Randomised Study Comparing 4 and 6 Cycles of Chemotherapy with CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) at 21-day Intervals, both with 6 Cycles of Immunotherapy with the Monoclonal anti-CD20 Antibody Rituximab in Patients with Aggressive CD20-positive B-Cell Lymphoma Aged 18 to 60 Years with no Risk Factor (Age-adjusted IPI=0) and no Bulky Disease (Diameter <7.5cm)

Short Title: FLYER 6-6/6-4-Study

Study number: DSHNHL 2004-2

Principal Investigator: Prof. Dr. M. Pfreundschuh

Author: M. Pfreundschuh

With the support of M. Klöss, N. Schmitz and F. Hartmann

Translated from the German Original by A. Schmitz and M. Pfreundschuh
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## 0 GENERAL ISSUES

### 0.1 Persons responsible for DSHNHL 2004-2

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<th>Contact Information</th>
</tr>
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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. Löffler, Leipzig
Prof. Dr. L. Trümper, Göttingen

0.2.2 Other members of the Study Management Committee

Prof. Dr. B. Glass, Göttingen
Prof. Dr. J. Schubert, Homburg
Dipl.-Math. M. Klöss, Leipzig
Dr. M. Nickelsen, Hamburg

0.2.3 Scientific Advisory Board

The Scientific Advisory Board decides on the support of scientific projects accompanying the study. In June 2005, the board has been composed of:

- One Member of the Study Management: Prof. Dr. L. Trümper (Göttingen)
- One Pathologist: Prof. Dr. A. C. Feller (Lübeck)
- One Biometrician: Dipl.-Math. M. Kloess (Leipzig)
- External Experts: Prof. Dr. M. Kneba (Kiel)
  PD 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:

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<thead>
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<th>Name</th>
<th>City</th>
<th>Position</th>
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<tr>
<td>Prof. M. Bentz</td>
<td>Karlsruhe</td>
<td>(5)</td>
</tr>
<tr>
<td>PD Dr. M. Dreyling</td>
<td>München</td>
<td>(5)</td>
</tr>
<tr>
<td>Prof. Dr. Eimermacher</td>
<td>Hagen</td>
<td>(5)</td>
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<tr>
<td>Dr. M. Engelhard</td>
<td>Essen</td>
<td>(3)</td>
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<tr>
<td>Prof. A. C. Feller</td>
<td>Lübeck</td>
<td>(2)</td>
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<tr>
<td>Prof. Dr. A. Franke</td>
<td>Magdeburg</td>
<td>(5)</td>
</tr>
<tr>
<td>PD Dr. N. Frickhofen</td>
<td>Wiesbaden</td>
<td>(5)</td>
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<tr>
<td>Prof. Dr. B. Glass</td>
<td>Göttingen</td>
<td>(1)</td>
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<tr>
<td>PD Dr. M. Hänel</td>
<td>Chemnitz</td>
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<td>Prof. Dr. F. Hartmann</td>
<td>Lemgo</td>
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<tr>
<td>PD Dr. M. Hensel</td>
<td>Heidelberg</td>
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<tr>
<td>Prof. Dr. U. Kaiser</td>
<td>Hildesheim</td>
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<td>Dipl. Math. M. Klöss</td>
<td>Leipzig</td>
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<tr>
<td>Dr. P. Koch</td>
<td>Münster</td>
<td>(5)</td>
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<tr>
<td>PD Dr. E. Lengfelder</td>
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<td>Prof. Dr. M. Löffler</td>
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<td>Dr. B. Metzner</td>
<td>Oldenburg</td>
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<td>Dr. M. Nickelsen</td>
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<td>Prof. Dr. M. Pfenningschuh</td>
<td>Homburg</td>
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<tr>
<td>PD Dr. M. Reiser</td>
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<td>Würzburg</td>
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<td>Dr. Ch. Rudolph</td>
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<td>Prof. Dr. Ch. Rübe</td>
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<td>PD Dr. H. Schmidberger</td>
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<td>PD Dr. S. Stilgenbauer</td>
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<tr>
<td>Prof. Dr. L. Trümper</td>
<td>Göttingen</td>
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(1) Representative of the DSHNHL Study Management Committee
(2) Representative of the Reference Pathology
(3) Representative of the Reference Radiotherapy
(4) Representative of the Oncologists in Private Practice
(5) Elected Members and Managers of the 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. Herrmann, 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 intermediate 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 Synopsis of Protocol DSHNHL 2004-2

**Study number:** DSHNHL 2004-2

**Short title of the study:** 6 x rituximab plus 6 x CHOP-21 vs. 6 x rituximab plus 4 x CHOP-21 (Favourable Low-Risk Young: Equivalency of Rituximab Regimens = FLYER 6-6/6-4)

**Therapeutic indication:** Aggressive CD20⁺ B-Cell Lymphoma in patients aged 18 to 60 years with age-adjusted IPI risk score = 0 and no bulky disease (<7.5cm)

**Primary aim of the study:** Reducing toxicity while maintaining efficacy of a combined immuno-chemotherapy with 6 cycles of the monoclonal anti-CD20 antibody rituximab by decreasing the number of cycles of chemotherapy with CHOP-21 from six to four.

**Secondary aims of the study:** Comparison of short-term and long-term side effects, quality of life and costs

**Study design:** Two arm, open-label, multicentre, prospective, randomised phase III study (therapy optimisation and quality assurance study)

**Study population:** Patients with untreated aggressive CD20⁺ Non-Hodgkin’s Lymphoma aged 18 to 60 years without major accompanying disorders with no risk factor according to IPI and no bulky disease (<7.5cm)

**Sample size:** 622 patients (ITT population), 560 patients (per-protocol-population) (311 per arm)

**Therapy:** Patients will be randomly assigned to receive 6 cycles of immunotherapy with the monoclonal anti-CD20 antibody together with either 6 or 4 cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristin and prednisone in standard dose at 21-day intervals (CHOP-21).

**Primary endpoint:** The main endpoint is the time to treatment failure (TTF), calculated from the time of randomisation.

