Randomized phase III study on the effect of early intensification of rituximab in combination with 2-weekly CHOP chemotherapy followed by rituximab maintenance in patients with diffuse large B-cell lymphoma

PROTOCOL

Principal Investigator : P.J. Lugtenburg
Study Coordinator : J.M. Zijlstra

Statistician : B. Van der Holt
Datamanagement : HOVON Data Center
Registration : HOVON Data Center
Erasmus MC – Daniel den Hoed
P.O. Box 5201
3008 AE ROTTERDAM
The Netherlands
Tel. +31.10.7041560
Fax +31.10.7041028
https://www.hdc.hovon.nl/top

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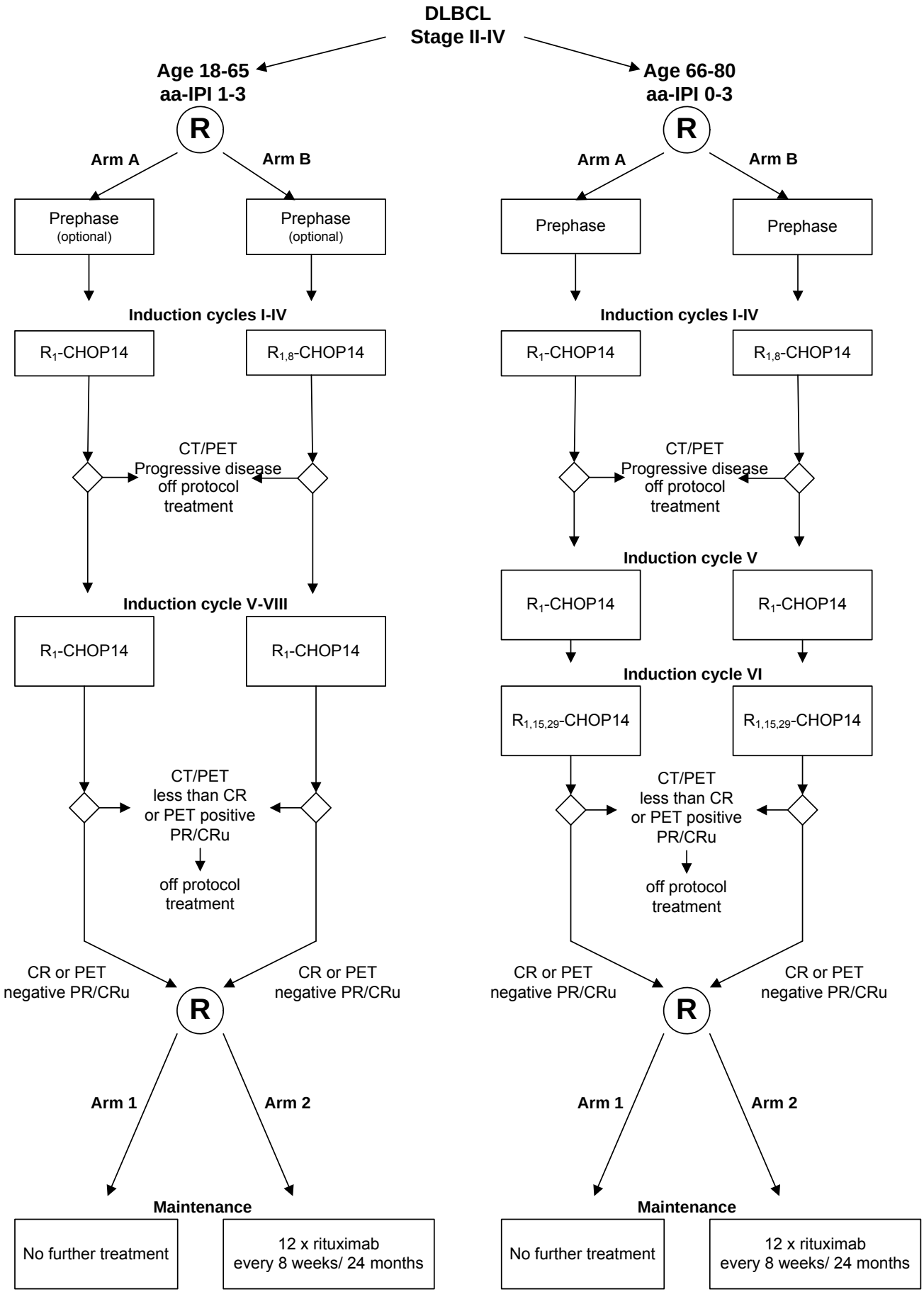
1 Scheme of study



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3 Synopsis

Study phase	Phase III
Study objectives	To evaluate the efficacy of a. early intensification of rituximab combined with 2-weekly CHOP+G-CSF (R-CHOP14) in remission induction treatment in comparison to standard R-CHOP14 b. maintenance treatment with rituximab in patients in remission after R-CHOP14 in comparison to no further treatment
Patient population	Patients with stage II-IV diffuse large B-cell lymphoma (DLBCL), CD20 positive, previously untreated, age 18-80 (inclusive) years and WHO performance status 0-2
Study design	Prospective, multi center, randomized
Duration of treatment	Expected duration of remission induction treatment is 16 weeks. For patients randomized to maintenance treatment the additional treatment time is 2 years
Number of patients	600 patients registered and randomized
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported
Planned start of recruitment	Start of recruitment IV 2007
Planned end of recruitment	End of recruitment IV 2012

4 Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
Principal Investigator	P.J. Lugtenburg	Erasmus MC, Rotterdam
Study Coordinator	J.M. Zijlstra	VUmc, Amsterdam
Writing Committee	J. Baars	AvL, Amsterdam
	H. Berenschot	Albert Schweitzer Hospital, Dordrecht
	D.H. Biesma	St. Antonius Hospital, Nieuwegein
	D.A. Breems	Hospital Network Antwerp, Antwerp
	R.E. Brouwer	Reinier de Graaf Hospital, Delft
	J.K. Doorduijn	Erasmus MC Daniel den Hoed, Rotterdam
	J. van Esser	Amphia Hospital, Breda
	G.W. van Imhoff	UMCG, Groningen
	G. Jie	Atrium MC, Heerlen
	M.J. Kersten	Academic Medical Center, Amsterdam
	M.H.H. Kramer	Meander MC, Amersfoort
	M. van Marwijk-Kooy	Isala Clinic, Zwolle
	M. MacKenzie	UMCN Radboud, Nijmegen
	G.J. Ossenkoppele	VUmc, Amsterdam
	M.E.D. Chamuleau	VUmc, Amsterdam
	M.R. Schaafsma	Medical Spectrum Twente, Enschede
	M. Schipperus	Haga Hospital, The Hague
	H.C. Schouten	University Hospital Maastricht
	P. Sonneveld	Erasmus MC, Rotterdam
	L.F. Verdonck	UMCU, Utrecht
	G.E.G. Verhoef	UZ Gasthuisberg, Leuven
	J.J. Wielenga	Walcheren Hospital, Vlissingen
	R. Willemze	LUMC, Leiden
Pathology review	K.H. Lam	Erasmus MC, Rotterdam
	Ph.M. Kluin	UMCG, Groningen
	J.J. Oudejans	VUmc, Amsterdam
PET review	E. Comans	VUmc, Amsterdam
	J. Pruim	UMCG, Groningen
	W. Oyen	UMCN Radboud, Nijmegen
Statistician	B. van der Holt	HOVON Data Center, Rotterdam
Datamanagement	HOVON Data Center	HOVON Data Center, Rotterdam
SAE notification	HOVON Data Center	Fax: +31.10.4391028
E-mail PI and study coordinator	p.lugtenburg@erasmusmc.nl	j.zijlstra@vumc.nl

4.1 Pathology review

Once a patient is registered in the study, the coordinating review pathologist will be notified by the HOVON Data Center by e-mail. The local pathologist will receive a request to sent material to the coordinating review pathologist.
In this request it is mentioned that there is informed consent of the patient for review and for the additional research on the (anonymized) material, including the construction of a tissue micro array (TMA) . According to the guidelines of HOVON, the name of the patient should be omitted from all correspondence, but the pathology number of the specimen, age and gender of the patient should be provided.
Pathology slides, including the immunohistochemical slides from the local pathology laboratory,of a representative lymph node biopsy or biopsy of a representative extra nodal site, together with a representative paraffin embedded tissue block (for confirming immunohistochemistry and for the construction of a tissue micro array; TMA) as well as a copy of the report should be sent to the coordinating review pathologist at the time of registration. In case of very little material (endoscopic biopsy samples, needle biopsy samples), or in case the patient does not consent with the preparation of the TMA for side studies, 10 unstained sections together with the report may be send for immunohistochemical confirmation only.
The central review will be done without knowledge of the patient outcome. Confirmation of diagnosis by the central pathology review committee is not necessary for registration and start of treatment.
The review is performed to confirm the diagnosis of diffuse large B-cell lymphoma (DLBCL) with its morphological variants, to confirm CD20 expression and to determine the currently accepted risk factors (whether the lymphoma is characterized by a germinal B-cell type or activated B-cell phenotype and to determine expression of BCL2 protein).
The initial review will be performed by the coordinating review pathologist, with or without one of the other review pathologist, depending on the complexity of the case. A review by two or all the review pathologists (Dr. J.J. Oudejans, Dr. K.H. Lam and Prof. Dr. Ph.M. Kluin) will be performed in case of discrepancy with the local pathologist or when judged appropriate. The logistics of the review process will be adapted should circumstances render that necessary.
Classification includes evaluation of the Hematoxylin-Eosin (HE) slide and the immunohistochemical stainings for CD20 or CD79a, CD5, CD10, BCL6, MUM1, and BCL2 from the local pathology laboratory. If the evaluation is not conclusive, the staining(s) will be repeated/supplemented and a more elaborate immunophenotypical characterization will be performed, using a standard panel of markers, including, but not limited to CD20, CD79a, CD5, CD10, BCL6, MUM1, and BCL2.
If a definite diagnosis cannot be attained based on histological and immunohistochemical findings alone, additional molecular studies may be performed.
Within 3 months after the review process, the slides will be returned to the local pathologist. The block will be returned to local pathologist after integration of the cores from the block in the TMA, usually within six months after receiving the block (depending on the accrual). If deemed necessary

(e.g. treatment decisions) by the local pathologist, the material will be returned upon the first request. In these cases the coordinating pathologist will contact the local pathologist to make additional arrangements
A copy of the results of the review will be sent to the local pathologist and to the HOVON Data Center.

