Phase II study on the feasibility and efficacy of consolidation with ^{90}Y-ibritumomab tiuxetan in patients with relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma having achieved partial or complete remission after induction with R-PECC chemotherapy.

PROTOCOL

Study Coordinators	:	P.J. Lugtenburg R.E. Brouwer G.W. van Imhoff
Statistician	:	W.L.J. van Putten
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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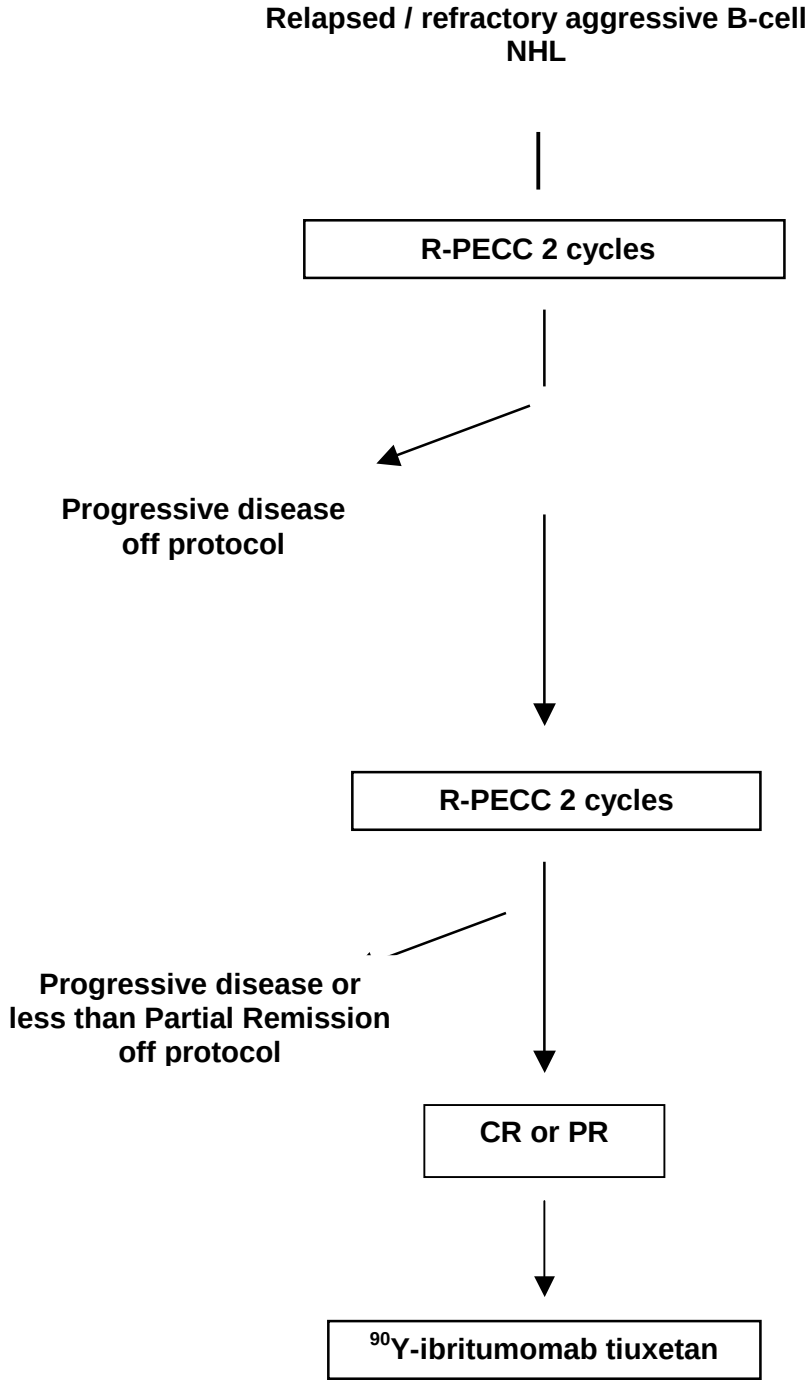
1 Scheme of study



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3 Synopsis

Study phase	Phase II
Study objectives	Evaluation of feasibility and efficacy of consolidation with ^{90}Y-ibritumomab tiuxetan in patients with relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma (NHL) having achieved partial or complete remission after induction with R-PECC chemotherapy
Patient population	Patients with histologically confirmed CD20 positive aggressive NHL (FL grade 3b, DLBCL) refractory or in first or second relapse, age $\geq$ 18 years with WHO performance status 0-2, after / not eligible for autologous stem cell transplantation (ASCT)
Study design	Prospective, multicenter, non-randomized trial
Duration of treatment	Expected duration of treatment is about 5-6 months
Number of patients	60 patients registered
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported
Planned start of recruitment	I 2008
Planned end of recruitment	III 2009

4 Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
Study Coordinators	P. Lugtenburg	Erasmus MC, Rotterdam
	R.E. Brouwer	Reinier de Graaf Hospital, Delft
	G.W. van Imhoff	UMCG, Groningen
Representative of Sponsor (HOVON)	P.C. Huijgens, chairman	VU University Medical Center Amsterdam
Writing Committee	J.W. Baars	A. van Leeuwenhoek Hospital, Amsterdam
	H. Berenschot	Albert Schweitzer Hospital, Dordrecht
	D.H. Biesma	St. Antonius Hospital, Nieuwegein
	L. Böhmer	Haga Hospital, The Hague
	J.K. Doorduijn	Erasmus MC Daniel den Hoed, Rotterdam
	H.C. Schouten	University Hospital, Maastricht
	M.H.H. Kramer	Meander MC, Amersfoort
	E. Meijer	UMCU, Utrecht
	M.J. Kersten	Academic Medical Center, Amsterdam
	J.M. Zijlstra	VUmc, Amsterdam
	M.R. Schaafsma	Medical Spectrum Twente, Enschede
	P. Sonneveld	Erasmus MC, Rotterdam
	R. Willemze	LUMC, Leiden
Pathology review	K.H. Lam	Erasmus MC, Rotterdam
	Ph.M. Kluin	UMCG, Groningen
	J.J. Oudejans	VUmc, Amsterdam
FDG-PET review	E. Comans	VUmc, Amsterdam
	J. Pruim	UMCG, Groningen
	W. Oyen	UMC St. Radboud Nijmegen
Statistician	W.L.J. van Putten	HOVON Data Center, Rotterdam
Datamanagement	HOVON Data Center	HOVON Data Center, Rotterdam
SAE notification	HOVON Data Center	Fax: +31 10 7041028
E-mail study coordinator	p.lugtenburg@erasmusmc.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, hospital number, age and gender of the patient should be provided.
Pathology slides 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. For refractory patients material from the original diagnosis should be sent. For patients in relapse, material of confirmation of relapse should be sent.
In case of very little material (endoscopic biopsy samples, needle biopsy samples) 10 unstained sections together with the report may be sent for immunohistochemical confirmation only.
Confirmation of diagnosis (by the review panel) is not necessary for registration and start of treatment.
Central review is performed to confirm the diagnosis of follicular lymphoma grade 3b and 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).
Classification includes immunophenotypical characterization by a standard panel of markers including CD20, CD79a, CD5, CD10, BCL6, MUM1, and BCL2. The review analysis will be done without knowledge of patient outcome.
If a definite diagnosis cannot be attained based on histological and immunohistochemical findings alone, additional molecular studies may be performed. A review by the two other review pathologists (Dr. J.J. Oudejans and Prof. Dr. Ph.M. Kluin) will be performed in case of discrepancy with the local pathologist or when judged appropriate.
Within 3 months after the review process and integration in the TMA, the material will be returned to the pathologist who has sent in the material. 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 85
Department of Pathology, Josephine Nefkens Institute
Erasmus MC
Dr. Molewaterplein 50
3015 GE ROTTERDAM