**Secondary endpoints:** Secondary endpoints are CR rate, rate of primary progression under therapy, survival, tumour control, disease-free survival, toxicity, parameters of health cost, adherence to protocol, and analysis of relapse.

**Evaluation:** The time to treatment failure in the respective two therapy arms will be compared using the log-rank test.

**Time Plan:** Study to commence in October 2005, end of recruitment approx. in September 2010. Assuming a recruitment rate of 124 patients per year, 622 patients will be randomised during a recruitment period of 5 years. Each patient will be observed for 3 years within the study, starting from completion of treatment. Afterwards, beyond clinical investigation, lifelong follow-up will be carried out.

**Supported by:** Deutsche Krebshilfe / Dr. Mildred Scheel Foundation
0.5 **Flow Chart of the Study**

**Aggressive CD20+ B-cell Lymphoma**

18-60 years IPI 0 without bulk

- **Staging**
  - Arm A: 3 x R-CHOP - 21
  - Arm B: 3 x R-CHOP - 21

- **Randomisation**
  - BI I (BI II)

- **Prephase treatment**
  - Arm A: 3 x R-CHOP - 21
  - Arm B: 1 x R-CHOP - 21 + 2 x Rituximab

- **Interim restaging**
  - PR/NC/PRO
  - RE

- **Final restaging**
  - PR/NC/PRO
  - RE

- **Follow-up**

**Documentation forms:**

- Notification of serious adverse event: SAE
- End-of-study form in case of death: D
### 0.6 Therapy plan and examinations to be conducted

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1. a: at patient enrolment  b: at end of prephase  c: minimum value during chemotherapy
2. a: leukoc., lymphoc., monoo., baso., neut., eos., platelets, Hb, ESR, LDH, GPT (ALT), AP, γGT, bilirubin, total protein, albumin, paraprotein, IgG, IgA, IgM, β2-microglobulin, creat., EF, pulmonary diffusing capacity
3. b: leukoc., platelets, Hb, LDH, GPT (ALT), AP, bilirubin, creatinine, electrolytes immediately prior to cycle
4. c: leukoc., lymphoc., monoo., baso., neut., eos., platelets, Hb, LDH, EF, pulmonary diffusing capacity
5. d: leukoc., platelets, Hb prior to cycle and at least 2 measurements in nadir range
6. if initially affected
7. if initially affected, check after end of therapy until no further signs
8. lumbar puncture with liquor cytology in cases of high cervical affection, affection of cranium viscerale, bone marrow or testes and in Burkitt-like and Burkitt-Lymphoma
9. Send complete diagnostic images to the study secretariat in Homburg, if possible in digital form (CD)
10. G-CSF: G-CSF should be administered in case of prolonged leukocytopenia (>3d with <1 x 10^9/l) starting on day 4 of the following cycles
0.7 Physician’s checklist

What is required prior to initiation of therapy?

1. Requirement: declaration of centre participation and ethics approval of the ethics committee responsible sent to study secretariat?
2. Diagnosis of primary pathologist with result of CD 20 immunohistology test available?
3. Risk factors determined using the IPI?
4. Bulky disease: yes / no?
5. Study assignment decided?
6. Pretherapeutic diagnostic images (CT, MRT – if possible on CD/electronic) sent to study secretariat Homburg for reference evaluation (of every patient!)?
7. All inclusion criteria met?
8. Any exclusion criteria applicable?
9. Information of patient, patient’s approval for randomisation and consent form sent to the study secretariat?
10. All staging examinations completed?
11. Staging-, Base Line Information I-, Base Line Information II- report forms and histology results submitted to the study secretariat?
12. Randomisation performed by study secretariat?
13. Serum, blood and bone marrow samples forwarded?

Treatment procedures:

1. Immuno-chemotherapy cycles 1 – 3
2. Interim restaging
3. Immuno-chemotherapy cycle 4
4. Immuno-chemotherapy cycles 5 – 6 arm A
5. Immunotherapy cycles 5 – 6 arm B
6. Final restaging 14 days after the last application of rituximab

What is required in connection with radiotherapy?

There is no radiotherapy planned!

What is required on completion of therapy?

1. Restaging examination 14 days after the last application of rituximab
2. Regular follow-up examinations (first follow up 3 months after final restaging, afterwards every 3 months in the first 2 years, every 6 months in years 3 – 5, subsequently on an annual basis)

What is required in progression, NC and relapse?

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

What is required on early discontinuation of therapy?

Inform the Study Secretariat of the reasons for early discontinuation. If possible, conduct a final 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.

What is required if severe adverse events (SAE) 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.

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.

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

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

− a combination of immuno- and chemotherapy is given in both arms
− etoposide is not given any more (cf. 2.3)
− no radiotherapy will be administered
− patients with cerebral involvement (intracerebral, meningeal and intraspinal) will not be included
− central review of primary diagnostic 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.
− the performance status will be assessed in ECOG

The GCP principles are being adhered to throughout the study.
# AIMS OF THE STUDY

## 1.1 Primary aim of the study

The aim of this study is to investigate the following issues by means of a randomised, multicentre clinical study in patients with untreated aggressive Lymphoma:

*Are four cycles of the CHOP protocol (cyclophosphamide, doxorubicin, vincristine and prednisone) in combination with six cycles of immunotherapy with the monoclonal anti-CD20 antibody rituximab as efficacious as six cycles of the CHOP regimen in combination with six applications of rituximab? To what degree is there a reduction of acute and chronic side effects?*

To be included in this clinical study are all patients with CD20 positive aggressive, very favourable NHL aged 18 to 60 years with no risk factor according to IPI\(^1\) (age-adjusted IPI 0) and no bulky disease (tumour masses, single or conglomerate, measuring <7.5 cm). The primary endpoint is the time to treatment failure (TTF). The objective is to exclude a difference in the 3-year TTF rate of 5%, with an error probability of 5% (one-sided), at a power of 80%.