All histological materials are to be sent to:

Dr K. Lam
Coordinating review pathologist HOVON 84
Department of Pathology, Josephine Nefkens Institute
Erasmus MC
Dr Molewaterplein 50
3015 GE ROTTERDAM
Tel: +31 704 4440
Fax: +31 10 704 4762
E-mail: k.lam@erasmusmc.nl

4.2 Side studies

Possible side studies on tumor materials might be initiated during the course of the trial. These studies will be initiated and performed according to the “guidelines for optimizing of pathology review and biological studies of pathology review and biological side-studies of HOVON coordinated clinical trials”.

4.3 Central PET review

For central PET review all FDG-PET scans, with and without attenuation correction, and CT-scans have to be sent on CD to:
Ms N.J. Hoetjes, research assistant of
Prof. Dr. E.F.I. Comans, nuclear medicine physician
Department of Nuclear medicine and PET research
VU University medical center
PO Box 7057
NL – 1007 MB Amsterdam
Tel: + 31 20 444 4214
Fax: + 31 20 444 3090
Email: n.hoetjes@vumc.nl

For the mid treatment and post treatment evaluation, the whole body scans will be displayed in both projection and volume views, the latter using coronal, sagittal and transaxial views. At least three experienced readers from the HOVON imaging group will independently interpret the images on an image display and score each lymph node region according to visual assessment as positive or negative. The PET scans are scored with knowledge of the CT data. A residual mass $\geq$ 2 cm in greatest transverse diameter on CT, regardless of their location, is considered positive on PET in case of clearly enhanced diffuse or focal uptake higher than that of mediastinal blood pool activity. A smaller residual mass or a normal sized lymph node (i.e., < 2cm in diameter) should be considered positive if its activity is above that of the surrounding background.
PET is also considered positive in case of new sites with focally enhanced uptake considered to represent lymphoma involvement. [1]

5 Introduction

5.1 Diffuse large B-cell lymphoma

The incidence of non-Hodgkin's lymphoma (NHL) is increasing and has reached an incidence of 15/100.000 per year in Western countries. The incidence rates increase among all age groups although the increase is larger in the elderly. Diffuse large B-cell lymphoma (DLBCL) is the most common NHL, accounting for 30%-40% of all new diagnosis and represents the predominant form of aggressive NHL.[2] The median age at presentation is in the mid-60s, and most patients present with advanced-stage disease. Patients older than 60 years have a worse prognosis than younger patients.[3] Several age-dependent factors are comorbidity, altered drug pharmacokinetics, reduced tissue tolerance, attenuated dose-intensity of chemotherapy, and different intrinsic susceptibility of NHL to chemotherapy.

5.2 CHOP21, CHOP14, R-CHOP21 and R-CHOP14

The cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy regimen has been the mainstay of therapy since its development in the 1970s. The standard CHOP regimen is given at 3-week intervals (CHOP21). Although most patients initially respond, only one third of the patients older than 60 years can be cured. Despite the development of newer therapeutic agents and more intensive chemotherapy regimens, no improvement in outcome was demonstrated.[4] In an attempt to improve the results, several recently reported randomized trials in elderly patients have focused on increasing dose frequency and intensity of CHOP, the addition of rituximab to CHOP or a combination of both strategies.

In the HOVON 25 study a small but significant improvement in dose-intensity was obtained by adding G-CSF to CHOP21. However, no effect was observed on the outcome of treatment.[5] The German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) demonstrated in a randomized 4-arm trial that reduction of the treatment intervals from 3 to 2 weeks (CHOP14) improved the outcome of the patients. Elderly patients with aggressive NHL were treated with a total of 6 courses of chemotherapy. Patients in the CHOP14 regimen received G-CSF to support recovery of granulocytes. Complete remission rates were 60% (CHOP21) and 76% (CHOP14). The five-year event-free and overall survival rates were 32% and 41%, respectively, for CHOP21 and 44% and 53%, respectively, for CHOP14. The toxicity of CHOP14 was comparable to CHOP21. The addition of etoposide to CHOP (CHOEP21 and CHOEP14) was associated with marked dose erosion due to increased toxicity and was therefore too toxic for this elderly population[6,7].

Rituximab (Mabthera®), a chimeric anti-CD20 immunoglobulin G1 monoclonal antibody, targets the CD20 cell surface protein. CD20 is present on mature B cells and most B-cell malignancies. Its effects are likely multifactorial and include complement-dependent cell lysis, cell-mediated cytotoxicity and induction of apoptosis.[8,9] Preclinical models suggested a synergistic effect when rituximab was combined with chemotherapy.[10]
The benefit of adding rituximab to CHOP21 (R-CHOP21) was demonstrated in a randomized trial (GELA) in elderly patients with DLBCL. Patients received 8 cycles of R-CHOP21 or CHOP21. The trial showed that the administration of rituximab 375 mg/m^2 on day 1 of each cycle alongside CHOP21 resulted in a significantly better CR/CRu rate (76% v. 63%), a better event-free survival (69% v. 49%) and a better survival (83% v. 68%). The improved outcome of the R-CHOP21 combination was observed in all IPI risk groups.[11] These results were confirmed in an updated report with a 5-year median follow-up.[12]

In elderly patients two randomized trials investigated whether combining rituximab to CHOP14 would improve the results of the CHOP14 regimen. Recently the final results of the RICOVER-60 trial of the DSHNHL were published, in which elderly patients with aggressive lymphoma were randomly assigned to receive six or eight cycles of CHOP14, both with or without eight cycles of rituximab[13]. Using six cycles of CHOP14 without rituximab as the reference, progression-free survival improved after six cycles of R-CHOP and eight cycles of R-CHOP, but overall survival improved only after six cycles of R-CHOP14. 3-Year overall survival of eight cycles of R-CHOP14 was 5.6% lower than after six cycles of R-CHOP14 (respectively 72.5% and 78.1%). Furthermore, there was no difference in event-free survival between eight cycles of R-CHOP14 and six cycles of R-CHOP14 when patients with complete response, unconfirmed complete response or partial response at interim staging after four cycles were compared. There were more dose-reductions and treatment delays in the eight-cycle regimens than in the six-cycle regimens. Moreover, the eight-cycle regimens were attended with more toxicity, as was indicated by a higher proportion of

treatment-associated deaths and more patients with anemia, mucositis and interventional antibiotics. Therefore, the favourable efficacy and toxicity profile of six cycles of R-CHOP14 makes this the preferred treatment regimen for elderly patients. These results are the best reported to date for elderly patients with DLBCL.[13]
The HOVON and Nordic Lymphoma Group trial (HOVON 46) comparing 8 cycles of CHOP-14 with the same chemotherapy plus 6 applications of rituximab also showed a significant improvement for the R-CHOP14 arm. An interim analysis in August 2005 on 197 evaluable patients indicated a significant improvement in 2 year failure free survival of 51% in the R-CHOP14 arm v. 23% in the CHOP14 arm (p = 0.005). There was a trend for better overall survival for R-CHOP14 compared to CHOP14. There were no differences in toxicity.[14]

Young patients aged 18-65 years with low-risk (no risk factor) and low-intermediate risk (one risk factor) according to age-adjusted International Prognostic Index (aa-IPI) have a better prognosis than young patients with intermediate-high and high risk, who present with two or three risk factors.
In a large international randomised study (MInT) in patients with aa-IPI 0-1, it was demonstrated that 6 courses of R-CHOP21-like compared to 6 courses of CHOP21-like therapy resulted in a significantly better 3-year event-free (79% vs 59%), progression-free survival (85% vs 68%) and overall survival (93% vs 84%)[15]. In a favorable subgroup of patients with no age-adjusted risk factors, no bulky disease and stage II, an excellent outcome with R-CHOP21 was achieved with a 3-year event-free survival of 97% and an overall survival of 100%. However, the less-favorable subgroups (with bulky disease or aa-IPI = 1, or both) had a 3-year event-free survival of 78% and an overall survival of 90%, which warrants further improvement[15]. These patients might benefit from dose-dense treatment with for example R-CHOP14.
There are no data from randomised trials that have established a role of rituximab for young intermediate-high and high-risk patients, although such a role can be expected from the results of randomised trials in young low-risk and elderly patients. A retrospective population based study in patients with DLBCL treated with R-CHOP21 demonstrated a 4-year progression-free survival of 57% and 51% and overall survival of 49% and 59%, in respectively, high-intermediate and high risk patients[16]. Therefore, in these “poor” risk patients the long-term chance of cure is in the range of 50% and these patients should be considered for investigational approaches.
The role of high-dose therapy followed by autologous stem cell transplantation as part of upfront treatment in high-risk patients is not clear. In a meta-analysis no evidence was found for a general benefit for high-dose chemotherapy with stem cell transplantation as first line treatment in patients with aggressive lymphoma[17]. Although selected high-risk patients may benefit from upfront transplantation, it is not clear how this approach compares to the addition of rituximab to standard CHOP and/or modified CHOP regimens with increased dose frequency and intensity.

Taken together these data indicate that the best results are obtained with combined immuno-chemotherapy, either with the R-CHOP21 or the R-CHOP14 regimen. Two international phase III studies comparing R-CHOP21 with R-CHOP14 are in progress. The results from these randomized trials must be awaited, before the standard treatment for patients with DLBCL can be established. Although treatment results have improved, results are not yet satisfactory. Therefore, novel strategies must be explored.