Tel: +31 10 4639222
Fax: +31 10 4087923
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 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 to:

Dr. J. Pruim, nuclear medicine physician
Department of Nuclear Medicine and Molecular Imaging
UMCG
PO box 30 001
9700 RB Groningen
tel: +31 50 361 3311
fax: +31 50 361 1687
e-mail: j.pruim@pet.umcg.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 a three point visual scoring system: 0= normal/benign; 1= indeterminate; 2= malignant. The PET scans are scored with knowledge of the CT data. PET is considered positive in case of clearly enhanced focal uptake (score 2) versus background in residual mass at CT. PET is also considered positive in case of new sites with focally enhanced uptake considered to represent lymphoma involvement.

5 Introduction

5.1 Aggressive non-Hodgkin's lymphoma

The majority of cases of aggressive non-Hodgkin's lymphoma (NHL) are observed in patients over 65 years of age. In elderly patients treatment with CHOP-like chemotherapy induces complete responses in only 40%-50%, with five-year disease-free survival and overall survival rates of respectively 40% and 24%[1]. These results can be improved by adding rituximab to the classical CHOP-21 or "dose-densified" CHOP (CHOP-14). However, the relapse rate is still high. Up to 30%-40% of patients relapse within two years[2,3].

Young patients with a chemosensitive relapse may be cured by high-dose therapy followed by stem cell transplantation[4]. However, only 50% of these young patients obtain at least a partial remission on second line (immuno)-chemotherapy and qualify for autologous stem cell transplantation. Moreover, eventually 25% will relapse. For elderly patients with relapsed aggressive NHL effective salvage regimens are hampered by their toxicity. In general, elderly patients are ineligible for stem cell transplantation. The results of second line chemotherapy regimens are disappointing. Although responses may be observed in 35%-55% of patients, these are usually of short duration and less than 15% of patients achieve a durable complete response[5]. The need for exploring new treatment modalities with substantial response rate and response duration is high.

5.2 Radioimmunotherapy, ^{90}Y-ibritumomab tiuxetan and Rituximab

Radioimmunotherapy (RIT) is a relatively new treatment for NHL that involves the linking of a high-energy, short-path length radionuclide to an antibody to form a radioimmunoconjugate (RIC). The goal of RIT is to use the targeting feature of a monoclonal antibody to focus radiation to the target cell population while sparing nearby normal tissues. The RIC kills tumor cells by the direct effects of the antibody as well as the effects of ionizing low-dose-rate radiation[6]. Radiolabeled antibodies may be particularly effective in treating non-Hodgkin's lymphoma, because lymphoma cells are highly sensitive to radiation. In addition, the local emission of radiolabeled antibodies is able to destroy cells in close proximity to the bound antibody, even though they do not express the target antigen ("crossfire" effect), therefore circumventing the problem of limited perfusion of poorly vascularized or bulky tumors.

^{90}Yttrium- (^{90}Y) ibritumomab tiuxetan was approved by the US Food and Drug Administration (FDA) in 2002 for the treatment of relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including rituximab-refractory follicular NHL. In 2004, European Medicines Agency (EMEA) approval was granted for the use of ^{90}Y-ibritumomab tiuxetan (Zevalin; Schering AG, Berlin, Germany) for the treatment of adult patients with rituximab relapsed or refractory CD20^{+} follicular B-cell NHL. The formation of ^{90}Y-ibritumomab tiuxetan requires the linking protein, tiuxetan, to chelate ^{90}Y to the

murine, anti-CD20 immunoglobulin, ibritumomab. CD20 is a good target for RIT for several reasons. CD20 expression is restricted to normal B-cells and almost all B-cell NHL are CD20 positive. CD20 is not internalized into the cell nor expressed on other normal tissues (including stem cells). Depletion of normal B-cells by these antibodies has not led to significant short- or long-term side effects. ^{90}Y has several advantages. It is a pure beta (β)-emitter without a gamma (γ)-component and delivers high β-energy to the tumor. Moreover, ^{90}Y has a short half-life of 64 hours. Lastly, because of its optimal path length of 5-10 mm, it kills both targeted and adjacent cells.
The anti-CD20 monoclonal antibody Rituximab, 250 mg/m^2, is administered before each dose of ^{90}Y-ibritumomab tiuxetan, to optimize biodistribution. Although the ibritumomab antibody is murine, human anti-mouse antibody development is very rare[7]. ^{90}Y-ibritumomab tiuxetan is administered in an outpatient setting over 10 minutes. Specialized isolation rooms are not required because the β-radiation is effectively shielded by plastic or acrylic[8]. Patients may be released immediately after treatment.

5.3 Efficacy ^{90}Y-ibritumomab tiuxetan

Clinical trials to assess toxicity and efficacy of ^{90}Y-ibritumomab tiuxetan were initially limited to patients with relapsed low or intermediate CD20 positive B-cell NHL (according to the working formulation). From the first phase I trial of ^{90}Y-ibritumomab tiuxetan it was concluded that pre-dosing with cold antibody improved the biodistribution of ^{90}Y-ibritumomab tiuxetan and that doses of ≤ 40 mCi were not myeloablative[9]. In the second phase I-II trial the maximum tolerated dose was determined that could be given to patients without the use of stem cells or prophylactic growth factors. All patients who received 0.4 mCi/kg were able to recover bone marrow function without growth factors or stem cell support[10]. A separate trial using a reduced dose ^{90}Y-ibritumomab tiuxetan of 0.3 mCi/kg was designed for patients with platelet counts between 100–149 x 10^9/l [11,12]. The median nadir platelet count was 26 x 10^9/l. These phase I/II trials demonstrated a 67%-83% overall response rate (ORR) in all patients with 26%-47% CR. The duration of response was 11.5-11.7+ months[10-12]. In a randomized trial the ORR of 80% and the CR rate of 30% in the ^{90}Y-ibritumomab tiuxetan arm were both significantly higher than the 56% ORR and the 16% CR rate for a standard course of rituximab[13]. Another trial was performed in rituximab refractory patients. This patient group was heavily pre-treated with a median of four prior therapies. The ORR was 74% with 15% CR[14].
In the phase I-II trial there were 14 patients with relapsed large cell NHL and 43% responded[10]. Four of 14 patients (29%) achieved a CR, and 2 patients (14%) achieved a PR. Recently, the results were reported of a phase II trial in 104 elderly patients with first relapsed or primary refractory diffuse large B-cell lymphoma[15]. The median age of the patients was 73 years. Treatment was given with one single dose of ^{90}Y-ibritumomab tiuxetan 0.4mCi/kg (no chemotherapy). The overall

response rate in patients previously treated with chemotherapy (primarily CHOP, n = 76) was 54%, with 32% complete responses. In patients who had experienced a first relapse to chemotherapy plus rituximab (n = 28, of whom 36% were primary refractory to chemo-immunotherapy, this was a very bad prognostic subgroup) the overall response rate was 19%. At a median follow-up of 18 months, approximately 40% of the patients in the study were considered to have achieved a durable response.