## 1.2 Secondary aims of the study

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

1. Side effects:
   - rate of neutropenia
   - rate of thrombocytopenia
   - rate of anaemia
   - rate of infection
   - rate of antibiotic therapy
   - rate of blood transfusion
   - rate of platelet transfusion
   - rate of secondary neoplasia
2. Efficacy (cf. 7.2.2.1):
   - rate of complete remission
   - rate of progress under therapy
   - disease-free survival
   - survival
   - tumour control
3. Health-economic aspects (cf. 7.2.2.3)
4. Adherence to protocol (cf. 7.2.2.4)

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\(^1\) International Prognostic Index
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\textsuperscript{1,2} are aggressive malignant diseases of the lymphatic system which rapidly cause death if they remain untreated. Radiotherapy is only curative in cases of localised lymphoma stages, with a marked decline of cure rates in patients over the age of 60 years\textsuperscript{3}. 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. 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\textsuperscript{4}, despite increases in the dosage of individual cytostatics and the introduction of new cytostatics into the second and third generation treatment protocols\textsuperscript{5-10}. 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\textsuperscript{11}. 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)\textsuperscript{12}. 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\%.

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\textsuperscript{12}. It is thus possible to differentiate between four risk groups on the basis of the number of risk factors present (\(\leq 1, 2, 3, >3\)); 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 verified in independent study populations, e.g. in the patients of the "National High Priority Study" where it was found to have a similarly good discriminatory function in respect to patient collectives with different prognoses [Fisher, personal communication]. The IPI is in particular scientifically significant 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 and shortening the therapy intervals from 3 to 2 weeks there was an improved outcome of good-prognosis (aaIPI=0,1) patients. This was demonstrated by the NHL-B1 study which was supported by the Deutsche Krebshilfe / Mildred Scheel Foundation (figure 1).
Despite this progress, it still appeared necessary to further improve results of young good-prognosis (aaIPI=0,1) patients with aggressive lymphoma. In the 1999-2 ("High-CHOEP") study of the second study generation of the DSHNHL it was investigated whether by significantly increasing the doses of cyclophosphamide, doxorubicin, and etoposide the outcome of young good-prognosis (aaIPI=0,1) patients was actually improved. This was done under the impression of the concept of "effective dose" 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 in January 2004, including 233 patients and a mean observation period of 23 months, showed that both therapy arms were equal regarding treatment failure and survival (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 was 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 the DSHNHL study.
Several centres of the DSHNHL participated in the "MINT" study, an international intergroup 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 (aaIPI=0,1) patients were included according to IPI except for young good-prognosis patients with stage I without bulky disease, who were excluded from the MinT study. Just as in the high-CHOEP study, patients with "bulky disease" and/or extranodal disease were given radiotherapy to the corresponding regions. The first interim results as of November 2003, including 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. A significance level of p=0.0000308 favoured the combined approach. It was two log intervals below the critical α-value of 0.000105 (figure 3). That was why the international data safety monitoring board, comprising G. Brittinger, B. Coiffier and P. Carde, decided to prematurely terminate the study in December 2003 when there were still 45 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 interim analysis, as did an analysis of the corresponding intention-to-treat population which was performed at the same time. 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 relapse therapy which is able to take 50% of patients into long lasting remission.
Figure 3: Time to treatment failure 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 observation period of 16 months).

Although survival differences between the two arms are diminished by salvage therapy, there is a significant advantage apparent after 2 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 after 6 cycles of CHOP-like chemotherapy compared with 6 cycles of CHOP-like chemotherapy 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 that adjusted for therapy arm, risk factor according to IPI and bulk demonstrated an association of TTF with therapy arm and bulk, and to a lesser degree with IPI. There were in fact marked differences regarding TTF and overall survival when patients of the MInT study without risk factor and bulk were compared (figure 5).

Figure 5: TTF of patients within the MInT study. Patients with IPI=0 and without bulk who were treated with chemotherapy alone (1) or chemotherapy 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

The results of the MinT study have demonstrated that young (aged 18 to 69 years) patients with aggressive lymphoma without risk factor according to IPI or bulk (single or conglomerate tumour) ≥7,5 cm do have an excellent prognosis. The therapy endpoints for these patients (per protocol population) are:

- CR rate: ...............................................................97%
- Progress under therapy .........................................3%
- TTF after 2 years and 3 years.............................94%
- Survival after 2 years and 3 years ................... 100%

Within the 2004-2-equivalent population, the final event already occurred after 6 months. The TTF curve showed a plateau afterwards. It can therefore be assumed that there will be 100% overall survival after a prolonged follow up period. It is remarkable that the most favourable population (stage IA without bulk) is not included in this population. There will certainly be an improvement of results if this prognostically most favourable population is included. The intention-to-treat population of the MInT study is running a little worse. This is partly due to an inability to confirm the diagnosis of a CD20-positive aggressive B-cell lymphoma in 13% of patients. Within the studies of the DSHNHL, less then 5% of exclusions are due to non-confirmation of diagnosis by the reference pathology. It can therefore be assumed that the TTF of the 2004-2 population will be better than the statistically anticipated 94% (based on a conservative approach) after 3 years.

In conclusion, it clearly appears that a large proportion of patients are overtreated on the assumption that there is a TTF > 94% and an overall survival >100%. We are facing the unique situation in the history of the therapy of aggressive lymphomas that a reduction of therapy is not only possible, but also reasonable.
2.3 **Standard regimens / 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 six cycles of chemotherapy together with six applications of the chimeric monoclonal anti-CD20 antibody rituximab are the best which have been reported for this patient collective. This also applies to a shortened course of chemotherapy (three times CHOP) with a comparably high-dosed "involved-field" radiotherapy\(^{16,17}\), as well as to approaches using a an intensified chemotherapy, compared to CHOP(E)P, like "High-CHOEP" (see above), or the intensified 2-week-CHOP variant ACVB of the French study group GELA\(^{18}\). In this study, three cycles of such treatment were significantly superior to a shortened chemotherapy with four cycles of CHOP in combination with “involved-field” radiotherapy. Since the side effects after six cycles of R-CHEMO within the MInT study do not differ from those after six cycles of the respective CHOP-like chemotherapy, six cycles of R-CHEMO can presently be considered as the optimum treatment for this patient collective. Since the collective of young good-prognosis patients with favourable prognosis (IPI=0, no bulk) was not given radiotherapy within the MInT study it can be assumed that radiotherapy is not indicated in these patients.