5.3 Rituximab intensification

The original rituximab schedule of 375 mg/m^2 weekly for 4 consecutive weeks was developed based on two phase I studies demonstrating that this dose was safe, non toxic and active.[18] The rationale for this schedule was based mostly on empiric and logistic considerations. Pharmacokinetic analysis in the first pivotal study of rituximab in patients with indolent NHL indicated that patients maintaining a higher and more prolonged blood level of rituximab had an increased chance of responding.[19] Serum levels increased with each infusion of rituximab. The terminal elimination half-life (T½) of rituximab increased from 3.2 days after the first infusion to 8.6 days after the fourth infusion, and was concomitant with a four-fold decrease in clearance of rituximab.[18,19] The increase in T½ is most likely related to destruction of circulating CD20 positive normal B cells and dead tumor cells. The mean serum rituximab concentration was inversely correlated with measurements of tumor bulk and with the numbers of circulating B cells at baseline.[19] This is consistent with the importance of accessible lymphoma in influencing the serum levels of rituximab. The association of high rituximab concentration and response and the association of high serum rituximab concentration with low tumor bulk suggest that higher doses (or more doses) of rituximab may be necessary to induce responses in some subsets of patients, such as those with bulky disease. Approximately 40%-60% of patients with DLBCL present with bulky disease.[11,13] In CLL patients higher rituximab dose levels up to 2250 mg/m^2 resulted in a better response rate without an increase in toxicity.[20]
For DLBCL rituximab at 375 mg/m^2 given immediately before CHOP chemotherapy has become the standard mode of application, more or less based on empirical grounds. Rituximab proved to be active and safe at this dose and frequency. Little data exist on the pharmacokinetics of rituximab in aggressive lymphoma patients. In a small series of 20 patients serum levels and pharmacokinetics of rituximab were measured during the R-CHOP14 regimen in elderly patients with DLBCL.[21] Rituximab levels increased slowly up to cycle 5. Thereafter rituximab levels reached a plateau. Median pre-infusional serum levels were lower than levels detected in follicular NHL.[19]
In the HOVON 46 trial the CR/CRu rate in the R-CHOP14 arm was 66%. Only 16% of these patients were in CR/CRu after 3 to 4 cycles.[14] Thus, remissions were reached rather late during treatment and efforts should be made to increase the remission rate.
One of the aims of the current study is to improve treatment outcome by increasing rituximab levels early during treatment. Half of the patients will receive one extra application of rituximab during each

of the first 4 cycles of R-CHOP14. Although intensification of rituximab is not associated with an increased myelotoxicity, a high infection rate was seen in a small pilot study when 12 applications of rituximab were combined with 6 R-CHOP14 cycles. In addition, one third of the patients developed an interstitial pneumonia. These complications occurred at the end of treatment with fully recovered neutrophil counts. After institution of Pneumocystis carinii and CMV prophylaxis this toxicity was not observed anymore (Pfreundschuh, personal communication). Others have reported the occurrence of Pneumocystis carinii pneumonia in 6% of the patients treated with R-CHOP14 in absence of routine cotrimoxazole prophylaxis.[22] Therefore, in the current study special attention will be given to supportive care measurements with a mandatory prophylaxis of infection. Moreover, elderly patients will receive a prephase treatment with prednisone to improve the performance status of the patient and to reduce toxicity of the first chemotherapy cycle.

5.4 Rituximab maintenance therapy

Although in the last decade treatment results of patients with DLBCL have improved, still 30%-40% of patients relapse.

Several studies in follicular NHL have demonstrated that rituximab maintenance can improve duration of response after initial cytoreductive chemotherapy. In a randomized study by the ECOG in patients with untreated follicular lymphoma rituximab maintenance was given after CVP induction. Progression free survival at 4 years was increased from 34% in the observation arm to 58% in the maintenance arm. Moreover a survival benefit was suggested.[23] Recently two trials were completed in patients with relapsed or refractory follicular lymphoma. The GLSG showed that rituximab maintenance improved progression free survival compared to observation only (median not reached at 3 years v. 19 months respectively) in patients with responses to induction therapy, which importantly also included prior rituximab use in combination with the FCM regimen.[24] The observation that rituximab maintenance is also beneficial after initial immunochemotherapy consisting of rituximab plus standard chemotherapy was confirmed in a large intergroup study. In this trial patients who had been treated with R-CHOP at relapse had a substantial benefit from rituximab maintenance therapy with a median progression free survival of 59 months v. 23 months in the observation arm.[25] In all studies no clinically relevant toxicity was observed with prolonged rituximab therapy.[23-25]

Recently, the results were published from a trial on rituximab maintenance in elderly patients with DLBCL.[26] This trial compared CHOP21 v. R-CHOP21 (4 or 5 applications of rituximab) and included a second randomization to rituximab maintenance (4 weekly infusions every 6 months for two years) v. observation. Rituximab maintenance showed a statistically significant benefit in failure free survival over observation. This effect was only observed in patients that had not been treated with rituximab during induction treatment. However, this result was shown in an unplanned subgroup analysis. Moreover, the induction schedule used in this trial may not have been adequate, as a

suboptimal number of rituximab infusions and chemotherapy cycles were applied. In this study grade 3 or 4 granulocytopenia was more common in the rituximab maintenance arm compared with observation patients (12% v. 4%). No differences in infections were reported between the two arms.[26]

Therefore, the question if rituximab maintenance can improve the outcome of patients with DLBCL after an optimal induction therapy has not been answered yet and will be addressed in the current study.

The optimal maintenance regimen is not known. To date, a number of dosing schedules have been used for maintenance therapy, ranging from 4 single infusions every 2 months to 4 weekly infusions every 6 months for 2 years. In a phase II trial an individualized dosing of rituximab was tested in patients with mainly indolent NHL. After initial treatment with 4 weekly infusions of rituximab, patients received a single infusion of rituximab when serum levels of rituximab decreased below a certain threshold. The mean time between rituximab applications was 3 months, however a wide range was observed from 2-5 months.[27]

In the current study one infusion will be given every 8 weeks. This scheme is used in most ongoing studies with rituximab maintenance. As most relapses of DLBCL occur within two years after therapy a 24 months maintenance period was chosen.

In the current study, designed for both young and elderly DLBCL patients, Ann Arbor stage II-IV, we will compare standard treatment with 8 cycles (in young patients) or 6 cycles (in elderly patients) of R-CHOP14 with the same treatment schedule combined with 4 additional applications of rituximab during the first 4 cycles. Patients in complete remission (including PET negative partial remission or unconfirmed complete remission) after induction treatment will be randomized between observation and rituximab maintenance.

6 Study objective

To assess in a prospective, multicenter, randomized phase III study in patients with DLBCL:

- the effect of early intensification of rituximab combined with 2-weekly CHOP +G-CSF (CHOP14) in comparison to no intensification of rituximab on the response rate (complete remission and FDG-PET negative partial remission/unconfirmed complete remission) and time to reach response
- the efficacy of maintenance treatment with rituximab in comparison to no further treatment on failure free survival

7 Study design

Details of all treatments (dose and schedule) are given in chapter 9.

7.1 Remission induction

Patients with CD20-positive DLBCL meeting all eligibility criteria (see 8.1) will be randomized at entry between:

For young patients 18-65 (inclusive) years:

Arm A: 8 cycles of R-CHOP14 plus G-CSF: pegfilgrastim (Neulasta®). Rituximab (MabThera®) will be administered at day 1 of each cycle

and

Arm B: 8 cycles of R-CHOP14 plus G-CSF: pegfilgrastim (Neulasta®) with intensification of rituximab (MabThera®) during the first 4 cycles. Rituximab will be administered at day 1 and 8 of cycle I-IV and at day 1 of cycle V-VIII

For elderly patients 66-80 (inclusive) years:

Arm A: 6 cycles of R-CHOP14 plus G-CSF: pegfilgrastim (Neulasta®). Rituximab (MabThera®) will be administered at day 1 of cycle I-V, and at day 1, 15 and 29 of cycle VI

and

Arm B: 6 cycles of R-CHOP14 plus G-CSF: pegfilgrastim (Neulasta®) with intensification of rituximab (MabThera®) during the first 4 cycles. Rituximab will be administered at day 1 and 8 of cycle I-IV, at day 1 of cycle V, and at day 1, 15 and 29 of cycle VI

All patients will be evaluated for response after 4 cycles of R-CHOP14. Patients with progressive disease on CT-scan will go off protocol treatment. All other patients will receive another 2 cycles (elderly patients) or 4 cycles (young patients) of R-CHOP14. After 6 cycles (elderly patients) or 8 cycles (young patients) of R-CHOP14 patients will be evaluated for response (if applicable, otherwise after last cycle administered). All patients who have not attained a CR (or FDG-PET negative PR/CRu) after the end of remission induction therapy will go off protocol treatment.

7.2 Maintenance

Patients attaining a CR (or FDG-PET negative PR/CRu) after 6 cycles (elderly patients) or 8 cycles (young patients) of R-CHOP14 (arm A and arm B) will be randomized between:

Arm 1: no further treatment

and

Arm 2: maintenance treatment with rituximab (MabThera®) once every 8 weeks until relapse (for a maximum period of 24 months)

8 Study population

All eligible patients have to be registered before start of treatment (see chapter 16).