Recently preliminary results were presented of two trials concerning ^{90}Y-ibritumomab tiuxetan consolidation after rituximab-chemotherapy in aggressive lymphoma. In the first trial ^{90}Y-ibritumomab tiuxetan consolidation was given in elderly patients with diffuse large B-cell lymphoma after induction therapy with 6 cycles of rituximab-CHOP[16]. The second trial was performed in patients with mantle cell lymphoma. ^{90}Y-ibritumomab tiuxetan consolidation was given after 3 to 6 cycles of fludarabine, cyclophosphamide and mitoxantrone with or without rituximab[17]. The dose of ^{90}Y-ibritumomab tiuxetan in both trials was 0.4 mCi/kg.

The toxicity of ^{90}Y-ibritumomab tiuxetan consolidation was manageable and was mainly hematologic. Hematologic toxicity was similar to single agent toxicity of 90Y-ibritumomab tiuxetan, with slightly greater thrombocytopenia (CTC grade 3 and 4 of 46% and 15% respectively[16]. Hematologic toxicity started 2-4 weeks after the administration of ^{90}Y-ibritumomab tiuxetan. The median nadir counts occurred at week 4-7. No patient developed life-threatening infections or haemorrhages.

5.4 Safety of ^{90}Y-ibritumomab tiuxetan

The safety of ^{90}Y-ibritumomab tiuxetan has been reported in the abovementioned trials and also in aggregate[7,18]. Infusion-related toxicities associated with ^{90}Y-ibritumomab tiuxetan are rare. No significant acute organ dysfunction was noted. The main toxicity was myelosuppression. The nadir typically occurred at 7-9 weeks and lasted approximately 1-4 weeks. Following the 0.4 mCi/kg dose, grade 4 neutropenia, thrombocytopenia and anemia occurred in 30, 10 and 3% of patients, respectively. Patients with bone marrow involvement had a significantly greater incidence of myelosuppression than patients without bone marrow involvement. Seven percent of patients were hospitalized with infection (3% with neutropenia) and 2% had grade 3 or 4 bleeding events.

In the relapsed diffuse large B-cell lymphoma trial the observed myelotoxicity occurred earlier than in the trials with relapsed low-grade lymphoma patients. Thrombocytopenia was the most significant side effect, typically occurring 4 weeks after ^{90}Y-ibritumomab tiuxetan was administered and lasting 1-4 weeks. Grade 4 thrombocytopenia occurred in 8.5% of patients. The incidence of severe infections was low, with only 7.6% of patients hospitalized with infection during the treatment period[15].

Therefore special attention must be paid to the myelotoxicity of ^{90}Y-ibritumomab tiuxetan, which, unlike chemotherapy, induces a rather late decrease of counts, lasting 1-4 weeks, followed by a gradual recovery over the ensuing weeks.
After administration patients and family members are recommended to avoid direct exposure to the patient's body fluids such as blood, urine and stool. The dose of radiation to family members of the patient is similar to background radiation[19]. It is recommended to use condoms during sexual intercourse for one week after ^{90}Y-ibritumomab tiuxetan administration[8]. Females of childbearing potential as well as males should use effective contraceptive methods during treatment with ^{90}Y-ibritumomab tiuxetan and for 12 months afterwards.

5.5 Rationale for consolidation with ^{90}Y-ibritumomab tiuxetan after R-PECC induction chemotherapy

The aim of this phase II study is to evaluate the initial safety and efficacy of a single course of ^{90}Y-ibritumomab tiuxetan after R-PECC induction chemotherapy in patients with relapsed or refractory aggressive B-cell NHL after or not appropriate for ASCT. In these patients conventional chemotherapy achieves only short remissions and does not improve the poor clinical outcome. In several Dutch hemato-oncological centers Rituximab-PECC (Prednisone, Etoposide, Chlorambucil, Lomustine) combination chemotherapy is being used as a salvage treatment for patients with relapsed aggressive NHL or Hodgkin's lymphoma who are not eligible for stem cell transplantation. PECC is a completely oral schedule. It has mild acceptable toxicity[20]. The major toxicity is myelosuppression. The reported overall response rate of R-PECC in a heavily pretreated group of patients is approximately 50%-60% (personal communication).
Radioimmunotherapy consolidation with ^{90}Y-ibritumomab tiuxetan after R-PECC induction is thought to benefit these NHL patients for several reasons:

- Aggressive B-cell lymphomas are radiosensitive tumors.
- Immunotherapy with the anti-CD20 monoclonal antibody rituximab can induce responses in patients with relapsed aggressive B-cell NHL.
- Single agent treatment with ^{90}Y-ibritumomab tiuxetan in patients with relapsed aggressive B-cell lymphomas resulted in promising response rates.
- By significantly reducing the tumor load through remission-induction immunochemotherapy, patients might achieve a macroscopic reduced tumor load or minimal residual disease. At this stage most can be expected from radioimmunotherapy.

There are no data available on the feasibility of consolidation with ^{90}Y-ibritumomab tiuxetan after R-PECC induction. For this reason this phase II study (with strict stopping rules, see paragraph 17.3) will be conducted.

6 Study objectives

To assess the feasibility and efficacy of ^{90}Y-ibritumomab tiuxetan consolidation treatment after R-PECC chemotherapy as second or third line treatment in patients with refractory or relapsed aggressive B-cell NHL.

Primary objective:

- Assessment of the feasibility of this treatment approach. Measured primarily by the percentage of patients that reach CR or PR after R-PECC and proceed to ^{90}Y-ibritumomab tiuxetan treatment, and by the fraction of patients that endure the ^{90}Y-ibritumomab tiuxetan treatment without major problems, i.e. the safety and tolerability of ^{90}Y-ibritumomab tiuxetan after R-PECC chemotherapy.

Secondary objectives:

- Efficacy of the ^{90}Y-ibritumomab tiuxetan treatment, measured by the fraction of PR PET positive patients who become PET negative after ^{90}Y-ibritumomab tiuxetan treatment and by the failure free survival and overall survival measured from the start of ^{90}Y-ibritumomab tiuxetan.
- Assessment of the results of the whole treatment approach in terms of the overall response rate, duration of response, failure free survival and overall survival from start of R-PECC treatment.

7 Study design

Details of all treatments (dose and schedule) are given in chapter 9.
Patients with refractory or relapsed aggressive B-cell NHL meeting all eligibility criteria (see 8.1.1 and 8.1.2) will be registered and treated with R-PECC and ^{90}Y-ibritumomab tiuxetan. Patients will be evaluated for response after 2 cycles of R-PECC and after 4 cycles of R-PECC. All patients, who have not attained at least a stable disease after 2 cycles of R-PECC and a PR after 4 cycles of R-PECC, will go off protocol treatment. Patients in PR or CR after 4 cycles of R-PECC will be treated with a single dose of ^{90}Y-ibritumomab tiuxetan.
A cytoreductive pre-phase is permitted, see paragraph 9.1.2 for details.

