening"
2.11R	♦ Salivary glands (RTOG)	N	Mild dry mouth or taste perversion, viscous saliva; normal nutrition possible	Moderate dry mouth or taste perversion, saliva very viscous; solid to mushy nutrition possible	Complete dry mouth, complete loss of taste; liquid nutrition required	Acute necrosis, deep ulceration; parenteral nutrition / PEG
[3]	**Heart/circulation**					
03.01	Arrhythmia	None	Transient; no therapy required	Occurs repeatedly or is persistent; no therapy required	Persistent; therapy required	Ventricular tachycardia or fibrillation; monitoring required
03.02	Function (N = original volume)	N	Reduction in left ventricular ejection fraction by <20 % of N	Reduction in left ventricular ejection fraction by ≥20 % of N	Mild congestive heart failure; responsive to therapy	Severe congestive heart failure; non-responsive to therapy
03.03	Ischaemia	None	Asymptomatic, unspecific T –wave suppression	Asymptomatic, clear ST - and T – wave alterations → ischaemia	Moderate clinical symptoms, angina pectoris without evidence of infarction	Life-threatening symptoms, acute infarction
03.04	Pericardium	N	Asymptomatic effusion; no intervention required	Pericarditis symptoms, rubbing, chest pain, ECG alterations	Symptomatic pericardial effusion; drainage or specific therapy required	Pericardial tamponade; immediate drainage required
03.05	Other	-	Mild	Moderate	Severe	Life-threatening
03.06	Hypertension (D = diastolic blood pressure in mmHg)	None	Transient increase: RR >20 (D) or to RR >150/100	Repeated/persistent increase: RR >20 (D) or to RR >150/100	Severe/persistent increase; antihypertensive therapy required	Life-threatening increase; hypertensive crisis
03.07	Hypotension	None	Mild; no therapy required (temporary therapy possible)	Moderate; volume substitution or other therapy required, no hospital therapy	Severe; hospital therapy required to ensure normalisation within 48 hours	Hospital therapy required. Not normalised after 48 hours
03.08	■ Phlebitis/thrombosis /embolism	None	- -	Superficial thrombophlebitis	Deep phlebothrombosis	Infarction (cerebral, hepatic, pulmonary or other) or lung embolism
03.09	■ Oedema	None	Only in the evening	Over whole day; no special therapy required	Over whole day; special therapy required	Generalised anasarca

DSHNHL 2004-3 Version 4.0 of 22 November 2012 104

	Toxicity/Degree	0 = "None"	1= "Slight"	2 = "Moderate"	3 = "Severe"	4 = "Life-threatening"

DSHNHL

[4]	**Lung/respiratory organs**					
04.01	Dyspnoea	None	No symptoms, pathological lung function test	Dyspnoea under severe stress	Dyspnoea under normal stress	Dyspnoea at rest
04.02	■ Blood gasses (in mmHg)	pO_2:>85 pCO_2: ≤ 40	pO_2: 71 - 85 or pCO_2: 41 - 50	pO_2: 61 - 70 or CO_2:51 - 60	pO_2: 51 - 60 or pCO_2: 61 - 70	$p0_2$: ≤ 50 or pCO_2 > 70
04.03	■ Lung function	> 90 %	76 - 90 % of baseline	51 - 75 % of baseline	26 - 50 % of baseline	≤ 25% of baseline
04.04	■ Lung fibrosis	None	X-ray signs without symptoms	-	X-ray signs with symptoms	-
04.05	■ Pulmonary oedema	None	X-ray signs without symptoms	-	X-ray signs; diuretics required	Rapid intubation required
04.06	■ Pneumonitis	None	X-ray signs without symptoms	Mild symptoms; steroids required	Severe symptoms; oxygen required	Artificial ventilation required
04.07	■ Pleural effusion	None	Present	-	-	-
04.08	■ ARDS (Adult Respiratory Distress Syndrome)	None	Mild	Moderate	Severe	Life-threatening
04.09	■ Cough	None	Low; weak antitussives	Moderate; strong antitussives required	Severe; uncontrollable cough	-
04.10	♦Larynx (RTOG)	N	Mild or intermittent hoarseness, irritable cough, mild mucosal erythema; no therapy required	Constant hoarseness, irritable cough, ear, nose/mouth and throat fibrinous exudate, moderate vocal chord oedema; mild antitussives required	"Whispered speech", severe pain; confluent fibrinous exudate; widespread vocal chord oedema; potent analgesics and antitussives required	Massive dyspnoea, stridor or haemoptysis; intubation or tracheostoma required
[5]	**Kidney and bladder**					
05.01	■ Haematuria	None	Only microscopically visible	Macrohaematuria without clots	Macrohaematuria with clots	Life-threatening; transfusion required
05.02	■ haemorrhagic cystitis	None	Only microscopically visible	Macroscopically visible blood	Bladder irrigation required	Cystectomy/transfusion required
05.03	■ Incontinence	None	Stress incontinence (sneezing etc.)	Spontaneous; control possible	Uncontrolled	-
05.04	■ Dysuria	None	Mild pain or burning; no therapy	Moderate pain or burning; controllable with medication	Severe pain or burning; not controllable with medication	-