8.1 Eligibility criteria for registration

8.1.1 Inclusion criteria

- Patients with a confirmed histologic diagnosis of diffuse large B-cell lymphoma (DLBCL) based upon a representative histology specimen according to the WHO classification (see appendix A)
- DLBCL must be CD20 positive
- Ann Arbor stages II-IV (see appendix C)
- Age 18-65 (inclusive) years and aa-IPI 1-3 (see appendix G)
  OR
  Age 66-80 (inclusive) years and aa-IPI 0-3 (see appendix G)
- WHO performance status 0 – 2 (see appendix E)
- Written informed consent

8.1.2 Exclusion criteria

- Age 18-65 (inclusive) years and aa-IPI 0 (no risk factors, see appendix G)
- Intolerance of exogenous protein administration
- Severe cardiac dysfunction (NYHA classification III-IV, see appendix F) or LVEF < 45% Congestive heart failure or symptomatic coronary artery disease or cardiac arrhythmias not well controlled with medication. Myocardial infarction during the last 6 months

- Severe pulmonary dysfunction (vital capacity or diffusion capacity < 50% of predicted value) unless clearly related to NHL involvement
- Patients with uncontrolled asthma or allergy, requiring systemic steroid treatment
- Significant hepatic dysfunction (total bilirubin $\geq$ 30μmol/l or transaminases ≥ 2.5 x upper normal limit), unless related to NHL
- Significant renal dysfunction (serum creatinine ≥ 150 umol/l or clearance ≤ 60 ml/min), unless related to NHL
- Clinical signs of severe cerebral dysfunction
- Suspected or documented Central Nervous System involvement by NHL
- Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant and adversely affecting compliance to study drugs
- Testicular DLBCL
- Primary mediastinal B cell lymphoma
- Transformed indolent lymphoma
- (EBV) post-transplant lymphoproliferative disorder
- Secondary lymphoma after previous chemotherapy or radiotherapy
- Major surgery, other than diagnostic surgery, within the last 4 weeks
- Patients with active uncontrolled infections
- Patients known to be HIV-positive
- Active chronic hepatitis B or C infection
- Serious underlying medical conditions, which could impair the ability of the patient to participate in the trial (e.g. ongoing infection, uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease)
- Life expectancy < 6 months
- Prior treatment with chemotherapy, radiotherapy or immunotherapy for this lymphoma, except a short course of prednisone (< 1 week) and/or cyclophosphamide (< 1 week and not in excess of 900 mg/m^2 cumulative) or local radiotherapy in order to control life threatening tumor related symptoms
- History of active cancer during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma

8.2 Eligibility criteria for second randomization

Patients achieving a CR (or FDG-PET negative PR/CRu) after 6 cycles (elderly patients) or 8 cycles (young patients) of R-CHOP14 will be randomized to maintenance treatment with rituximab or no further treatment.

- Patients in complete remission or FDG-PET negative partial remission/unconfirmed complete remission at least 4 weeks after the last cycle of R-CHOP14 (including last rituximab administration)
- Time interval since last cycle of R-CHOP14 (including last rituximab administration) between 4 and 8 weeks
- No rituximab-related adverse event necessitating stopping of rituximab administration
- No active infection
- Written informed consent

9 Treatments

9.1 Remission induction treatment young patients (18-65 years)

9.1.1 Prephase

A prephase treatment before the start of the study treatment is left at the discretion of the treating physician in young patients. If given, it must be documented in the CRF. The prephase consists of a 5-day course of prednisone.

Agent	Dose/day	Route	Days*
Prednisone	100 mg	p.o.	-4, -3, -2, -1, 0

*day 1 = day 1 of R-CHOP14 therapy

9.1.2 Arm A: R_1-CHOP14 cycle I-VIII

R_1-CHOP14 chemotherapy + G-CSF

Agent	Dose/day	Route	Days
Cyclophosphamide	750 mg/m^2	i.v.	1
Doxorubicin	50 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2 (max. 2 mg)	i.v.	1
Prednisone	100 mg	p.o.	1,2,3,4,5
G-CSF (pegfilgrastim, Neulasta®)	6 mg	s.c.	2
Rituximab (Mabthera®)	375 mg/m^2 (max 750 mg)	i.v.	day 1

Patients in arm A will be treated with 8 cycles of R-CHOP14, every 2 weeks. In addition they will receive G-CSF (pegfilgrastim) on day 2 of each cycle of R-CHOP14. Rituximab will be given on day 1 of each cycle (8 rituximab administrations in total).

Because the 1st rituximab infusion (during R-CHOP14 course no.1) will usually take a few hours, this 1st infusion may also be scheduled on day 2 for logistic reasons (see also 9.4).
Assessment of response after 4 cycles is described in 11.2. Patients who have progressive disease on CT-scan will go off protocol treatment. All other patients will receive another 4 cycles of R-CHOP14 + G-CSF every 2 weeks.

9.1.3 Arm B: $R_{1,8}$-CHOP14 cycle I-IV and R_1-CHOP14 cycle V-VIII

$R_{1,8}$-CHOP14 chemotherapy + G-CSF

Agent	Dose/day	Route	Days
Cyclophosphamide	750 mg/m^2	i.v.	1
Doxorubicin	50 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2 (max. 2 mg)	i.v.	1
Prednisone	100 mg	p.o.	1,2,3,4,5
G-CSF (pegfilgrastim, Neulasta®)	6 mg	s.c.	2
Rituximab (Mabthera®)	375 mg/m^2 (max 750 mg)	i.v.	day 1,8 cycles I-IV day 1 cycles V-VIII

Patients in arm B will be treated with 8 cycles of R-CHOP14, every 2 weeks. In addition they will receive G-CSF (pegfilgrastim) on day 2 of each cycle of R-CHOP14. Rituximab will be given on day 1 and 8 of cycles I-IV and on day 1 of cycles V-VIII (12 rituximab administrations in total).
Because the 1st rituximab infusion (during R-CHOP14 course no.1) will usually take a few hours, this 1st infusion may also be scheduled on day 2 for logistic reasons (see also 9.4).
Assessment of response after 4 cycles is described in 11.2. Patients who have progressive disease on CT-scan will go off protocol treatment. All other patients will receive another 4 cycles of R-CHOP14 + G-CSF every 2 weeks.

9.2 Remission induction elderly patients (66-80 years)

9.2.1 Prephase

A prephase treatment before the start of the study treatment is mandatory in all elderly patients. It must be documented in the CRF. The prephase consists of a 5-day course of prednisone.

Agent	Dose/day	Route	Days*
Prednisone	100 mg	p.o.	-4, -3, -2, -1, 0

*day 1 = day 1 of R-CHOP14 therapy

9.2.2 Arm A: R_1-CHOP14 cycle I-VI

R_1-CHOP14 chemotherapy + G-CSF

Agent	Dose/day	Route	Days
Cyclophosphamide	750 mg/m^2	i.v.	1
Doxorubicin	50 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2 (max. 2 mg)	i.v.	1
Prednisone	100 mg	p.o.	1,2,3,4,5
G-CSF (pegfilgrastim, Neulasta®)	6 mg	s.c.	2
Rituximab (Mabthera®)	375 mg/m^2 (max 750 mg)	i.v.	day 1 (cycle I-V) day 1, 15, 29 (cycle VI)

Patients in arm A will be treated with 6 cycles of R-CHOP14, every 2 weeks. In addition they will receive G-CSF (pegfilgrastim) on day 2 of each cycle of R-CHOP14. Rituximab will be given on day 1 of each cycle and on day 1, 15 and 29 of cycle VI (8 rituximab administrations in total).
Because the 1st rituximab infusion (during R-CHOP14 course no.1) will usually take a few hours, this 1st infusion may also be scheduled on day 2 for logistic reasons (see also 9.4).
Assessment of response after 4 cycles is described in 11.2. Patients who have progressive disease on CT-scan will go off protocol treatment. All other patients will receive another 2 cycles of R-CHOP14 + G-CSF every 2 weeks.

9.2.3 Arm B: $R_{1,8}$-CHOP14 cycle I-IV and R_1-CHOP14 cycle V-VI

$R_{1,8}$-CHOP14 chemotherapy + G-CSF

Agent	Dose/day	Route	Days
Cyclophosphamide	750 mg/m^2	i.v.	1
Doxorubicin	50 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2 (max. 2 mg)	i.v.	1
Prednisone	100 mg	p.o.	1,2,3,4,5
G-CSF (pegfilgrastim, Neulasta®)	6 mg	s.c.	2
Rituximab (Mabthera®)	375 mg/m^2 (max 750 mg)	i.v.	day 1,8 cycles I-IV day 1 cycle V day 1, 15, 29 (cycle VI)

Patients in arm B will be treated with 6 cycles of R-CHOP14, every 2 weeks. In addition they will receive G-CSF (pegfilgrastim) on day 2 of each cycle of R-CHOP14. Rituximab will be given on day 1 and 8 of cycles I-IV, on day 1 of cycle V and on day 1, 15 and 29 of cycle VI (12 rituximab administrations in total).

Because the 1st rituximab infusion (during R-CHOP14 course no.1) will usually take a few hours, this 1st infusion may also be scheduled on day 2 for logistic reasons (see also 9.4).
Assessment of response after 4 cycles is described in 11.2. Patients who have progressive disease on CT-scan will go off protocol treatment. All other patients will receive another 2 cycles of R-CHOP14 + G-CSF every 2 weeks.

9.3 Dose modifications R-CHOP14

Dose modifications will not be made in the first R-CHOP14 course. During the next courses modifications of the treatment will only be made in case of:

a) Myelosuppression
If neutrophils are < 1.5 x 10^9/l and/or platelets are < 80 x 10^9/l by the scheduled day 1 of the next cycle, the next cycle is postponed by 3 or 4 days and blood counts must be repeated. If threshold neutrophils and/or platelet counts are not reached by then, the next cycle will again be postponed by 3 or 4 days.

In case the threshold neutrophil and/or platelet counts are not reached one week after the scheduled day 1 of the next cycle, blood counts will be repeated every 3 to 4 days, until thresholds are passed. The following cycle of chemotherapy will then be given at reduced doses:

Delay of next cycle	**cyclophosphamide**	**doxorubicin**	**vincristine**	**prednisone**
0 to 7 days	100%	100%	100%	100%
8 to 14 days	75%	75%	100%	100%
> 14 days	50%	50%	100%	100%

If peripheral blood counts are recovered after a reduced cycle, full doses can be given for the following cycle. If dose reduction was necessary for two consecutive cycles, the reduction must be maintained. The 75% or 50% doses should always be calculated from the original full doses.

b) Neurotoxicity
Dose modifications of vincristine are made at the discretion of the treating physician.

c) Cardiotoxicity
In case of documented doxorubicin induced cardiomyopathy developed during treatment, LVEF should be repeated. In case of a reduction of LVEF by > 15% (absolute values, e.g. from 60% to 44%) the patient will go off protocol treatment.