8 Study population

8.1 Eligibility criteria for registration

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

8.1.1 Inclusion criteria R-PECC induction

- Histologically confirmed aggressive B-cell NHL according to the World Health Organization (WHO) classification (see appendix A):
  - Follicular lymphoma grade 3b
  - Diffuse large B-cell lymphoma
- Refractory disease or histologically confirmed first or second relapse
  (Refractory is defined as no response or partial remission according to CT. Patients in partial response (PR) can only be included in case of positive PET scan or positive biopsy)
- CD20 positive (assessed at 1st diagnosis or from fresh histology at confirmation of relapse or immunophenotyping of circulating CD20-positive NHL cells from peripheral blood)
- Current measurable disease, i.e. measurable in two perpendicular dimensions on physical examination or computerized tomography (CT) scan using standardized response criteria for NHL (Cheson et al[21], 1999) (see appendix B)
- Age $\geq$ 18 years
- WHO performance status 0, 1 or 2 (see appendix E)
- Life expectancy of at least 3 months
- Absolute neutrophil count > 1.5 x 10^9/l and platelet count > 100 x 10^9/l (unless caused by NHL infiltration in the bone marrow)
- Written informed consent

For elderly patients who reached a PR after R-CHOP it is strongly recommended to include them in the HOVON77. If this is not feasible or when the patient does not meet the criteria, the HOVON 85 study is an option.

8.1.2 Exclusion criteria R-PECC induction

- Prior allogeneic stem cell transplantation
- Prior radioimmunotherapy
- Patients who have received chemotherapy or radiotherapy within 6 weeks prior to study entry or who have not recovered from toxicities related to prior therapies
- Eligibility for ASCT

- ASCT within 12 months of study entry
- Investigational drugs within 4 weeks prior to entry on this study or persistent toxic side effects of such therapy
- Treatment with external-beam radiation therapy to more than 25% of active bone marrow (see appendix F)
- A history of intolerance to rituximab
- Severe cardiac, pulmonary, neurological, psychiatric or metabolic disease which could compromise participation in the study, or serious underlying medical conditions which could impair the ability of the patient to participate in the trial
- Hepatic dysfunction, bilirubin or transaminases ≥ 2.5 x upper normal limit (unless caused by the NHL)
- Renal dysfunction, serum creatinine ≥ 180 μmol/l or clearance ≤ 40 ml/min (unless caused by the NHL)
- Active uncontrolled infections
- Patients known to be HIV-positive
- Current or chronic hepatitis B or hepatitis C infection
- Symptomatic NHL localization in the central nervous system (CNS). Lumbal puncture is not required unless CNS involvement with NHL is clinically suspected
- Transformed indolent lymphoma
- Post-transplant lymphoproliferative disorder
- Pregnant or breast-feeding female patients. Negative serum pregnancy test at study is mandatory for female patients of childbearing potential

8.2 Eligibility criteria for ^{90}Y-ibritumomab tiuxetan consolidation

Patients achieving a CR or PR after 4 cycles of R-PECC will be eligible for consolidation treatment with ^{90}Y-ibritumomab tiuxetan.

8.2.1 Inclusion criteria ^{90}Y-ibritumomab tiuxetan consolidation

- Patients with PR or CR after 4 cycles of R-PECC
- Less than 25% bone marrow involvement (confirmed by bone marrow biopsy of at least 1.5 cm, if initially positive)
- WHO performance status 0, 1, or 2
- Time interval since the start of the 4th R-PECC between 6 and 12 weeks
- No rituximab-related adverse event necessitating stopping of rituximab administration

8.2.2 Exclusion criteria ^{90}Y-ibritumomab tiuxetan consolidation

All exclusion criteria mentioned in paragraph 8.1.2 apply, plus the following:

- Extensive pleural effusion or ascites
- Impaired bone marrow reserve, as indicated by one or more of the following:
  - Absolute neutrophil count $\leq$ 1.5 x 10^9/l, platelet count $\leq$ 100 x 10^9/l, Hemoglobin $\leq$ 5.0 mmol/l
  - Hypoplastic bone marrow at biopsy
- Administration of systemic corticosteroids at doses higher than 20 mg/day prednisolone or equivalent 2 weeks prior to ^{90}Y-ibritumomab tiuxetan administration.

9 Treatment

9.1 Induction treatment

9.1.1 R-PECC induction

Agent	Dose/day	Route	Days*
Rituximab	375 mg/m^2 (max 750 mg)	i.v.	1 or at day 0, before PECC
Lomustine** (Cecenu, Belustine®)	80 mg/m^2	p.o.	1
Etoposide	100 mg/m^2	p.o	1-5
Chlorambucil	8 mg/m^2	p.o.	1-5
Prednisone	40 mg/m^2	p.o.	1-5

*Next cycle day 29

**Lomustine is available in 40 mg capsules

All patients will receive R-PECC chemotherapy irrespective to earlier treatment with rituximab. Patients will be treated with 4 cycles of R-PECC, every 4 weeks. Rituximab will be given i.v. at a dose of 375 mg/m^2 (max. 750 mg) on day 1 of each cycle. After rituximab infusion PECC is given. It is allowed to give rituximab one day before the chemotherapy, preferably preceded by a gift of prednisone (the day 1 gift from the PECC course).

Assessment of response after 2 cycles of R-PECC is described in paragraph 11.2.1 Patients who have progressive disease after 2 cycles of R-PECC will go off protocol treatment. All other patients will receive another 2 cycles of R-PECC. Assessment of response after 4 cycles of R-PECC is described in paragraph 11.2.1.

9.1.2 Cytoreductive pre-phase

Patients with relevant B-symptoms or raising peripheral lymphocyte counts but incomplete diagnostic reports may receive a pre-phase therapy of 100 mg prednisone per day for 1 to 5 days before registration in the study. The pre-phase therapy should not be started before all necessary biopsies are taken.

9.2 Dose modifications R-PECC

R-PECC will be administered at 4-weekly intervals. Dose reductions may be needed because of toxicity. Dose modifications will not be made in the first course. There will be no dose modifications of prednisone and rituximab.
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% and 50% doses should always be calculated from the original full doses.

During the next courses modifications of the treatment schedule will only be made in case of myelosuppression:

- If pre-existing values for leucocytes and platelets are reached or if leucocytes are $\geq 3.0 \times 10^9$/l and platelets are $\geq 100 \times 10^9$/l by the scheduled day 1 of the next cycle, the next cycle can be given without dose modification of R-PECC
- If leukocytes and/or platelets are < pre-existing values or leucocytes are $< 3.0 \times 10^9$ /l and/or platelets are $< 100 \times 10^9$ /l by the scheduled day 1 of the next cycle, therapy will be postponed for one week.

If after a delay of one week (day 35):

- Leucocytes are $\geq 3.0 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l, the next cycle can be given without dose modification of R-PECC
- Leucocytes remain $< 3.0 \times 10^9$/l or platelets remain $< 100 \times 10^9$/l, then the doses of Lomustine, etoposide and chlorambucil have to be reduced according to the following scheme:

Leucocytes x 10^9/l		**Platelets x 10^9/l**	**Lomustine**	**Etoposide**	**Chlorambucil**	**Prednisone**	**Rituximab**
≥ 3	and	≥ 100	100%	100%	100%	100%	100%
≥ 3	and	≥ 75	50%	100%	100%	100%	100%
2-3	and	≥ 75	50%	75%	75%	100%	100%
1-2	or	50 - 100	50%	50%	50%	100%	100%
<1	or	< 50	postpone treatment for another week				

If after a delay of a second week (day 42):

- Leucocytes are ≥ 1 x 10^9/l and platelets are ≥ 50 x 10^9/l the treatment is given at the dosage corresponding to the blood cell counts in the scheme above
- Leucocytes are < 1 x 10^9/l or platelets are < 50 x 10^9/l treatment should be postponed for another week.