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 (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 2004-2 study:

1. 6 cycles of R-CHOP have produced so far the best results in young good-prognosis patients with a very favourable risk profile.
2. 6 cycles of R-CHOP-21 are well tolerated by patients aged ≤60 years, with a very good feasibility (mean relative dose intensity: 99%).
3. A further improvement in results of the collective of young good-prognosis patients with favourable prognosis (IPI=0, no bulk) is not possible anymore. Chemotherapies of higher intensity are therefore not indicated.
4. The excellent results with 6 cycles of R-CHOP were obtained in this patient population without radiotherapy. Radiotherapy is therefore not indicated in this patient population.
5. 6 cycles of R-CHOP is therefore the appropriate reference arm of this study.

All these points justify the selection of 6 cycles of R-CHOP-21 as the reference arm of the DSHNHL 2004-2 study.

2.4 **Rationale for the treatment optimisation protocol**

2.4.1 **Strategies of therapy optimisation in CD20\(^+\) B-NHL**

As shown above, the combination of 6 cycles of a CHOP-like chemotherapy with 6 cycles of the monoclonal antibody rituximab in CD 20\(^+\) diffuse large-cell lymphoma has produced results in the group of young good-prognosis patients with favourable risk profile (IPI=0, no bulk) that cannot be improved regarding time to treatment failure and overall survival. These results clearly demonstrate that a significant proportion of this patient collective is overtreated using 6 cycles of R-CHOP. Although this therapy is comparably well tolerated, it appears to be indicated to reduce the acute and long-term adverse effects (e.g. secondary neoplasias) if such a reduction is possible without loss of efficacy.
2.4.2 Role of radiotherapy

The role of radiotherapy in the treatment of high grade non-Hodgkin lymphoma is not clearly defined\textsuperscript{20}. The outstanding results of the MInT study regarding young good-prognosis patients with favourable prognostic profile were produced without radiotherapy. Radiotherapy is therefore not an issue in this population whose results cannot be improved anymore. Since it is impossible to improve the results any more, radiotherapy is not indicated here.

2.4.3 Reduction of chemotherapy

The issue of the number of CHOP-like chemotherapy cycles for the treatment of aggressive lymphoma has not been investigated yet in a randomised fashion. In the DSHNHL study 1999-1 (RICOVER-60) the issue of 6 vs. 8 cycles is currently being investigated. The issue of 6 vs. 8 cycles in the collective of young good-prognosis (aIPI=0,1) patients with favourable prognostic profile (IPI=0, no bulk) was implicitly covered by the MInT study. Since it is impossible to improve the excellent results after 6 x R-CHO(E)P, the administration of more than 6 cycles of chemotherapy is not justified.

There are also no data regarding the issue of using less than 6 cycles. Although the results of the MInT study might set a new standard worldwide for the population of young good-prognosis (aIPI=0,1) patients, there are regions and study groups that are already administering a reduced number of cycles. This is, however, not based on the results of randomised studies. Because of the SWOG results\textsuperscript{16}, most patients in North America are given 3 cycles of CHOP with an intensive "involved-field" radiotherapy. The GELA, who compared such a concept with chemotherapy alone, came to the contrary conclusion. Since such a chemotherapy produced better results\textsuperscript{18}, they are treating young patients with early stages of aggressive lymphoma with 3 cycles of ACVBP and thus ¾ of cycles that are given patients in advanced stages.

At the meeting of the protocol committee of the DSHNHL in Juny 2004 in Hamburg, it was finally discussed whether 3 or 4 cycles are sufficient. In view of the lack of data from randomised studies, the protocol committee and study participants unanimously decided in favour of 4 cycles. The crucial argument for using 4 instead of 3 cycles was formulated in order to make sure that the cure rates of this patient collective should by no means be put at risk. Further reductions could always be tested in protocols following 2004-2.

\textit{In summary, a reduction of chemotherapy from 6 to 4 cycles appears to be clinically safe. It is associated with a clinically relevant reduction of expected adverse effects. This issue is of great interest since the duration of a chemotherapy that is associated with lots of adverse effects is reduced to 2/3. This would mean a considerable gain in quality of life. The fact that the 2004-2-equivalent population of the MInT study already achieved all complete remissions after 3 cycles of combined immuno-chemotherapy indicated that there should be no worsening of therapy results after a reduction from 6 to 4 cycles of chemotherapy. There should also be no increase in the rate of primary progress. In the 2004-2-equivalent population all instances of primary progress occurred within the first three cycles.}

2.4.4 Possibility of a reduction of immunotherapy

There is no optimum number of rituximab applications that is founded on data from randomised studies as there is no optimum number of chemotherapy cycles. In aggressive lymphoma, eight cycles of rituximab were given together with eight cycles of CHOP-21 in the GELA study\textsuperscript{21} or together with 6 or 8 cycles of CHOP-14 in the RICOVER study of the DSHNHL up to now. The issue of 6 vs 8 cycles of rituximab in the collective of young good-prognosis (aIPI=0,1) patients
with favourable prognostic profile (IPI=0, no bulk) has been implicitly decided by the MInT study just as the issue of the optimum number of chemotherapy cycles. Since it is impossible to improve the results of 6 x R-CHO(E)P, it is not justified to administer more than 6 cycles of rituximab in this population.

There are no data from randomised studies referring to the issue of using less than 6 cycles of rituximab. Six cycles of rituximab constitute the smallest number of rituximab applications that was successfully compared with chemotherapy alone in a randomised fashion\textsuperscript{21,22}. The application of rituximab is possible without the occurrence of additional adverse effects. The protocol committee and study participants of the DSHNHL unanimously decided therefore at their last meeting in June 2004 to stick to the number of six rituximab applications in the experimental arm of the DSHNHL 2004-2 study. A reduction of rituximab applications, attractive for financial reasons in particular, could be put to the test in following protocols.