	Toxicity/Degree	0 = "None"	1 = "Slight"	2 = "Moderate"	3 = "Severe"	4 = "Life-threatening"

05.05	■ Ischuria	None	Residual urine > 100 cm^3; occasional dysuria or catheter required	Catheter required for each drainage	Surgery required (transurethral resection or dilatation)	-
05.06	■ Increased desire to urinate	N	Slightly elevated or increased desire to urinate at night 2 x N	Moderately elevated desire to urinate. ≥2 x N. but ≤ 1 x / h	Highly elevated desire to urinate > 1 x / h, or catheterisation required	-
05.07	■ Bladder spasms	None	-	Present	-	-
05.08	■ Urethral obstruction	None	Unilateral; no surgery required	Bilateral; no surgery required	Incomplete bilateral; operation (shunt, ureteroplasty, nephrotomy) required	complete bilateral obstruction
05.09	■ Development of fistulae	None	-	-	Present	-
[6]	**Nervous system**					
06.01	Sensory	N	Loss of deep tendon reflexes, mild paraesthesias	Moderate, objective loss of sensitivity, moderate paraesthesias	Severe, objective loss of sensitivity, paraesthesias with reduced function	-
06.02	Motor	N	Mild subjective weakness, no loss of function	Moderate objective weakness, without significant loss of function	Severe objective weakness, with major loss of function	Paralysis
06.03	Consciousness	Clear, conscious	Mild somnolence or agitated mood	Moderate somnolence or agitated mood	Severe somnolence, agitation, disorientation or hallucinations	Coma, fits or toxic psychosis
06.04	Coordination	N	Mild dyscoordination or dysdiadochokinesia	Moderate intention tremor, dysmetria, unclear speech or nystagmus	Severe locomotor ataxia	Cerebella necrosis
06.05	Mood	N	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal tendencies
06.06	■ Headache	None	Mild, transient	Moderate to severe but temporary	Very severe and prolonged	-
06.07	■ Behavioural changes	None	Changes without negative consequences for themselves or family	Negative effects for themselves or family	Danger to themselves or others (or to the environment)	Psychotic behaviour
06.08	■ Dizziness/vertigo	None	Mild but present, controllable	Moderate, difficult to control	Severe, uncontrollable. Unable to work	-
06.09	■ Taste	N	Slightly altered. e. g. metallic	Clearly altered	-	-
06.10	■ Sleep disorders	None	Mild occasional medication	Moderate; controllable frequent medication	Sleep disorders despite Medication	-

	Toxicity/Degree	0 = "None"	1 = "Slight"	2 = "Moderate"	3 = "Severe"	4 = "Life-threatening"
[7]	**Endocrine System**					

07.01	■ Libido	N	Slightly reduced	Moderately reduced and impaired	Severely impaired	
07.02	■ Amenorrhoea - women	None	Yes	-	-	-
07.03	■ Gynaecomastia - men	None	Mild	Clear and painful	-	-
07.04	■ Hot flushes	None	Mild or < 1 x / day	Moderate and ≥ 1 x /day	Severe and frequent very debilitating	-
07.05	■ Cushing syndrome	None	Slightly detectable	More noticeable or clearly detectable	-	-
[8]	**Sensory organs**					
08.01	Hearing/ hearing ability	N	Asymptomatic hearing loss, detectable with audiometry only	Moderate symptoms: tinnitus, mild hypoakusia under audiometry	Severe debilitating loss of hearing; hearing aid required	Non-correctable deafness
08.06R	♦ Otitis (RTOG)	None	Mild erythema, Otitis externa, pruritus; no therapy	Moderate (serous) Otitis externa and media; topical therapy required	Severe serosanguineous Otitis externa and media; intensive therapy required	-
08.02	Eyes / visual acuity	N	Slightly reduced	Moderately reduced	Symptomatic subtotal loss of vision	Unilateral/ bilateral blindness
08.03C 08.03R	♦Conjunctivitis /keratitis (RTOG)		Mild erythema, chemosis or conjunctivitis with / without sclera injection, severe "watering eyes"; no steroids or antibiotics.	Moderate erythema, chemosis or conjunctivitis with/without keratitis, iritis with photophobia; steroids or antibiotics required	Severe keratitis with corneal ulcerations or visual impairment, objective loss of vision (visual impairment), acute glaucoma, panophthalmia	-
08.04	■ "Dry eye"	No	Mild; no therapy required	Moderate; artificial tears required	-	Enucleation required
08.05	■ Glaucoma	None	-	-	Yes, present	-
08.07	♦Nose / sense of smell	N	Slightly altered	Clearly altered	-	-