9.4 Special management rituximab administration

Antibody infusions may be given to patients in an outpatient clinic setting or following hospital admission as an inpatient. A peripheral or central intravenous (IV) line will be established. Vital signs (blood pressure, pulse, respiration, temperature) should be monitored every 15 minutes during the first hour or until stable and then hourly until the infusion is discontinued and vital signs are stable. Pre-medication with paracetamol (1000 mg) and/or anti-histaminics (e.g. clemastine 2 mg) is advised. In addition, it is recommended to give the prednisone dose of the CHOP as a pre-medication prior to the infusion of rituximab (if applicable). If no adverse events are seen with the first rituximab infusion, no corticosteroid pre-medication has to be given before the next infusions (day 8). Otherwise it is advised to give pre-medication with corticosteroids (e.g. methylprednisolone 25 mg i.v. or hydrocortisone 100 mg i.v.). The initial rituximab dose should be 50 mg/hr for the first 30 minutes. If no adverse event is seen, the dose may be escalated in 30 minutes intervals with increment steps of 50 mg/hr, to a maximum of 400 mg/hr. Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 antibody. When any of the following events is noted, antibody infusion should be temporarily discontinued, the patient should be observed and the severity of the adverse events should be evaluated:

- fever > 38.5 ^{o}C;
- mild/moderate rigors;
- mild/moderate mucosal congestion or edema;
- drop in systolic blood pressure > 30 mm Hg.

The patient should be treated according to the best available local practices and procedures. Following observation, if the patients systems improve, the infusion should be continued at 1/2 the previous rate. Following the antibody infusion, the IV line should be kept open for medications. If there are no complications, the IV line may be discontinued after one hour of observation. If complications occur during infusion, the patient should be observed for two hours after the completion of the infusion.

If no adverse event is seen with the previous infusion, the next rituximab dose may be dissolved in 250 ml NaCL 0.9%. The first 50 ml may be infused in 30 minutes. If no adverse events occur, the remaining 200 ml may be infused in 1 hr.[28] If the patient encounters an adverse event, the rituximab infusion should be interrupted until the symptoms have been resolved. There after the infusion can be restarted according the following scheme: the first 30 minutes 50ml/hr, if no symptoms occur the infusion rate will be increased to 50 ml in 30 minutes, if no symptoms occur the infusion rate will be increased further to 150 ml/hr for 30 minutes, and finally the rest will be infused with an infusion rate of 200 ml/hr.

9.5 Patients with detectable circulating tumor cells and rituximab treatment

In patients with detectable circulating lymphoma cells, the initial rate of infusion should be reduced to 25 mg/hr. Patients with detectable circulating lymphoma cells may experience transient fever and rigors, shortness of breath and hypotension with infusion of chimeric anti-CD20 antibody. When these adverse events are noted, antibody infusion should be temporarily discontinued, the patient should be observed and severity of the adverse events should be evaluated. The patient should be treated according to the best available local practices and procedures. If the patients' symptoms improve during observation, the infusion should be continued at ½ the previous rate. Upon resolution of all adverse events and in judgment of the investigator, the patient may be gradually escalated to a maximum infusion rate of 400 mg/hr, and the remainder of the treatment can be carried out. Following the antibody infusion, the IV line should be kept open for medications. If there are no complications, the IV line may be discontinued after one hour of observation. If complications occur during infusion, the patient should be observed for two hours after completion of the infusion.

9.6 Special management orders during R-CHOP14

Appropriate supportive measures should be provided during treatment and a close monitoring is recommended. Elderly patients should be examined on a weekly basis, so that any side effects of the treatment will be recognized at an early point of time and appropriate treatment can be provided. Prophylaxis against Pneumocystis carinii and herpes infections is mandatory in both young and elderly patients. Adequate fluid intake should be ensured.

- Allopurinol

  Allopurinol will be applied according to local practices. The dose should be adapted if the creatinine clearance is decreased.

- Anti-emetics

  It is advised to administer ondansetron (Zofran®) 8 mg twice or thrice daily or granisetron (Kytril®) 1 mg once or twice daily orally with each chemotherapy cycle according to local practices.

- Prednisone tapering

  A gradual reduction of the prednisone dose is recommended to prevent marked fatigue after prompt discontinuation of prednisone. Prednisone 50 mg can be administered on day 6, 25 mg on day 7 and 10 mg on day 8.

  For patients complaining of fatigue after tapering of prednisone, hydrocortisone 20 mg orally in the morning and 10 mg orally at 12:00hr is recommended.

- Prophylaxis of infection

  Pneumocystis carinii prophylaxis is mandatory in all patients. This consists of cotrimoxazol 480 mg p.o. once daily. Starting with the prephase treatment until 4 weeks after the last R-

CHOP14 cycle. In case of cotrimoxazol intolerance this can be substituted by aerosolized pentamidine 300 mg once every 4 weeks.

Prophylaxis against herpes infections is mandatory in all patients. This consists of valaciclovir 500 mg p.o. twice a day. Starting with the prephase treatment until 4 weeks after the last R-CHOP14 cycle.

9.7 Maintenance treatment

Patients in arm 2 will receive maintenance treatment with one infusion of rituximab 375 mg/m^2 (with a maximum of 750 mg), once every 8 weeks for twelve consecutive cycles or until relapse. Maintenance treatment starts 4-8 weeks after the last R-CHOP14 cycle (including last rituximab administration).

9.8 Concomitant medication and treatment

No anti-cancer therapy or study medication other than outlined in the protocol is allowed.

9.8.1 Drugs

Concomitant medication introduced in the patient since the beginning of treatment, with the exception of medication which is an integral part of standard prophylactic institutional medication used in conjunction with chemotherapy (anti-emetics, allopurinol) and rituximab (antihistaminic, paracetamol) will be recorded on the Case Report Form (CRF) in case of any adverse event of CTCAE grade $\geq$ 2. Patients should receive full hematological supportive care including blood transfusions and other blood products, antibiotics, anti-emetics etc., where applicable.

9.8.2 Radiotherapy

Radiotherapy before or during protocol treatment is only permitted for major localized problems, i.e. in case of potential or actual life threatening symptoms due to localized lymphoma mass or infiltration. No radiotherapy after end of treatment is allowed. Therefore, testicular DLBCL and primary mediastinal B-cell lymphoma are not eligible for this study.

10 End of protocol treatment

Reasons for going off protocol treatment are:

1. Normal completion of protocol treatment
2. Progressive disease on CT-scan after the first four R-CHOP14 cycles (arm A and arm B)

3. Progression on protocol including relapse/progression after initial PR or CR(u) (i.e. before completion of treatment)
4. No CR or FDG-PET negative PR/CRu after eight (young patients) or six (elderly patients) R-CHOP14 cycles (arm A and arm B)
5. Manifest cardiomyopathy (reduction of LVEF > 15%)
6. Other excessive toxicity requiring stopping of protocol treatment (including toxic death)
7. Intercurrent death
8. Lost to follow up
9. Major protocol violation
10. No compliance of the patient (especially refusal to continue treatment)

11 Required clinical evaluations

Also see appendix B for a specification of staging and restaging evaluations

11.1 Observations prior to start of treatment

- History (including B symptoms)
- Physical examination (including WHO performance status, consultation ENT specialist)
- Laboratory tests (including Hb, WBC and differential, platelet count, sodium, potassium, calcium, creatinine, uric acid, bilirubin, alkaline phosphatase, y-GT, ALAT, ASAT, LDH, protein, albumin, immuno-electrophoresis, glucose)
- Quantitative IgG, IgA and IgM
- Routine urine analysis
- Imaging + bidimensional measurements (including chest X-ray, CT neck, thorax and abdomen)
- A baseline (pre-treatment) FDG-PET scan is optional, but recommended
- In case of clinical suspicion: bone scan, gastroscopy (recommended in case of tonsillar involvement), any clinically indicated examinations
- Lymph node biopsy for morphology and immunopathology of involved site
- Immunophenotyping of lymph node for CD20, CD3 (CD19 or CD79a optional)
- Cryo-preservation of lymph node tissue for central PA review and ancillary biological studies
- Bone marrow aspirate and biopsy at least 1.5 cm (including CD20/CD79a stain).
- Peripheral blood microscopical smear examination
- ABO and RhD blood group, irregular antibody screening
- Anti-HIV, anti Hepatitis B and C
- ECG

- Left ventricular ejection fraction (LVEF) or cardiac ultrasound/Doppler (only for elderly patients 66-80 years)
- Pulmonary function test: TLC, VC, FEV1 and diffusion capacity

11.2 Observations after 4 and 6 or 8 cycles of R-CHOP14

- History (including B symptoms)
- Physical examination (including WHO performance)
- Laboratory tests (including Hb, WBC and differential, platelet count, sodium, potassium, calcium, creatinine, uric acid, bilirubin, alkaline phosphatase, y-GT, ALAT, ASAT, LDH, protein, albumin, glucose)
- Immuno-electrophoresis if initially abnormal
- Quantitative IgG, IgA and IgM
- Routine urine analysis
- Imaging + bidimensional measurements of involved and/or new areas (including chest X-ray, CT neck, thorax and abdomen)
- FDG-PET scan is mandatory in all patients. The FDG-PET scan after 4 cycles should be performed just (1 to 3 days) before start of the 5^{th} cycle to avoid interference with the G-CSF and the R-CHOP. The FDG-PET scan after 6 cycles (elderly patients) or 8 cycles (young patients) should not be performed within 3 weeks after the R-CHOP (including the last rituximab administration)
- Bone marrow aspirate and biopsy (if positive at previous evaluation, including CD20/CD79a stain)

11.2.1 Response assessment after 4 and 6 or 8 cycles of R-CHOP14

Response will be formally evaluated according to the criteria of response in Appendix B (Cheson criteria). In addition to these criteria, PR or CR by CT will be reclassified to CR in case of a negative FDG-PET scan at originally involved nodal sites as defined by CT. If possible, a biopsy should be performed in case of PR on CT after treatment with a positive FDG-PET scan to confirm the presence of viable tumor. Patients with a positive biopsy, or (if biopsy is not feasible) unequivocal FDG-PET accumulation (preferably confirmed by repeat FDG-PET scanning), in sites identified as PR sites on CT scanning after 6 or 8 cycles of R-CHOP14 will be considered treatment failures. In case of inconsistency and absence of histological confirmation, final response after 6 or 8 cycles of R-CHOP14 will be classified according to the classical Cheson criteria. All relevant information on drug dose, measurable lesions, tumor response and treatment-related toxicity will be collected.