In summary, it would seem problematic to reduce the immunotherapy, in particular to reduce the number of rituximab applications together with a reduction of the chemotherapy from 6 to 4 cycles. In case of inferiority of the experimental arm, there would be no way to determine whether this was due to a reduction of chemotherapy, reduction of immunotherapy or the combination of both.

2.4.5 Summary of the rationale

The points that were discussed in sections 2.4.1 to 2.4.4 demonstrate that the prospective comparison of six cycles of R-CHOP-21 with four cycles of R-CHOP-21 plus two cycles of rituximab in the collective of patients aged 18 to 60 years with good-prognosis (aaIPI=0,1) aggressive CD20-positive B-cell lymphoma and favourable risk profile (IPI=0, no bulk) will provide important information. In our view a significant reduction of adverse effects can be currently best achieved by reducing the number of cycles of CHOP-21, maintaining simultaneously the efficacy of a combination of immunotherapy with rituximab and CHOP-like chemotherapy. We therefore suggest to compare by means of a prospective randomised study six cycles of a combined immuno-chemotherapy using the chimeric monoclonal anti-CD20 antibody rituximab with four cycles of this combination, supplemented with two additional applications of rituximab, with regard to maintenance of efficacy and occurrence of acute and long term adverse effects. The aim is to demonstrate that by reducing the number of chemotherapy cycles from six to four there will be a TTF rate less than 5% worse than the previous TTF rate of the 6x R-CHEMO arm of the MInT study. A difference is to be excluded with a power of 80%. The expected difference between the two therapy arms with regard to adverse effects and costs of therapy would be clinically relevant. We assume that, at a recruitment rate of 124 patients per year over a 5 year period, the questions asked in this study will be answered with sufficient power.
3 STUDY PROTOCOL

3.1 Study design

The 2004-2 study of the DSHNHL is a prospective randomised two-arm treatment optimisation study. Its aim is to investigate whether a combination of four cycles of CHOP-21 and six cycles of rituximab (4 x R-CHOP-21 plus 2 x R) is equivalent to a combination of six cycles of CHOP-21 and six cycles of rituximab (6 x R-CHOP-21) with regard to efficacy. It is 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 2004-2 study. We assume that these centres will be able to enroll 622 patients during an approximate 5-year recruitment period from October 2005 to September 2010.

3.3 Duration of study

Immunotherapy with rituximab will be administered for 18 weeks in both arms. The treatment that is associated with relevant side effects, i.e. chemotherapy, will be given in the control arm and experimental arm for 18 and 12 weeks, respectively.

3.4 Discontinuation of study

3.4.1 Discontinuation of study by individual patients

Post-randomisation non-qualification: Since this study will be analysed according to internationally agreed criteria 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 the 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.

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 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, very favourable (age-adjusted IPI=0; for definitions see appendix 13.11), no bulk (largest single or conglomerate tumour <7.5 cm in diameter)

3. Histology:
   Diagnosis of a CD20-positive aggressive B-cell lymphoma, confirmed by an excisional biopsy of a lymph node or by a sufficiently extensive biopsy of an 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
   - Mantle-cell lymphoma (blastoid)
   - aggressive marginal zone lymphoma (monocytoid)

   **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 0-1 time of randomisation; definitions see appendix 13.10. A performance status ECOG >1 (2-4) is a risk factor according to IPI and thus a reason for exclusion from this study!

5. Declaration of participation provided by the study centre and the written consent of 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/mm³, leukocytes < 2,500/mm³
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. Risk factor according to age-adjusted IPI (LDH > nl, stage III/IV, ECOG >1)
14. Evidence of bulk (single or conglomerate tumour ≥ 7.5 cm)
15. CNS involvement of lymphoma (intracerebral, meningeal, intraspinal)
16. MALT lymphoma
17. Planned radiotherapy of extranodal involvement
18. Non-application of inclusion criteria.

**Patients with primary ZNS 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 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

a) 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
   – ESR
   – LDH
   – GPT (ALT)
   – alkaline phosphatase (serum)
   – γ-GT
   – bilirubin
   – total protein + albumin with protein elektrophoresis und immunoelektrophoresis (paraprotein)
   – immunoglobulins IgG, IgA, IgM
   – β₂-microglobulin
   – creatinine
   – HIV serology (after separate informed consent)
   – hepatitis serology
   – pregnancy test
4. Chest X-ray in two planes in upright position
5. Abdominal ultrasound
6. CT scan of the neck/thorax/abdomen
7. Bone marrow biopsy (histology und cytology)
8. Lumbar puncture with CSF cytology in cases of high cervical involvement and in involvement of the cranium viscerale, the bone marrow or the testes
9. Resting electrocardiogram
10. Echocardiography (alternatively: determination of the ejection fraction by radionuclide ventriculography) prior to initiation of treatment (recommended by the Medical Council of North Rhine)
11. Determination of pulmonary diffusing capacity

b) Optional tests
1. Total body bone scan
2. Gastroscopy (obligatory in case of tonsil involvement)
3. Examination by an ENT specialist (obligatory in cervical involvement)
4. Haemoccult test
5. Lumbar puncture with CSF cytology, if not obligatory (cf. 5.1a)
6. Gallium scintigraphy, positron emission tomography, NMR tomography, cervical sonography
7. Liver biopsy
8. 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) and Cotswolds conference\(^2\). 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. intermediate high 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 13.11 of the study protocol. **Only patients in stage I/II and a good general condition (ECOG 0,1), with normal LDH and without bulk can be included in this study, as the stages III/IV, poor general condition (ECOG 2-4) and elevated LDH are risk factors according to IPI and therefore a reason for exclusion!**

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.

Radiotherapy on extranodal involvement will not be administered in this study!

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, 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, they retain the right of access to their patient records and that personal data required for the scientific monitoring of the disease will be collected and assessed. The aim and purpose of the collection of data will be explained to the patient. In addition, the 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 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 together by the treating physician. The patients will be given the copies of these forms with a copy of the Patient Information Leaflet. In addition, the patients will receive a copy of the insurance policy.