If after this third week (day 49):

- Leucocytes are ≥ 1 x 10^9/l and platelets are ≥ 50 x 10^9/l the treatment is given at the dosage corresponding to the blood cell counts in the scheme above
- Leucocytes are < 1 x 10^9/l or platelets are < 50 x 10^9/l the protocol treatment will be stopped and this will be considered treatment failure. It is advised to perform bone marrow investigation to look for progression of disease, bone marrow hypoplasia or myelodysplasia.

In case of severe myelosuppression with nadir platelet count < 50 x 10^9/l for more than 7 days and recovery to platelet count > 75 x 10^9/l after 4 weeks, it is strongly advised to reduce the dose of lomustine to 50% in subsequent cycles.

9.2.1 Hematopoietic growth factors

Use of hematopoietic growth factors is allowed and at the discretion of each individual investigator. Secondary prophylactic use of G-CSF (pegfilgrastim, Neulasta®) may be implemented if CTC grade 4 neutropenia ≥ 7 days, CTC grade 3 febrile neutropenia, or CTC grade 4 neutropenia with infection is observed.
G-CSF should then be administered on day 6 of R-PECC. G-CSF should never be given simultaneously with the chemotherapy.

9.2.2 Special management orders during R-PECC

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

9.3 Rituximab administration

9.3.1 Special management with 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 PECC as a pre-medication prior to the infusion of rituximab (if applicable). 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 patient's systems improve, the infusion should be continued at ½ 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.[22] If the patient encounters an adverse event, the rituximab infusion should be interrupted until the symptoms have been resolved. Thereafter 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.

9.3.2 Patients with detectable 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 patient's symptoms improve during observation, the infusion should be continued at ½ the previous rate. Upon resolution of all adverse events and in judgement 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.

9.4 ^{90}Y-ibritumomab tiuxetan consolidation

9.4.1 ^{90}Y-ibritumomab tiuxetan administration

Patients who have achieved a PR or CR after 4 cycles of R-PECC (and met all criteria specified in paragraph 8.2) will receive one single treatment course of ^{90}Y-ibritumomab tiuxetan. This treatment must be started between 6 to 12 weeks after the start of the 4th R-PECC course. Patients must have been recovered from the toxic effects of R-PECC. Treatment should be postponed until the eligibility criteria are met. If consolidation treatment has not started 12 weeks after the last R-PECC the patient will go off protocol treatment.

The treatment course consists of an infusion of rituximab at 250 mg/m^2 followed one week later by a second infusion of rituximab at 250 mg/m^2 followed immediately by a single dose of ^{90}Y-ibritumomab tiuxetan.

The exact dose will be based on the patient's weight, with the following dose:

	Dose ^{90}Y- ibritumomab tiuxetan
No prior autologous SCT and platelets ≥ 150 x 10^9/l	14.8 MBq/kg / 0.4 mCi/kg (max 1184 MBq or 32 mCi)
Prior autologous SCT or platelets 100-149 x 10^9/l	11.1 MBq/kg / 0.3 mCi/kg (max 1184 MBq or 32 mCi)

^{90}Y-ibritumomab tiuxetan should be administered intravenously as a slow intravenous push over 10 minutes. ^{90}Y-ibritumomab tiuxetan may be directly infused by stopping the flow from the intravenous bag and injecting the radiolabeled antibody directly into the line. A 0.22 micron filter must be on line between the patient and the infusion port. The line should be flushed with at least 10 ml of normal saline after ^{90}Y-ibritumomab tiuxetan has been infused (see appendix H).

9.4.2 Preparation of ^{90}Y-ibritumomab tiuxetan

Conjugated ibritumomab tiuxetan will be radiolabeled with ^{90}Y using radiolabeling kits. The radiolabeling kits, tested for sterility and pyrogenicity, will be provided to the study center by Bayer Schering Pharma (BSP). The components of the radiolabeling kits are described in Appendix. H

^{90}Y labeled ibritumomab tiuxetan should be prepared according to appendix H. After preparation of ^{90}Y labeled ibritumomab tiuxetan, a radiochemical purity assay will be performed at the clinical site for release purposes. This assay ensures that an acceptable percentage of the radioisotope is chelated by the antibody conjugate. The release specification for radiochemical purity is ≥ 95% for ^{90}Y-ibritumomab tiuxetan. The radiopharmacist at the clinical site should record release test results. Based on the results, he/she will release or reject the ^{90}Y-ibritumomab tiuxetan dose for patient use.

9.4.3 Storage and stability of study medication

Rituximab and the radiolabeling kits should be stored in a secure refrigerator at 2 to 8 °C. The ^{90}Y isotopes should be stored at room temperature.
Rituximab solution for infusion is stable at 2 to 8 °C for 24 hours and at room temperature for 12 hours.
^{90}Y-ibritumomab tiuxetan solutions are stable at 2 to 8 °C for up to 8 hours following preparation. Due to the relatively short half-life of the isotopes, the actual dose will degrade and have to be recalculated if not used soon after the calibration time (see appendix G).

9.4.4 Supportive care

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, anti-emetics etc, where applicable, according to local guidelines.
Two weeks after the administration of ^{90}Y-ibritumomab tiuxetan the blood counts can be expected to start decreasing. The nadir will occur after 4 weeks. If platelets drop below the level of 30 x 10^9/l a complete blood count including platelet count has to be performed 3 times weekly, until the unsupported platelet count recovers above 30 x 10^9/l. It is strongly recommended to use prophylactic platelet transfusions to maintain a minimum platelet count of 10 x 10^9/l to reduce the risk of hemorrhage.
Furthermore, it is essential that patients will not be given other myelosuppressive anti-neoplastic agents (off protocol treatment, see 9.5.1) until their hematological nadir has recovered following treatment with ^{90}Y-ibritumomab tiuxetan.

9.5 Prior and concomitant medication and treatment

All **prior** chemotherapy, biologic, immunologic, radiation therapy and surgery will be recorded on separate pages of the CRF.
The use of systemic corticosteroids should be reduced to a minimum, but is permitted (see 8.2.2., eligibility criteria for consolidation).

9.5.1 Other therapies

Concurrent administration of cytotoxic, biologic, or hormonal therapies, which might affect efficacy assessment, is **prohibited**.

9.5.2 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, provided that the patient has additional site(s) of measurable disease not encompassed by the local radiotherapy. No radiotherapy after end of treatment is allowed.

10 End of protocol treatment

Protocol treatment will be discontinued in the following circumstances:

1. Progressive disease on CT scan after the first 2 R-PECC cycles
2. Progressive disease or less than PR on the CT scan after 4 R-PECC cycles

3. Excessive toxicity deemed by the investigator or the patient as unacceptable, including toxic death
4. No start of ^{90}Y-ibritumomab tiuxetan consolidation treatment within 12 weeks after the start of the 4th R-PECC, or delay of R-PECC of more than 3 weeks
5. The patient is noncompliant with study procedures or refuses further protocol treatment
6. Intercurrent death
7. Lost to follow-up
8. Major protocol violation
9. Normal completion of protocol treatment

At the time of discontinuation of treatment, assessments should be performed as described in paragraph 11.2.

11 Required clinical evaluations

See appendix B for a specification of staging and restaging evaluations for NHL.