11.3 Observations during maintenance treatment and no further treatment phase

To be performed in both arms (arm 1 and arm 2). Visits will be planned at least every 8 weeks during the first two years or until an event occurs.

Every 8 weeks:

- History (including B symptoms)
- Physical examination
- Hb, WBC and differential, platelet count
- Creatinine, bilirubin, alkaline phosphatase, y-GT, ALAT, ASAT, LDH
- Any clinically indicated examinations
- Any documentation of abnormal events (e.g. secondary malignancies)
- Any treatment off protocol

At 6, 12, 18 and 24 months

- Quantative IgG, IgA and IgM
- CT neck, thorax and abdomen

There after follow up will be planned at least every 6 months during the next 3 years and annually thereafter until an event occurs. After relapse, patients will be followed until death.

12 Toxicities

12.1 CHOP14

CHOP is a common used chemotherapeutic regimen with well-known side effects. The most frequent side effect is myelosuppression, which may hamper patient adherence to the projected schedule of CHOP14. The pancytopenia can induce septic or hemorrhagic complications.

12.2 Rituximab

Side effects of rituximab may include fever, rigors, mucosal congestion or edema, drop in systolic blood pressure and anaphylactic shock in rare cases. These side effects are only observed during rapid infusion of rituximab. Special management is provided in paragraphs 9.4 and 9.5. In patients who experience side effects the infusion rate has to be restricted to 100 mg/hr.

Toxicities will be scored according to the NCI Common Terminology Criteria of Adverse Events, version 3.0 (Appendix D).

13 Safety evaluations and adverse events reporting

13.1 Definitions

Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject during protocol treatment. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse reaction (AR)

Adverse reactions (AR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected.

Serious adverse event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose results in:

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- significant / persistent disability
- a congenital anomaly / birth defect
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)

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

Unexpected SAE

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

Suspected unexpected serious adverse reaction (SUSAR)

All suspected ARs which occur in the trial and that are both unexpected and serious.

Protocol treatment period

The protocol treatment period is defined as the period from the first study-related procedure until 30 days following the last dose of protocol treatment or until the start of another systemic anti-cancer treatment off protocol, if earlier.

13.2 Reporting of (serious) adverse events

Adverse event

AEs will be reported on the CRF. All adverse events of Grade 2 or higher, with the exception of progression of disease, occurring during the protocol treatment period will be reported. Adverse events occurring after that period should also be reported if considered related to protocol treatment.

SAE and Unexpected serious adverse event

All SAEs occurring during the protocol treatment period must be reported to the HOVON Data Center by fax **within 24 hours of the initial observation of the event**, except hospitalizations for:

- a standard procedure for protocol therapy administration. Hospitalization or prolonged hospitali-zation for a complication of therapy administration will be reported as a Serious Adverse Event.
- the administration of blood or platelet transfusion. Hospitalization or prolonged hospitali-zation for a complication of such transfusion remains a reportable serious adverse event.
- a procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). Hospitalization or prolonged hospitali-zation for a complication of such procedures remains a reportable serious adverse event.
- prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- a procedure that is planned (i.e., planned prior to starting of treatment on study; must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the protocol treatment remains a reportable serious adverse event.

All details should be documented on the **Serious Adverse Event and Death Report**. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 2 working days and sent to the HOVON Data Center. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.

At any time after the protocol treatment period, Serious Adverse Events that are considered to be at least suspected to be related to protocol treatment must also be reported to the HOVON Data Center using the same procedure, **within 24 hours after the SAE was known to the investigator**.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship to the protocol treatment (also include pre-existing conditions)
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

13.3 Processing of serious adverse event reports

The HOVON Data Center will forward all reports within 24 hours of receipt to the study coordinator and the study central data manager. The report of an SAE will be the signal for the central data manager to ask the investigator or the responsible local data manager to complete and send as soon as possible all relevant CRF's for the involved patient with details of treatment and outcome.

Any suspected unexpected serious adverse reactions (SUSARs), from any source, will be reported by HOVON Data Center to the investigators, the Ethics Committee that approved the study, and to all applicable Health Authorities within required timelines.

14 Endpoints

See appendix B for a complete definition of endpoints.

First randomization

Primary endpoint

- Response rate (complete remission and FDG-PET negative partial remission or unconfirmed complete remission)

Secondary endpoints

- Failure free survival measured from the date of registration. Patients still alive or lost to follow up are censored at the last day they were known to be alive
- Overall survival measured from the time of registration
- Time to reach response
- Toxicity

Second randomization

Primary endpoint

- Failure free survival (measured from the date of second randomization)

Secondary endpoints

- Overall survival (measured from the date of second randomization)
- Toxicity

The definition of failure used in failure free survival (whichever comes first) will be:
- No response on induction treatment (whereby response is defined as CR or PET negative PR/CRu)
- Relapse
- Death (from any cause)

15 Data collection

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

- inclusion and exclusion criteria;
- baseline status of patient including medical history and stage of disease;
- timing and dosage of protocol treatment;
- adverse events;

- parameters for response evaluation;
- any other parameters necessary to evaluate the study endpoints;
- survival status of patient;
- reason for end of protocol treatment.

Each CRF page will be identified by a pre-printed trial number, and a unique combination of patient study number (assigned at registration), hospital and patient name code (as documented at registration) to be filled out before completing the form.
The CRF will be completed on site by the local investigator or an authorized staff member. Each page must be dated and signed by the local investigator upon completion. All CRF entries must be based on source documents. The CRF and written instructions for completing the CRF will be provided by the HOVON Data Center.
Copies of the CRF will be kept on site. The original CRF pages must be sent to the HOVON Data Center at the requested time points. How and when to send in forms is described in detail in the CRF header and the CRF instructions.
All data from the CRF will be entered into the study database by the HOVON Data Center.

16 Registration and randomization

16.1 Registration and randomization for induction treatment

The patient should be registered immediately after satisfactory completion of screening tests and obtaining informed consent, and before the start of chemotherapy.
Patients need to be registered at the HOVON Data Center of the Erasmus MC - Daniel den Hoed by phone call: +31.10.7041560 or fax +31.10.7041028 Monday through Friday, from 09:00 to 17:00, or via the Internet through TOP (Trial Online Process; https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Patient's initials or code
- Patient's hospital record number (optional)
- Sex
- Date of birth
- Age-adjusted IPI risk score
- PA number

- Original PA laboratory (pathologist and institution)
- Eligibility criteria

All eligibility criteria will be checked with a checklist.
Patients will be randomized, stratified by center, age group (18-65 vs. 66-80 years) and age-adjusted IPI score with a minimization procedure, ensuring balance within each stratum and overall balance. Each patient will be given a unique patient study number. This number and the result of randomization will be given immediately by TOP or phone and confirmed by fax or email.

16.2 Randomization for maintenance treatment

All patients eligible for randomization will be randomized through the HOVON Data Center by phone, fax or through TOP.

The following information will be required:
1. Protocol number + NB: second randomization
2. Institution number (name)
3. Name of caller/responsible investigator
4. Patient's study number
5. Eligibility criteria

Randomization will be stratified by center, age group (18-65 vs. 66-80 years) and age-adjusted IPI and induction treatment arm with a minimization procedure. The result of randomization will be given immediately by TOP or phone and confirmed by email or fax.

17 Statistical considerations

17.1 Sample size and accrual

Calculation of the sample size is based on the primary endpoints of the study: response rate on induction treatment (defined as CR and PET-negative PR/CRu) and failure free survival (FFS) from second randomization for maintenance treatment.
For the control arm, we assume:

	≤ 65 years	≥ 66 years
Age distribution at entry / 1st randomization	40%	60%
Probability of CR or PET-neg PR/CRu	80%	75%
Probability of no 2nd randomization (e.g. due to toxicity), despite CR or PET-neg. PR/CRu	5%	15%
Age distribution at 2nd randomization	44%	56%
3-year FFS from diagnosis	64%	53%[1]
3-year FFS from 2nd randomization (and FFS = 100% at 2nd rand.)	78%	67%[2]

[1] Observed in the R-CHOP arm from the HOVON 46 NHL

[2] Divide 53%[1] by .75 (= response rate), assume a constant failure rate, and assume 2nd randomization will take place about 4 months after entry

In order to detect with 80% power an improvement of the FFS from 2nd randomization with hazard ratio (HR) = 0.60 (2-sided significance level α = 0.05), 126 events are required. Assuming a proportional hazard for young vs elderly patients of ln(.78)/ln(.67) = 0.62, an accrual period of 5 years, and 2 years of follow up after the last patient was included in the maintenance randomization, this would require 395 patients (174 young and 221 elderly). Therefore it is required that 174/.76 + 221/.64 = 575 patients will be registered in this trial.
This will also give a power of 86% to detect an improvement in response rate (CR or PET-neg PR/CRu) from 77% to 87%.
In order to overcome dropout due to ineligibility, 600 patients will be registered.

17.2 Analysis

All analyses will be done according to the intention-to-treat principle.

17.2.1 Efficacy analysis

Logistic regression will be used to assess differences in response rate. The test for differences between the arms in failure free, progression free and overall survival will be done by Cox Regression analysis. All analysis will be stratified by age group. Additionally, Kaplan-Meier curves will be estimated.

17.2.2 Toxicity analysis

The incidence of adverse events will be evaluated through tabulation by type, grade and treatment arm, for all patients together, as well as for younger and elderly patients separately.

17.2.3 Interim analysis and stopping rules

Interim analyses are planned after the inclusion of 200 and 400 evaluable patients, primarily to guard against unfavorable results in the experimental arm. Before the first interim analysis, the serious adverse event rate in both treatment arms will be closely monitored in order to pick up any (unexpected) trends. If this is the case an earlier interim analysis will be done.
At each interim analysis a detailed report will be generated and presented to the Data and Safety Monitoring Board (DSMB). The report includes for both randomizations by treatment arm the number of randomized patients and at that time evaluable patients, treatment given, response rate and/or FFS, and incidence of (S)AE's (CTC grade).
The DSMB is free in her public recommendations to the study coordinators and the confidential recommendations to the study statistician, but below some guidelines are given.