**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 main treatment).

<table>
<thead>
<tr>
<th>RANDOMISATION BY THE STUDYSECRETARIAT OF THE DSHNHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tel: +49-6841-16-23084</td>
</tr>
<tr>
<td>Fax: +49-6841-16-23004</td>
</tr>
<tr>
<td>e-mail: <a href="mailto:dshnhl@uniklinikum-saarland.de">dshnhl@uniklinikum-saarland.de</a></td>
</tr>
</tbody>
</table>

Patients who have given their written consent to participate, but do not receive immuno-chemotherapy after prephase treatment, must be reported to the Study Management Centre.

For the randomisation procedure, please send the completed Baseline Information Form I, Baseline Information Form 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
- identification of the patient
- age
- gender
- histopathologic subtype (WHO classification) and determination whether CD20\(^+\) aggressive Lymphoma
- confirmation that patient conforms to eligibility criteria
- confirmation that no exclusion criteria apply
- IPI criteria:
  - LDH and upper normal limit of LDH in the respective laboratory
  - performance status (ECOG score)
  - Ann Arbor stage
  - presence of extranodal involvement (number, site)
presence of bulky disease (site)
sites of lymphoma involvement
haematological status

Note:
As the randomised study allocations and stratifications of the DSHNHL studies are based on the (age-adjusted) International Prognostic Index score, 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. The extent of extranodal involvement must be determined.

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 the result of the randomisation by fax and by surface mail.

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.

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. The main therapy must not be initiated before randomisation and must directly follow the prephase treatment. Randomisation must be performed prior to commencement of study treatment with R-CHOP-21 (6-6) / R-CHOP-21 (6-4). It is therefore permitted to start prephase therapy in case of emergency prior to notification of the Study Management Centre. Prephase therapy is not obligatory. It precedes the main therapy consisting of R-CHOP-21. The main therapy consists of 6 cycles of immunotherapy with rituximab, independently of therapy arm, and 6 or 4 cycles of chemotherapy, depending on randomisation. Interim restaging will take place after cycle 3. Salvage treatment will be recommended to all patients who show no 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). Definite restaging will take place 2 weeks after the last rituximab application. Those patients who are not in CR or CRu by then are in need of further therapy and can be treated with salvage therapy. As a
rule, salvage therapy will consist of a different type of chemotherapy, but may consist of radiotherapy if the treating physician considers this to be appropriate.

Patients should be examined on a weekly basis by an experienced physician so that any side effects from chemotherapy (e.g. mucositis, polyneuropathy, deterioration 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 with vincristine:

- **Vincristine**: 1 mg i.v. day* -6 (single dose!)
- **Prednisone**: 100 mg p.o day* -6 to day 0 (i.e. 7 days)

*day 1 = day 1 of R-CHOP therapy

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, 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 CHOP-21 is the same in both therapy arms:

- **Arm A**: 6 x R-CHOP-21
- **Arm B**: 4 x R-CHOP-21 plus 2 x R

R-CHOP-21 schedule:

- **Cyclophosphamide**: 750 mg/m² i.v. d1
- **Doxorubicin**: 50 mg/m² i.v. d1
- **Vincristine**: 2 mg i.v. d1
- **Prednisone**: 100 mg (absolut) p.o. d1-5
- **Rituximab**: 375 mg/m² i.v. d1

To be repeated on day 22

**G-CSF (Lenograstim®)** should be given if the next therapy cycle was delayed due to leukocytopenia and in case of prolonged leukocytopenia (i.e. leukocytopenia lasting > 3 days with leukocyte count <1x10⁹/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. Prerequisites for the continuation of therapy are:

1. Patient has passed the leukocyte and platelet nadir
2. Leukocyte count > 2500/mm³ on day 22 after discontinuation of G-CSF (Lenograstim®) and
3. Platelet count > 80 000/mm³ on day 22
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 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. In case of a delay or prolonged leukocytopenia, it is indicated to administer G-CSF (Lenograstim®). In these cases, administration of G-CSF is to be continued 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 (cf.5.7.2) are not met after a delay of 1 week, i.e. on 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.

1. Postponement of therapy 0-7 days:
   No reduction

2. Postponement of therapy 8-14 days:
   Cyclophosphamide .............. 75%
   Doxorubicin ..................... 75%
   Vincristine....................... 100%
   Prednisone....................... 100%
   Rituximab......................... 100%

3. Postponement of therapy >14 days:
   Cyclophosphamide .............. 50%
   Doxorubicin ..................... 50%
   Vincristine....................... 100%
   Prednisone....................... 100%
   Rituximab......................... 100%

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. The dose reduction applies to all of the following cycles.

5.7.2.2 Administration of rituximab

Rituximab: 375 mg/m² iv., to commence 48 - 2 hours prior to initiation of CHOP-21.

Repeat: every 3 weeks, six applications in total, synchronous with CHOP-21 (in arm B: 4 x R-CHOP-21 + 2 x R, 5th and 6th rituximab application also at 3-week intervals).

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 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 50 - 100 mg diphenhydramine hydrochloride. Rituximab must be administered via a peripheral or central venous catheter. Prior to the first infusion, it should be ensured that epinephrine and diphenhydramine hydrochloride are available in case an allergic reaction occurs. All necessary equipment for the treatment of anaphylactic shock should be readily available.

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

In case of involvement of testes, high cervical sites of involvement or involvement of the cranium viscerale and in all cases of Burkitt-Lymphoma and Burkitt-like Lymphoma, CNS prophylactic treatment should be given on days 1 and 5 of cycle 1 and 2 in the form of 15 mg methotrexate i.th., followed after 3 hours by 1 tablet folinic acid (leucovorin 15 mg) p.o. 6-hourly x 8 (i.e. administration of folinic acid must be continued for up to 45 hours after methotrexate administration). CNS prophylactic treatment can be alternatively administered on day 1 of cycle 1 to 4. No additional prophylactic CNS radiotherapy will be given.

5.7.2.4 G-CSF therapy

Patients are usually not given G-CSF. However, G-CSF (Lenograstim®) should be given in cases of leukocytopenia-induced delay of therapy (see above) and prolonged leukocytopenia (i.e. leukocytopenia lasting >3 days with leukocyte counts <1x10⁹/l). In these cases, G-CSF (Lenograstim®) should be given during the following cycles starting from day 4.