	Toxicity/Degree	0 = "None"	1 = "Slight"	2 = "Moderate"	3 = "Severe"	4 = "Life-threatening"
[9]	**Skin/allergy**					

09.01	Epidermis local (e. g. after injections)	N	Mild pain and swelling	Moderate pain and swelling with inflammation or phlebitis	Severe pain and swelling, ulceration	Plastic surgery treatment required
09.02C	Epidermis systemic (relevant to whole skin)	N	Sporadic macular or papular eruption or erythema without pruritus or other associated symptoms	Densely spread macular or papular eruption or erythema with pruritus or other associated symptoms	Generalised macular papular or vesicular eruption with severe associated symptoms	Generalised exfoliative or ulcerative dermatitis
09.03	Allergy	None	Transient, chills and fever <38.0°C	Urticaria, chills, fever ≥ 38.0° C, mild bronchospasm	Serum sickness, bronchospasm; parenteral medication required	Anaphylaxis
09.04	♦Skin/subcutis local (RTOG) (in radiation field)	N	Mild erythema, epilation, dry desquamation, reduced sweat secretion	Moderate erythema, isolated moist epitheliolysis (< 50%), moderate oedema; topical therapy possible	Severe erythema, confluent, moist epitheliolysis (≥ 50%), severe oedema; intensive topical therapy required	Deep ulceration, bleeding or necrosis; surgical therapy required
[10]	**General symptoms**					
10.01	■ Appetite	N	Slightly reduced	Transient: < 1 week reduced	Prolonged: ≥ 1 week reduced	Total loss of appetite
10.02	Weight increase	< 5.0 %	5.0 - 9.9%	10.0 - 19.9%	≥ 20.0 %	-
10.03	Weight decrease	< 5.0 %	5.0 - 9.9%	10.0 - 19.9%	≥ 20.0 %	-
10.04	Bleeding (clinical)	None	Mild; no transfusions	Moderate: 1 – 2 transfusions/ episode	Severe: 3 – 4 transfusions/episode	Massive: > 4 transfusions/episode
10.05	Alopecia	None	Minimal, not noticeable	Moderate, patchy, clearly detectable	Total but reversible	Total non-reversible
[11]	**Fever/infection**					
11.01	Body temperature	N	37.1 - 38.0° C	38.1 - 40° C	> 40.0° C for < 24 h	> 40.0° C for ≥ 24 h; hypotension
11.02	Infection	None	Mild; no therapy required	Moderate; oral antibiotics required	Severe; i.v. antibiotics/antimycotics	Life-threatening sepsis
11.03	■ Chills	None	Mild or transient	Severe and prolonged	-	-
11.04	■ Myalgia/arthralgia	None	Mild, no impairment	Moderate, mobility impaired	Unable to work	-
11.05	■ Sweating	N	Mild and occasionally increased	Frequent and wet from sweating	-	-
12.xx	■ Other findings	N	"slight" / "mild"	"moderate" / "clearly detectable"	"severe"/ "marked"	"Life-threatening"

13.14 Documentation forms

13.14.1 Web based

In order to facilitate downloading of the protocol, the documentation forms have been removed. You can find all the documents required for the randomisation of a patient on the homepage in the internet:

http://www.lymphome.de/Studien & Studiengruppen/Studienregister

Please select the appropriate study in order to get to the site containing the required documents and documentation forms.
The access to the complete study protocols and documentation forms is restricted by **pass word** for confidential reasons. The access data will be sent to you after **online registration** (http://www.lymphome.de) via the head office of Compentence Net of Malignant Lymphomas.
For inquiries regarding registration please contact the head office of Compentence Net of Malignant Lymphomas:

Zentrale des Kompetenznetz Maligne Lymphome

Tel.: 0221/478-7400 oder -7403
Fax: 0221/478-7406
E-Mail: lymphome@medizin.uni-koeln.de

13.14.2 Conventional

Participants without access to the internet can furhermore obtain the documents from the study secretariat of the DSHNHL in Homburg/Saar:

Study Secetariat of the DSHNHL
Prof. Dr. M. Pfreundschuh
University Hospital Complex of Saarland
Med. Clinic and Outpatients Clinic
Internal Medicine I, Building 40
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You will furthermore find the documents concerning:

- **Declaration of participation by institution**
- **Patient information and consent**

within the protocol.