- Primary purpose of the interim analyses is to guard against a higher failure rate in the experimental arms compared with the standard treatment arms. A higher failure rate in the experimental arm in one of the randomizations with a P-value <0.10 is a good reason to recommend stopping of that randomization or recommendations for modifications of the treatment.
- A benefit in terms of a lower failure rate in an experimental arm of a randomization is in general no reason to recommend stopping of that randomization, unless the associated P-value is very extreme (P<0.001) and the number of evaluable patients in each arm of that randomization is at least 100.

17.3 Statistical analysis plan (SAP)

Before the final analysis, a SAP will be prepared by the trial statistician and approved by the principal investigators. It will describe in detail the analyses to be performed. Deviations from the analyses specified in paragraphs 17.1 and 17.2 will be discussed with the study coordinators and can only affect the exploratory analyses, but not the primary (confirmatory) analyses on which the sample size is based. All except the primary analyses should be considered as hypothesis-generating only.

17.4 Data and safety monitoring board

A Data and Safety Monitoring Board (DSMB) will be installed before start of the study.

18 Ethics

18.1 Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

18.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP Guidelines and the EU directive Good Clinical Practice (2001-20-EG). The local investigator is responsible for ensuring that the study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical Practice (GCP), EU directive Good Clinical Practice (2001-20-EG), and applicable regulatory requirements.

18.3 Patient information and consent

Written Informed consent of patients is required before randomization. The procedure and the risks and the opinions for therapy in NHL will be explained to the patient.
All research using patient's tissues will be governed by the "Code for Proper Secondary Use of Human Tissue in the Netherlands" as developed by the Dutch Federation of Medical Scientific Societies. Explicitly written informed consent is required for use of the patient's tissues in side studies, including, but not limited to, inclusion in tissue micro-array's (TMA). The patient may withhold his/her permission for side studies at any time. This will not affect his/her status in the trial.

19 Trial insurance

The HOVON insurance program covers all patients from participating centers in The Netherlands according to Dutch law (WMO). The WMO insurance statement can be viewed on the HOVON Web site www.hovon.nl.
Individual participating centers from outside the Netherlands have to inform the HOVON about the national laws regarding the risk insurance of patients participating in a study.

19.1 Intergroup studies

The HOVON insurance program does not cover the risk insurance of patients from centers participating within another cooperative group taking part in an intergroup study. The other participating groups will cover the insurance of patients registered/randomized through their offices.

20 Publication policy

The final publication of the trial results will be written by the Principal Investigator and Study Coordinator(s) on the basis of the statistical analysis performed at the HOVON Data Center. A draft manuscript will be submitted to the Data Center and all co-authors (and the sponsor, where applicable) for review. After revision by the Data Center, the other co-authors (and the sponsor), the manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the Principal Investigator and Study Coordinator(s), the lead investigators of the major groups (in case of intergroup studies) investigators who have included more than 5% of the evaluable patients in the trial (by order of number of patients included), the statistician(s) and the HOVON data manager in charge of the trial, the review pathologists and others who have made significant scientific contributions.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analysis, but no comparisons between randomized treatment arms may be made publicly available before the recruitment is discontinued.

Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This also includes studies based on biopsy material or any other biological material retrieved from patients during the study. This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparison between randomized treatment arms nor an analysis of any of the study end-points unless the final results of the trial have already been published.

21 Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
AL(A)T	Alanine Amino Transferase
AR	Adverse reaction
AS(A)T	Aspartate Amino Transferase
BM	Bone Marrow
CLL	Chronic Lymphatic Leukemia
CMV	Cytomegalovirus
CR	Complete Remission
CRu	Complete Remission unconfirmed
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, Vincristine, Prednisone
DLBCL	Diffuse Large B-cell Lymphoma
DSHNHL	Deutsche Studien gruppe High grade Non Hodgkin Lymphoma
EBV	Epstein Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ENT	Ear Nose Throat
FCM	Fludarabine, Cyclophosphamide, Mitoxantrone
FDG-PET	Fluordeoxyglucose Positron Emission Tomography
FEV1	Forced Expiratory Volume in 1 second
G-CSF	Granulocyte Colony Stimulating Factor
GCP	Good Clinical Practice
GELA	Groupe d'Etude de Lymphomes de l'Adulte
GLSG	German Low grade Study Group
γGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HOVON	Dutch/Belgian Hemato-Oncology Cooperative Group
HR	Hazard Ratio
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IPI	International Prognostic Index
IV	Intravenous
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
NaCl	Sodium Chloride
NCI	National Cancer Institute

NCRI	National Cancer Research Institute
NHL	Non-Hodgkin's Lymphoma
NYHA	New York Heart Association
PA	Pathology
PB	Peripheral Blood
PD	Progressive Disease
PO	Per Os
PPD	Product of the two largest Perpendicular Diameters
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable disease
SC	Subcutaneous
SPD	Sum of the Products of the two largest perpendicular Diameters
SUSAR	Suspected Unexpected Serious Adverse reaction
TLC	Total Lung Capacity
TOP	Trial Online Process
ULN	Upper Limit of Normal
US	Ultrasound
VC	Vital Capacity
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen
WBC	White Blood Count

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A. NHL WHO classification

B-cell neoplasms

WHO		
1		Precursor B-cell lymphoblastic leukemia / lymphoma
2		B-cell chronic lymphocytic leukemia / small lymphocytic lymphoma
3		B-cell prolymphocytic leukemia
4		Lymphoplasmocytic lymphoma
5		Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type
6		Nodal marginal zone lymphoma (+/- monocytoid B cells)
7		Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes)
8		Plasma cell myeloma / Plasmocytoma
9		Follicular lymphoma; grade I, grade II, grade III
10		Mantle-cell lymphoma
11		Diffuse large B-cell lymphoma Subtypes: Primary mediastinal B cell lymphoma Intravascular B cell lymphoma T cell rich B cell lymphoma Primary effusion lymphoma (not eligible in this trial)
12		Burkitt's lymphoma
13		Unclassifiable

T-cell neoplasms

WHO		
21		Precursor T-cell lymphoblastic leukemia / lymphoma
22		T-cell prolymphocytic leukemia
23		T-cell granular lymphocytic leukemia
24		Aggressive NK-cell leukemia
25		Adult T-cell leukemia / lymphoma (HTLV1+)
26		Extranodal NK / T-cell lymphoma, nasal-type
27		Enteropathy type T-cell lymphoma
28		Hepatosplenic γ / δ T-cell lymphoma
29		Subcutaneous panniculitis-like T-cell lymphoma
30		Mycosis fungoides/Sézary syndrome
31		Anaplastic large cell lymphoma, primary cutaneous type
32		Peripheral T-cell lymphoma (not otherwise characterized)
33		Angioimmunoblastic T-cell lymphoma
34		Anaplastic large cell lymphoma (T- and null-cell types), primary systemic type
35		Unclassifiable

B. HOVON Staging and Response Criteria for Non Hodgkin's Lymphomas

This document describes the minimally required staging and evaluation procedures and response criteria that will be applied in all HOVON NHL studies. It is based on international working group recommendations (Cheson et al., JCO, Vol.17, 1999, pp1244-1253).

Response is currently assessed on the basis of clinical, radiologic, and pathologic (i.e., bone marrow) criteria. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL.

Immunophenotyping of blood or bone marrow has not been included as standard minimum requirement for the staging and restaging of lymphoma, even though it may be done standard in some centers (Hanson, Blood, Vol 94, 1999, pp 3889-3896). It may be a requirement in specific studies involving monoclonal antibodies.

Staging and restaging procedures
Only minimal requirements are specified.

A. Staging at on study before start of treatment
- History (including B symptoms)
- WHO Performance status
- Physical examination
- Laboratory tests
  - Hb, WBC, differential, platelet count, LDH
  - Calcium, creatinine, uric acid, glucose, albumin, bilirubin, ALT
  - paraprotein by immuno-electrophoresis
  - quantitative immunoglobulins only if immuno-electrophoresis abnormal
  - Hepatitis-B in case of abnormal liver function tests
  - HIV test
- Tumor biopsy for histology and immunohistology
- Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology
- Bone marrow aspirate for cytology
- Peripheral blood for cytology
- Imaging
  - CT thorax and abdomen including pelvis
  - US cervical region strongly recommended (Br J Hem. 88 (3) 626-8, 1994); alternative: CT cervical region
- Consultation of ear-nose-throat specialist if indicated (i.e. complaints or gastro-intestinal lymphoma)
- Gastroscopy if indicated (i.e. localization ENT, thyroid)
- Lumbal punction if indicated (i.e. localization testis, nasopharynx or brain)

B. Restaging for the evaluation of treatment
Restaging for the evaluation of treatment should be performed within 2 months after the end of treatment to assess response. Additional moments of restaging, e.g. after 3 cycles of CHOP, are specified in the study protocol.
- History (including B-symptoms)
- WHO Performance status
- Physical examination
- Laboratory tests
  - Hb, WBC, platelet count, LDH
  - Repeat previously abnormal tests
- Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology if involved previously
- Bone marrow aspirate for cytology if involved previously
- Peripheral blood for cytology if involved previously

Imaging
- CT thorax and abdomen including pelvis
- US of cervical region; alternative: CT cervical region
- Assessment of other localizations only if involved previously

C. Restaging during follow-up to determine remission status (until progression)
In case of CRu (see below) repeat CT 2-4 months after last CT for response evaluation.
- Physical examination
- WHO Performance status
- Laboratory tests
  - Hb, WBC, platelet count, LDH
- **Only if indicated**, i.e. LDH elevation or clinical signs of progression:
  - Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology (if indicated)
  - Bone marrow aspirate for cytology (if indicated)
  - Peripheral blood for cytology (if indicated)
  - Imaging
    - CT thorax and abdomen including pelvis (if indicated)
    - US of cervical region; alternative CT of cervical region (if indicated)