5.7.2.5 Adverse effects of the treatment modalities applied

- **Cyclophosphamide:** myelosuppression, nausea/vomiting, alopecia, haemorrhagic cystitis
- **Doxorubicin:** myelosuppression, nausea/vomiting, alopecia, cardiomyopathy (max. cumulative dose: 550 mg/m²), necrosis after paravasal injection.
- **Vincristine:** peripheral polyneuropathy, paralytic ileus, necrosis after paravasal injection
− **Prednisone:** restlessness, stomach upset, increased appetite, osteoporosis, myopathy, steroid-induced diabetes mellitus

− **Rituximab:** allergic reactions, with anaphylactic shock in severe cases. In particular during the first application: nausea, difficulty swallowing, headache, fatigue. During and after rituximab therapy there is a higher incidence of viral infections (HSV stomatitis, herpes zoster).

− **Intrathecal treatment:** Headache, nausea, vomiting after prophylactic administration of MTX.

### 5.7.2.6 Supportive measures

1. **Selective intestinal decontamination:**
   
not required as a rule; however, prophylactic oral administration of an antibiotic [e.g. ciprofloxacin (Ciprobay®) 500 mg twice daily or levofloxacin (Tavanic®) 500 mg once daily] is recommended during leukocytopenia <1000/mm³.

2. **Pneumocystis carinii prophylaxis:**
   
not required

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

4. **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.

5. **Oral hygiene:**
   
a good standard of oral hygiene is to be maintained: this applies particularly to patients with dental prostheses. Prophylactic mouth rinsing with chlorhexidine (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: it is expected that leukocyte nadir will be reached on days 10-12)

− 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/m² doxorubicin (recommended by the Ethics Committee of the Medical Council of North Rhine)
5.8 Restaging and follow-up procedures

5.8.1 Interim restaging

Approximately 2 weeks after the commencement of cycle 3 (assuming that treatment can be continued on time):

- 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

14 days after the sixth rituximab application, the same examinations are to be performed as 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 all other primary manifestations (e.g. bone marrow biopsy)
- evaluation and documentation of results of therapy (cf. 5.8) and side effects (cf. 6).

5.8.3 Restaging in case of early discontinuation of therapy

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

5.8.4 Follow-up examinations

Follow-up of patients will continue until the completion of the study and the planned observation period, i.e. at least until June 2013. The first follow up examination will be 3 months after the final restaging. Follow-up examinations thereafter will be performed during the initial 2 years every 3 months, in years 3 to 5 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. 0.6) and are to be recorded in the follow-up 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 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 and have been appropriately modified for application within a large-scale multicentre trial in aggressive lymphomas.

5.9.1 Complete remission (CR)

CR means the disappearance of all disease symptoms (clinical, radiological and laboratory [LDH]). In this case, the result of therapy is to be classified as "CR with complete regression" (abbreviation: CR). All enlargement of organs (spleen, liver, kidneys) attributable to lymphoma must have regressed and no more lymphoma masses should be detectable. Blood counts must have normalised, with granulocytes >1500/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:

1. Lymphoma tissue still present (histological confirmation in all doubtful cases), but a
2. definite reduction at all involved sites and reduction of the total lymphoma volume by at least 50%;
3. no new lymphoma manifestations;
4. 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). A working classification of PR indicates that the treating physician considers further treatment appropriate; in view of the growth dynamics of aggressive lymphomas, however, it must also be assumed that in any case of a supposed
CRu in which active tumour tissue is still present, there may be renewed tumour growth within 2 months after a therapy-free interval, so that the actual outcome 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 all lesions (including small, well-defined lesions and diffuse involvement). Thus, the measurement of all 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 signs 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!

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, PR or NC during interim restaging after 3 cycles of immuno-chemotherapy will receive 3 more cycles of R-CHOP-21 (arm A) or one more cycle of R-CHOP-21 plus two cycles of rituximab (arm B).
- Non-responders (PRO) will be given salvage treatment.
- Patients in CR/CRu will receive no further therapy.
- Patients not in CR/CRu on completion of the whole treatment will receive salvage therapy.

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 again be documented during the interim restaging examination after three cycles of chemotherapy (cf. 5.8.1) and during the restaging examination on completion of systemic therapy (cf. Fehler! Verweisquelle konnte nicht gefunden werden.). Blood counts will be monitored on initiation of chemotherapy cycles and at least twice during each cycle, particularly during the nadir phase. The performance status of the patient (ECOG) will be determined prior to therapy, before each chemotherapy cycle and at the final restaging.

6.2 Adverse events (AEs)

6.2.1 Definition of expected/unexpected 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 Krebgesellschaft [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 = "life-threatening"

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

- myelosuppression
- nausea/vomiting
- alopecia
- infections, particularly during phases of leukozytopenia
- peripheral polyneuropathy

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 in all chemotherapy CRFs. If side effects occur which are not explicitly mentioned in the documentation forms, the relevant CTC number of the adverse event and the grade of severity should be classified as specified in Protocol Appendix 13.13 and recorded in the CRFs with the relevant CTC number. Adverse events which do not appear in the CTC list should be described in detail and the grade of severity should be documented in analogy with the CTC criteria as defined in 6.2.1.
Relevant fields are provided on the basis of a diagnosis key (cf. Appendix 13.13) in 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 events**

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) (cf. Appendix 13.14).

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 MInT 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. The randomisation algorithm will be applied using the ORACLE database. The minimisation method allows therapy arms and strata to be balanced. There will be randomisation into both treatment arms at a ratio of 1:1 and stratification according to centre, stage (I vs. II) and extranodal involvement (yes vs. no). As it cannot be excluded that stage II and extranodal involvement could be prognostically less favourable, these criteria have been added to the stratification.