11.1 Observations prior to start of treatment

- Complete medical history (including: B-symptoms, IPI risk classification at time of first diagnosis, duration of previous response, prior NHL treatment)
- Complete physical examination
- WHO performance status
- Consultation ENT specialist, if indicated
- Measurements of all involved palpable lesions in mm
- Laboratory tests (including Hb, WBC and differential, platelet count, sodium, potassium, calcium, creatinine, uric acid, bilirubin, alkaline phosphatase, γ-GT, ALAT, ASAT, LDH, protein, albumin, immuno-electrophoresis, glucose)
- Routine urine analysis
- Imaging + bidimensional measurements (including chest X-ray, CT neck, thorax and abdomen and pelvis)
- A baseline (pre-treatment) FDG-PET scan is optional
- Lymph node (or tissue) biopsy for morphology and immunopathology of involved site for confirmation of relapse
- Immunophenotyping of lymph node for CD20, if not initially assessed (CD3 CD19 or CD79a optional)
- Bone marrow aspirate and biopsy at least 1.5 cm (including CD20/CD79a stain)

- Lumbal punction, if indicated
- ABO and RhD blood group, irregular antibody screening
- Anti-HIV, anti-Hepatitis B and C

Laboratory assessments and imaging should be performed within 4 weeks of study entry.

11.2 Observations after 2 and 4 cycles of R-PECC and after ^{90}Y-ibritumomab tiuxetan

- Medical history (including B-symptoms)
- Complete physical examination
- WHO performance status
- Laboratory tests (including Hb, WBC and differential, platelet count, sodium, potassium, calcium, creatinine, uric acid, bilirubin, alkaline phosphatase, γ-GT, ALAT, ASAT, LDH, protein, albumin, glucose)
- Immuno-electrophoresis if initially abnormal
- Imaging + bidimensional measurements of involved and/or new areas (including CT neck, thorax, abdomen and pelvis)
- FDG-PET scanning after the fourth R-PECC and 8 weeks after ^{90}Y-ibritumomab tiuxetan
- Bone marrow aspirate and biopsy (if positive at previous evaluation, including CD20/ CD79a stain)

11.2.1 Response assessments after 2 and 4 cycles of R-PECC and after ^{90}Y-Ibritumomab tiuxetan

Response will be formally evaluated:

- after the second R-PECC
- after the fourth R-PECC
- 8 weeks after ^{90}Y-ibritumomab tiuxetan

Response will be evaluated according to the criteria of response in appendix B (Cheson criteria). In addition to these criteria, the PET status will be evaluated.

All relevant information on drug dose, measurable lesions, tumor response and treatment-related toxicity will be collected.

11.3 Observations during follow up

After the end of the treatment period each individual patient will be followed for disease progression and survival to collect data for failure free survival and overall survival.

Follow up will be planned at least every 2 months during the first year, every 4 months during the second year and every 6 months thereafter. Patients who have not achieved PR and relapsed patients will be followed until death. Follow-up data will be collected (including treatment and survival data).

The following test will be performed at months 2, 4, 6, 8 and 12 after the ^{90}Y-ibritumomab tiuxetan infusion or at the time of disease progression, whichever comes first:

- Medical history
- Physical examination (including WHO performance)
- Blood count, creatinine, alkaline phosphatase, ALAT, ASAT, LDH, total bilirubin, γ-GT
- Any clinically indicated examination
- CT neck, thorax, abdomen and pelvis after 6 and 12 months (or when indicated)
- Any documentation of abnormal/ relevant events (e.g. secondary malignancies)

Any decisions on further anti-lymphoma treatments will be made by the treating physician, but will be documented.

12 Toxicities

Special attention should be paid to the occurrence of toxicity throughout every stage of the study.

12.1 PECC

PECC is a chemotherapeutic regimen commonly used in the Netherlands for relapsed Hodgkin's lymphoma and NHL. The most frequent toxicity is myelosuppression, which may hamper the patient adherence to the projected schedule for PECC. All the chemotherapeutic agents used in the protocol cause pancytopenia and can induce septic or hemorrhagic complications.

12.2 Rituximab

Side effects of rituximab may include fever, rigors, mucosal congestion or edema, and drop in systolic blood pressure. These side effects are only observed during rapid infusion of rituximab. Special management is provided in 9.3.1 and 9.3.2. In patients who experience side effects the infusion rate has to be restricted to 100 mg/hr.

12.3 ^{90}Y-ibritumomab tiuxetan

Investigators should be familiar with toxicities, which have been previously observed in association with ^{90}Y-ibritumomab tiuxetan. In previous clinical trials toxicities were reported as primarily transient and reversible hematologic toxicities, with grade 4 neutropenia, thrombocytopenia and anemia occurring in 32%, 8.5%, and 4.3% of patients, respectively. Blood count levels recovered, except in those cases where patients went on to other therapy, had pre-existing cytopenia's, or died of rapidly progressive disease or concomitant illness. Platelets may fall to levels in which life-threatening hemorrhage occurs. Two deaths of patients with profound thrombocytopenia were reported. In one case, the cause of death was disease progression and thrombocytopenia, which possibly caused cerebral hemorrhage and neurologic symptoms. Regarding the second patient, a causal association between the study drug and gastrointestinal as well as fatal cerebral hemorrhage was assumed. Otherwise, the most common adverse reactions which are at least possibly related to the ^{90}Y-ibritumomab tiuxetan therapeutic regimen (which includes rituximab and radiolabeled ibritumomab tiuxetan) include asthenia, rigors, pyrexia and nausea. The frequently reported adverse reactions during treatment are listed below:

- General disorders and administration site conditions:
  - asthenia, rigors, pyrexia (≥ 1/10)
  - malaise, flu-like symptoms, peripheral edema, increased sweating, pain (≥1/100 to < 1/10)
- Cardiac disorders: tachycardia (≥ 1/1000 to < 1/100)
- Vascular disorders: hemorrhage while thrombocytopenic (≥ 1/100 to < 1/10)
- Blood and lymphatic system disorders:
  - thrombocytopenia, leukocytopenia, neutropenia, anemia (see aforementioned, ≥ 1/10)
  - febrile neutropenia, pancytopenia, lymphocytopenia (≥ 1/100 to < 1/10)
- Gastrointestinal disorders:
  - Nausea (≥ 1/10)
  - vomiting, diarrhoea, abdominal pain, dyspepsia, throat irritation, constipation (≥ 1/100 to <1/10)
- Immune system disorders: hypersensitivity reaction (≥ 1/100 to < 1/10)
- Metabolism and nutritional disorders: anorexia (≥ 1/100 to < 1/10)
- Musculoskeletal, connective tissue and bone disorders:
  - arthralgia, myalgia, back pain, neck pain (≥ 1/100 to < 1/10)
- Psychiatric disorders: anxiety, insomnia (≥ 1/100 to < 1/10)
- Nervous system disorders: dizziness, headache (≥ 1/100 to < 1/10)
- Respiratory, thoracic, and mediastinal disorders: rhinitis, cough (≥ 1/100 to < 1/10)

- Skin and subcutaneous tissue disorders: pruritus, rash (≥ 1/100 to < 1/10)
- Infections: infection, sepsis, pneumonia, urinary tract infection (≥ 1/100 to < 1/10)
- Neoplasms benign, malignant and unspecified: tumor pain, MDS/ AML (≥ 1/100 to < 1/10)

For detailed information on adverse reactions see most recent version of Summary of Product Characteristics (SmPC) ^{90}Y-ibritumomab tiuxetan. Because the ^{90}Y-ibritumomab tiuxetan therapeutic regimen includes the use of rituximab, see also the prescribing information of rituximab.
Toxicities will be scored according to the NCI Common Toxicity Criteria (CTC), version 3.0 (appendix D). See also chapter 13.