Staging & Remission Status Evaluation

	On Study	***Evaluation of Treatment***	***Follow up***
• *History*	*x*	*X*	*x*
• *WHO performance status*	*x*	*X*	*x*
• *Physical examination*	*x*	*X*	*x*
• *Laboratory tests*			
▪ *Hb*	*x*	*X*	*x*
▪ *WBC*	*x*	*X*	*x*
▪ *Differential*	*x*	*o.i.*	
▪ *Platelet count*	*x*	*X*	*x*
▪ *LDH*	*x*	*X*	*x*
▪ *Calcium*	*x*	*o.i.*	
▪ *Creatinine*	*x*	*o.i.*	
▪ *Uric acid*	*x*	*o.i.*	
▪ *Glucose*	*x*	*o.i.*	
▪ *Bilirubin*	*x*	*o.i.*	
▪ *ALAT*	*x*	*o.i.*	
▪ *Albumin*	*x*	*o.i.*	
▪ *Immuno-electrophoresis*	*x*	*o.i.*	
▪ *Quantitative immunoglobulins*	*o.i.*	*o.i.*	
▪ *Hepatitis-B*	*x*		
▪ *HIV test*	*x*		
• *Tumor biopsy*	*x*	*o.i.*	*o.i.*
• *BM biopsy*	*x*	*o.i.*	*o.i.*
• *BM aspirate*	*x*	*o.i.*	*o.i.*
• *PB for cytology*	*x*	*o.i.*	*o.i.*
• *Imaging**			
▪ *CT thorax*	*x*	*X*	*o.i.*
▪ *CT abdomen including pelvis*	*x*	*X*	*o.i.*
▪ *US/CT cervical region*	*r.*	*r.*	*o.i.*
▪ *FDG-PET scan*	*r.*	*X*	
• *ENT consultation*	*o.i.*	*o.i.*	*o.i.*
• *Gastroscopy*	*o.i.*	*o.i.*	*o.i.*
• *Lumbal punction*	*o.i.*	*o.i.*	*o.i.*

o.i. *on indication*
r. *strongly recommended*

Bone marrow evaluation
Bone marrow biopsy* must be adequate (≥ 20 mm biopsy core).
A bone marrow aspirate and biopsy should always be performed at diagnosis. If positive they should be repeated to determine response. They should also be performed in case of new abnormalities in the peripheral blood.

Bone marrow biopsies should be scored as
- positive unequivocal cytologic or architectural evidence of malignancy
- negative no aggregates or only a few well-circumscribed lymphoid aggregates
- indeterminate increased number or size of aggregates without cytologic or architectural atypia

The bone marrow report should be reported not only as positive or negative for lymphoma, but the percentage of invasion and the lymphoma subtype should be indicated, the latter to describe any discordance with the nodal disease.

* see also parargraph 11.1 for requirements of CD20/CD79a immunostain for this protocol.

Measurable disease and size of disease.
Response evaluation is primarily based on bi-dimensionally measurable nodes, nodal masses or nodules in liver or spleen.

Nodes with largest diameter ≤ 1 cm are considered normal and not pathologic. The size of a single node, nodal mass or nodule is defined as the product of the two largest perpendicular diameters (PPD). Nodes of which only one dimension is specified are considered as circular for the calculation of PPD size. If after treatment a nodal mass consisting of individual confluent nodes breaks up in separate nodes the sum of the PPD of the separate nodes must be compared with the size of the pretreatment nodal mass.
All nodules in liver and spleen are considered pathologic, irrespective of size.

The sum of the PPD (SPD) of a set of indicator lesions is used as a quantitative measure for response evaluation. The indicator lesions have to be chosen from the nodes and nodal masses in the following way. If the number of nodes or nodal masses before treatment is 6 or less, all these are considered as indicator lesions. If the number of nodes or nodal masses is more than 6, a minimum number of at least 6 indicator lesions have to be chosen. These nodes or nodal masses should be selected according to the following features:

a) they should be among the largest dominant sites
b) they should be clearly measurable in at least two perpendicular dimensions,
c) they should be from as disparate regions of the body as possible
d) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

The choice of the indicator lesions should be made before start of treatment. All indicator lesions must be numbered and measured bi-dimensionally before start of treatment and at the evaluation times specified in the protocol. The location and size must be documented and reported in the CRF.

Assessable disease
Assessable disease is considered all abnormalities that are not bi-dimensionally measurable, e.g. positive bone marrow or peripheral blood.

RESPONSE CRITERIA

Complete response (CR) requires the following:
1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy
2. Normal LDH (i.e. ≤ ULN). An elevated LDH detracts from a CR unless it is attributable to causes not related to NHL, e.g. hemolysis.
3. All nodes and nodal masses must have reduced in size to ≤ 1.0 cm in greatest transverse diameter, or
4. If some nodes have regressed to a size between 1.0 and 1.5 cm in greatest transverse diameter from a size over 1.5 cm, while none have a size over 1.5 cm, the SPD of the indicator lesions must have regressed by more than 75%.
5. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable and/or no longer considered enlarged on physical examination. However, no normal size can be specified, because of the difficulties in accurately evaluating splenic size. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
6. Any nodules in liver or spleen must have disappeared.
7. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site.

CR/unconfirmed (CRu) includes those patients who fulfill criteria 1, 2, 4 and 5 above, but with one or more of the following features/exceptions:
1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the PPD size. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD size compared with the size of the original mass. The SPD size of the indicator lesions must have regressed with more than 75%.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

In case of apparent CRu it is recommended to perform, if possible, a cytological punction or biopsy of a residual lymph node mass to determine the cytopathological status. It is also recommended in case of CRu to repeat CT or US of the residual lesion after 2-4 months.

Partial response (PR) requires the following:
1. ≥ 50% decrease in SPD of the indicator lesions.
2. ≥ 50% decrease in SPD of splenic and hepatic nodules if present and bi-dimensionally measurable at start of treatment.
3. No increase in the size of any single node, nodule, liver, or spleen by more than 25%.
4. No new sites of disease.
5. All patients who meet the criteria for CR or CRu except for an LDH >ULN that is not attributable to other causes than NHL or with remaining but decreased nodules in liver or spleen, or with remaining assessable disease are classified as PR.

Stable disease (SD) is defined as less than a PR (see above) but is not progressive disease (see below).

Progressive disease (PD) requires the following
1. ≥50% increase in the PPD-size of any at baseline identified abnormal node, nodal mass or nodule.
2. Appearance of any new lesion during or at the end of therapy.

Endpoints during follow up

Progression of disease is defined for all patients, irrespective of response on treatment. The following criteria apply:
1. ≥ 50% increase from nadir in the PPD-size of any previously identified abnormal node.
2. Appearance of any new lesion.

Relapse requires the following:
1. Previous achievement of CR or CRu.
2. Progression of disease as defined above.

Note:
1. *Relapse is the same as progression of disease after CR or CRu.*
2. *An abnormal or increasing abnormal LDH, not attributable to other causes than NHL, is not sufficient evidence for the determination of progression. Imaging studies must be performed in such a case.*
3. *Note the difference between PD as response category and Progression of disease as event during or after treatment. All patients whose best response on treatment is PD, per definition also have reached the endpoint Progression of disease. But also other patients with a better response may eventually show progression of disease.*

Failure is defined as
1. either no complete response (i.e. no CR or CRu) on treatment or
2. relapse

Definitions of End Points for Clinical Trials

End Point	Response Category	Definition	Point of Measurement
Overall survival	All patients	Death from any cause	Entry onto trial
Event-free survival	All patients	Failure or death from any cause	Entry onto trial
Progression-free survival	All patients	Disease progression or death from NHL	Entry onto trial
Disease-free survival	CR, CRu	Time to relapse	First documentation of response
Response duration	CR, CRu, PR	Time to relapse or progression	First documentation of response
Time to next treatment	All patients	Time when new treatment is needed	Entry onto trial
Cause-specific death	All patients	Death related to NHL	Entry onto trial

C. Ann Arbor staging classification

Stage	Definition
I	Involvement of a single lymph node region (I) or of a single extra-lymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extra-lymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized involvement of an extra-lymphatic organ or site (III_E) or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues, with or without associated lymph node involvement

B symptoms
The absence or presence of fever, night sweats, and/or unexplained loss of 10% or more of body weight in the six months preceding admission are to be denoted in all cases by the suffix letter A or B, respectively.

Extra-nodal involvement
Involvement of extra lymphatic tissue on one side of the diaphragm by limited direct extension from an adjacent nodal site is classified as extra-nodal extension and denoted by suffix letter E. The E category may also include an apparently discrete single extra-nodal deposit consistent with the extension from a regionally involved node. More extensive extra-nodal disease, e.g. multiple extra-nodal deposits, is classified as stage IV. A single extra-lymphatic site as the only site of disease should be classified as I_E.

Notes
1. For the purpose of defining the number of anatomical lymph node regions the following areas are considered as one region:
- All nodes at one side of the neck are considered as in one region, i.e. consisting of the sub-regions supra-clavicular, cervical, sub-mandibular, occipital, pre-auricular and post-auricular.
- The axillary region includes the infraclavicular nodes.
- The mediastinum is considered as one region, including the sub-carinal and pericardial nodes.
2. The lung-hilus is considered as a separate region. Thus involvement of both the mediastinum and a hilar localization implies stage II disease.
3. Hilar nodes should be considered lateralized and when involved on both sides constitute stage II disease.

D. Common Terminology Criteria for Adverse Events

The grading of toxicity and adverse events will be done using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 3.0, published Dec 12, 2003. A complete document (72 pages) may be downloaded from the following sites:

http://ctep.info.nih.gov/reporting/ctc.html
http://www.hovon.nl (under Studies > Documents)

E. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

F. NYHA* scoring list

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

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

G. Age-adjusted International Prognostic Index

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

Risk factors are:

- Ann Arbor stage III or IV
- WHO performance status 2-4
- LDH > 1x Upper limit of normal (ULN)

The age-adjusted IPI:

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