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 be only 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:

a) Disease progression during therapy (PRO)
b) Early discontinuation of therapy because of excessive toxicity and patient not in CR/CRu at this point in time
c) No CR/CRu on completion of therapy
d) Relapse after achievement of CR/CRu
e) Change to salvage therapy/additional therapy which is not according to protocol
f) 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 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 first day of therapy 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

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, 5.8)
- rate of secondary neoplasias

7.2.2.3 Secondary endpoints for 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
- days in hospital
- total number of days on which antibiotics were administered
- total numbers 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.
7.3 **Statistical phrasing of the questions to be investigated in this study and sample size formulation**

The following questions are to be investigated in this clinical study:

- Are four cycles of a CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) in combination with six cycles of immunotherapy with the monoclonal anti-CD20 antibody rituximab as efficacious as six cycles of the same chemotherapy combined with six cycles of rituximab? To what degree is there a reduction of acute and chronic side effects?

This is a non-inferiority study. The preferred method of analysis of such studies is through application of confidence intervals regarding the difference between the two therapy strategies. If differences occur, although not expected, these will result from treatment failure as well as from relapse behaviour. On the basis of the observed hazard rates in other study groups, estimation of tumour latency periods and theoretical models, it is assumed that the differences between the therapy arms in respect to TTF rate should become apparent within three years after commencement of therapy.

We do know from the interim analysis of the MInT study in May 2004 that there is a 3-year TTF rate of 89% in the R-CHEMO arm, in the collective of patients aged ≤ 60 years as defined by the MInT protocol. Since patients in stage I without bulk were excluded from the MInT study, we must assume that there will be a higher TTF rate in this study. It is therefore plausible to assume a 3-year TTF rate of 94%. Small changes in TTF level will have quite a big effect on the case number. The 3-year TTF rate must be reviewed during the first interim analysis for that reason and the case number adjusted accordingly.

The evidence of 10% improvement in TTF rate is considered a relevant progress as defined by preceding studies of the DSHNHL. The reduction of side effects through more conservative therapy must not compromise the progress that has been achieved in preceding studies. A tolerable drop in TTF rate must clearly be below 10%. At a meeting in June 2004, the protocol commission has decided to tolerate a 5% worsening of 3-year TTF rate if the side effects are noticeably reduced. In non-inferiority studies special emphasis is therefore put on analysis of protocol adherence and side effects.

The aim of this study is to show that there is no difference between the TTF rates of the two studies. A 5% difference in TTF rate is to be excluded, with a power of 80% and an error probability of \( \alpha = 5\% \) (one sided), assuming that there is no true difference.

For the calculation of case number, a procedure of Makuch and Simon\(^{25} \) is used. According to these calculations, a case number of 560 patients is necessary for the test, i.e 280 patients per therapy arm. There should be 10% more patients randomised in order to carry out the "per protocol" analysis (patients with report of reference pathology and conformity to entry criteria) in addition to the intention-to-treat analysis. This results in a **total case number of 622** patients.

7.4 **Interim analysis and criteria of early discontinuation of the study**

The evaluation of confidence intervals of the observed differences is central to the analysis of non-inferiority studies, not so much the testing of differences. The study will be prematurely discontinued if the omission of two cycles of CHOP-21 is associated with a larger difference in TTF rates than tolerated. Testing of differences is therefore employed as criterion of early discontinuation.

Events occurring during the study will be continuously monitored by the investigators and the biometricians. If the criteria specified in section 3.4.2 are met, the Study Management
Committee shall decide whether to discontinue the study or not. A formal criterion of early discontinuation will be defined using the so-called "alpha spending function". In contrast with standard group sequential designs, this design allows 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". This method requires almost conventional p-values for the final analysis, but makes it difficult to terminate the study early for unjustified reasons.

The alpha-spending function should uncover differences which are larger than 5% early. There will be a one-sided test using an error probability of 5%. 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 whether the difference is exceeding the tolerable 5% 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 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 360 patients are 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 be only 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 has occurred having 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 Management 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 therapy and availability of the completed first 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

Kaplan-Meier graphs will be used in order to describe time to treatment failure. Additionally, the 3-year TTF rate of the two therapy arms will be shown, with a 95% confidence interval. A 95% confidence interval will be calculated to assess the difference between the two therapy arms.

Within 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 endpoints can be analysed. Details of numbers of patients completing therapy, numbers of early discontinuation and at what time will be provided. In a study of non-inferiority, it is particularly important to demonstrate that the reduction from 6 to 4 cycles has actually taken place. 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 CR rates and rates of primary progression will be documented, together with the corresponding 95% confidence intervals (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 cytotoxic drugs, the antibody 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

8.2 The processing of completed documentation forms

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

<table>
<thead>
<tr>
<th>Study Secretariat of the DSHNHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Dr. M. Pfreundschuh</td>
</tr>
<tr>
<td>University Hospital of Saarland</td>
</tr>
<tr>
<td>Internal Medicine I</td>
</tr>
<tr>
<td>Kirrberger Strasse, Building 40</td>
</tr>
<tr>
<td>D-66421 H O M B U R G (Saar)</td>
</tr>
<tr>
<td>Germany</td>
</tr>
</tbody>
</table>

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

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

This will allow any medical problems to be identified at an early stage so that appropriate queries can be initiated. 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 directly be recorded on 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 Secretariat 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 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 On-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. Feller, Lübeck (Secretary of the Reference Panel)
- Prof. Hansmann, Frankfurt
- Prof. Möller, Ulm
- Prof. Müller-Hermelink, Würzburg
- Prof. Wacker, 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 absent lymph node involvement, the diagnosis can be based on the histologic examination of the biopsy of an appropriate sample of another organ involved. The diagnosis of "aggressive Lymphoma, CD20+" by the local pathologist justifies reporting and randomisation into the study.

Whenever possible, fresh biopsy material 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. 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 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 physician, 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 separately 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.
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 meeting held on 18th of June 2004. Version 1 of the study protocol was submitted for evaluation by the local ethics committee, 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.

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 database 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 (Cologne). A copy of the insurance conditions is to be handed out to the patients (cf. Appendix 13.7)
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


22. Pfreundschuh, M., Truemper, L., Ma, D., Österborg, R., Pettengell, R., Trneny, M., Shepherd, L., Walewski, J., Zinzani, P.-L., and Loeffer, M. Randomised Intergroup Trial of first line treatment for young low-risk patients (<61 years) with diffuse large B-