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 hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization 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

hospitalization 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 CRFs 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.

Furthermore HOVON will submit an annual safety report to the regulatory authorities and the Ethics Committee.

14 Endpoints

14.1 Feasibility and safety

Primary endpoint

- The incidence of grade ≥3 adverse events after treatment with ^{90}Y-ibritumomab tiuxetan.

Secondary endpoints

- Incidence and duration of hypoplasia after treatment with ^{90}Y-ibritumomab tiuxetan
- Incidence of adverse events (any grade) after treatment with ^{90}Y-ibritumomab tiuxetan
- Incidence of adverse events (any grade) after treatment with R-PECC
- Percentage of patients treated with R-PECC who proceed to ^{90}Y-ibritumomab tiuxetan treatment

14.2 Efficacy

See appendix B for a complete definition of endpoints.

Primary endpoint

- Failure free survival measured from the start of ^{90}Y-ibritumomab tiuxetan

Secondary endpoints

- Conversion to PET negative CR after ^{90}Y-ibritumomab tiuxetan treatment of patients who are PET positive before start of ^{90}Y-ibritumomab tiuxetan
- Overall survival measured from the start of ^{90}Y-ibritumomab tiuxetan
- Response rates to R-PECC and response duration
- Failure free survival and overall survival measured from the start of R-PECC

A patient counts as failure for failure free survival when he does not reach at least a PR on R-PECC treatment, in case of relapse or progression after PR or at death due to any cause. Otherwise, patients are censored at the date last seen. Patients who reach PR/CR on R-PECC, but stop further treatment due to adverse events are not considered treatment failures at that time as long as they are alive in continuing CR/PR.

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

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
- PA number:
  - of original diagnosis if refractory disease
  - of relapse diagnosis (if applicable)
- PA laboratory (pathologist and institution) of original or relapse diagnosis
- Eligibility criteria

All eligibility criteria will be checked with a checklist (registration form).
Each patient will be given a unique patient study number, which will be given immediately by TOP or phone and confirmed by fax or e-mail.

17 Statistical considerations

17.1 Sample size and accrual

The primary aim of this study is to assess the feasibility and the efficacy of consolidation treatment with ^{90}Y-ibritumomab tiuxetan of patients who have reached a PR or CR after salvage treatment with R-PECC for refractory or relapsed aggressive NHL. Primary endpoint for the evaluation of the efficacy of ^{90}Y-ibritumomab tiuxetan is failure free survival measured from the start of treatment with ^{90}Y-ibritumomab tiuxetan.
The target number of patients to be treated with ^{90}Y-ibritumomab tiuxetan is 30. It is expected that about 50% of the patients treated with R-PECC will achieve a PR and CR and will be eligible for treatment with ^{90}Y-ibritumomab tiuxetan. Thus the expected required number of patients to be entered in the study is 60. With an expected accrual of 40 patients per year the recruitment duration is expected to be 1.5 years.

The median failure free survival of patients in CR or PR after a rituximab containing chemotherapy regimen for relapsed or refractory aggressive B-cell lymphoma who do not qualify for stem cell transplantation is about 6 months. It is hoped that the ^{90}Y-ibritumomab tiuxetan consolidation treatment will increase this to 12 months.

17.2 Analysis

17.2.1 Feasibility analysis

The analysis of the feasibility of the whole treatment approach will be done by calculation of

- The percentage of patients who can proceed to ^{90}Y-ibritumomab tiuxetan treatment
- Tabulation of the incidence of adverse events with CTCAE grade 2 or more by type and grade

17.2.2 Efficacy analysis

Failure free survival and overall survival will be calculated with the method of Kaplan-Meier. The median and probabilities at 1 year will be calculated together with 95% confidence intervals.
This will be done for the whole group measured from the start of R-PECC induction treatment and also for the subgroup of patients who receive ^{90}Y-ibritumomab tiuxetan consolidation, measured from the start of ^{90}Y-ibritumomab tiuxetan treatment.
It is expected that about 60% of the PR/CR patients proceeding to ^{90}Y-ibritumomab tiuxetan will be PET positive. This subgroup has a dismal prognosis with a very short failure free survival of about 3

months. Therefore the failure free survival from start of ^{90}Y-ibritumomab tiuxetan will be calculated also separately for the subgroups of PET negative and PET positive patients. These estimates will be compared with estimates from published data of similar patients without ^{90}Y-ibritumomab tiuxetan consolidation. In the subgroups of PET positive patients the proportion of patients who will become PET negative and reach complete remission after ^{90}Y-ibritumomab tiuxetan treatment will be calculated.
The different types of response on R-PECC will be tabulated and the duration of response will be calculated separately for responding PET negative en responding PET positive patients.

17.3 Monitoring

The treatment approach with ^{90}Y-ibritumomab tiuxetan consolidation after R-PECC reinduction treatment will be considered feasible when a considerable fraction of patients do proceed to ^{90}Y-ibritumomab tiuxetan. We expect that about 50% will proceed to ^{90}Y-ibritumomab tiuxetan. The study may be stopped early if it turns out that the fraction of patients who proceed to ^{90}Y-ibritumomab tiuxetan is much less than 50%.

Another aspect of feasibility is the incidence of serious adverse events after ^{90}Y-ibritumomab tiuxetan consolidation in this population. The trial will be terminated if either:

- Treatment related mortality is observed in 4 or more of the first ten patients treated with ^{90}Y-ibritumomab tiuxetan
- Four or more of the first ten patients treated with ^{90}Y-ibritumomab tiuxetan experience grade 4 or irreversible grade 3 toxicity (except alopecia, nausea, vomiting and hematological toxicity)

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. 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) and applicable regulatory requirements.

18.3 Patient information and consent

Written Informed consent of patients is required before registration. The procedure and the risks and the opinions for therapy in relapsed or refractory aggressive B-cell NHL will be explained to the patient.

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.

20 Publication policy

The final publication of the trial results will be written by the 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 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.

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 in the trial, or any subgroup of the trial patients.

21 Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
ALAT	Alanine Amino Transferase
AR	Adverse reaction
ANC	Absolute Neutrophil Count
ASAT	Aspartate Animo Transferase
ASCT	Autologous Stem Cell Transplantation
ß	Beta
BM	Bone Marrow
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CNS	Central Nervous System
CR	Complete Remission
CRF	Case Report Form
CRu	Unconfirmed CR
CT	Computerized Tomography
CTC AE	Common Toxicity Criteria for Adverse Events
DLBCL	Diffuse Large B-Cell Lymphoma
ECOG	Eastern Cooperative Oncology Group
EBV	Epstein-Barr Virus
EFS	Event Free Survival
EMEA	European Medicines Agency
ENT	Ear, Nose, Throat
FDA	Food and Drug Administration (US)
FDG-PET	Fluordeoxyglucose Positron Emission Tomography
FL	Follicular Lymphoma
γ	Gamma
GBq	GigaBecquerel (Bq = unit of radioactivity)
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HOVON	Dutch/Belgian Hemato-Oncology Cooperative Group
ICH	International Conference on Harmonization of technical requirements For the Registration of Pharmaceuticals for Human Use
IK Data Center	Regional Cancer Data Center
IPI	International Prognostic Index
IRB	Institutional Review Board
IV	Intravenous

LDH	Lactate Dehydrogenase
MBq	MegaBecquerel (Bq = unit of radioactivity)
mCi	MilliCurie (unit of radioactivity; 1mCi = 37 MBq)
MRI	Magnetic Resonance Imaging
N	Number
NaCl	Sodium Chloride
NHL	Non-Hodgkin's Lymphoma
NCI	National Cancer Institute
NYHA	New York Heart Association
PA	Pathology
PECC	Prednisone, Etoposide, Chlorambucil, Lomustine
ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral Blood
PD	Progressive Disease
PO	Per Os
PR	Partial Response
R	Rituximab
RIC	Radioimmunoconjugate
RIT	Radioimmunotherapy
SAE	Serious Adverse Event
SC	Subcutaneous
SCT	Stem Cell Transplantation
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse reaction
TOP	Trial Online Process
ULN	Upper Limit of Normal
TMA	Tissue Micro Array
WBC	White Blood Count
WHO	World Health Organization
WMO	Wet Medisch Wetenschappelijk Onderzoek met mensen
Y	Yttrium

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A. WHO classification indolent and aggressive B-cell NHL

The ***** marked malignancies fulfill the entry criteria of this trial

Mature B-cell neoplasms

1 Chronic lymphocytic leukaemia/small lymphocytic lymphoma
2 B-cell prolymphocytic leukaemia
3 Lymphoplasmacytic lymphoma
4 Splenic marginal zone lymphoma
5 Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)
6 Nodal marginal zone B-cell lymphoma
7 Follicular lymphoma grade 1 and 2 and 3a
8 Follicular lymphoma grade 3b*
9 Mantle cell lymphoma
10 Diffuse large B-cell lymphoma*
11 Mediastinal large B-cell lymphoma
12 Intravascular large B-cell lymphoma
13 Primary effusion lymphoma
14 Burkitt lymphoma

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 (JCO, Vol.17, 1999, pp1244-1253 [Erratum, JCO, Vol.18, 2000, pp2351]).

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 bonemarrow has not been included as standard mimimum 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, bilirubine, ALAT
  - paraprotein by immuno-electrophoresis
  - quantitative immunoglobulins only if immuno-electrophoresis abnormal
  - Hepatitis-B in case of abnormal liver function tests
  - HIV test
- Lymph node biopsy for morphology and immunopathology
- 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.*
• *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.

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 bidimensionally 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 are considered all abnormalities that are not bidimensionally measurable, e.g. positive bone marrow or peripheral blood.

Response criteria

Complete respons (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**
   - 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%.
4. 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.
5. Any nodules in liver or spleen must have disappeared.
6. 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 respons (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)

A hardcopy may be obtained from the HOVON Data Center on request.

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. Radiation fields and bone marrow involvement

Skull	10%
Ribs and sternum	10%
Cervical spine	5%
Thoracal spine	15%
Lumbal spine	10%
Sacrum	15%
Pelvis and proximal femurs	25%
Mantle field	25%
Para-aortic	15%
Subtotal nodal	40%
Inversed Y	30%
Total nodal	70%

G. International Prognostic Index (IPI)

International Prognostic Index (IPI) for aggressive B-cell non-Hodgkin's lymphoma

Parameters:

- Age ≥ 60 years
- Advanced stage (III/IV)
- Extranodal involvement of > 1 site
- WHO Performance status ≥ 2
- Serum lactate dehydrogenase > normal

Risk group stratification (according to total number of above-listed features):

- 0 - 1 Low-risk
- 2 Low intermediate risk
- 3 High intermediate risk
- 4 - 5 High risk

The International Non-Hodgkin's Lymphoma Prognostic Factors Project.
A Predictive Model for Aggressive Non-Hodgkin's Lymphoma.
N Engl J Med 329:987-994, 1993

H. Preparation and dispensing information on ^{90}Y- Ibritumomab tiuxetan

I. Components and preparation of ^{90}Y-ibritumomab tiuxetan

A **Radioisotopes**: Yttrium-[90] chloride used for preparing ^{90}Y-ibritumomab tiuxetan will be obtained from vendors identified by Bayer Schering Pharma AG (BSP). All lots of isotopes will be sterile, pyrogen-free and supplied in septum vials designed to maintain these conditions.

The following yttrium-90 characteristics are required:

Total extractable activity to deliver at time of use	:	≥ 1.48 GBq
Radioactivity concentration at time of use	:	1.67 to 3.34 GBq/ml
HCl concentration	:	0.035-0.045 M
Chloride identification	:	Positive
Yttrium identification	:	Positive
Radiochemical purity of the yttrium-90 chloride solution	:	≥ 95% of free ionic yttrium-90
Radiochemical purity of the radiolabeled	:	≥ 95% incorporation of yttrium-90 onto the monoclonal antibody preparation
Bacterial endotoxins	:	≤ 150 EU/ml
Sterility	:	No growth
Radionuclidic purity, strontium-90 content	:	≤ 0.74 MBq strontium-90 / 37 GBq yttrium-90
Metal impurities		
Total metals*	:	≤ 50 ppm
Individual metals*	:	≤ 10 ppm each

B **Ibritumomab tiuxetan:** The murine anti-CD20 monoclonal antibody ibritumomab is an IgG1 kappa antibody. It is produced in Chinese hamster ovary (CHO) cells in suspension culture. The purified antibody is then joined covalently to the chelating agent tiuxetan (conjugated antibody "Ibritumomab tiuxetan"). Ibritumomab tiuxetan is provided as part of the radiolabeling kit in the form of a 3 ml glass vial containing 2 ml (3.2 mg) of ibritumomab tiuxetan at a concentration of 1.6 mg/ml in low metal normal saline.

C **Radiolabeling kit components:** Conjugated ibritumomab tiuxetan will be radiolabeled with Yttrium-[90] using a radiolabeling kit. The radiolabeling kit will be provided by Bayer Schering Pharma AG (BSP) to the clinical site. All kit components will be tested for sterility and pyrogenicity.

The kit should be stored at 2 - 8°C and consists of the following components:

1) Three ml glass septum vial (blue cap) containing 2 ml (3.2 mg) ibritumomab tiuxetan in low-metal normal saline at 1.6 mg/ml
2) Three ml glass septum vial (green cap) containing 2 ml low-metal 50 mM sodium acetate
3) Ten ml glass septum vial (red cap) containing 10 ml formulation buffer (1x PBS containing 7.5% human serum albumin and 1 mM DTPA, pH 7.2)
4) Ten ml glass septum reaction vial (yellow cap, empty)

D **Preparation of 90-ibritumomab tiuxetan:** Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves and ring dosimeters should be utilized in the preparation and determination of radiochemical purity assay of ^{90}Y-ibritumomab tiuxetan. The radiolabeling of ^{90}Y-ibritumomab tiuxetan should be done according to the following directions using the radiolabeling kit described above.

GENERAL INSTRUCTIONS:

- Perform ALL COMPOUNDING CALCULATIONS prior to labeling
- Perform labeling preferably in a laminar flow hood strictly adhering to sterile technique
- Arrange & set-up work station for RAPID addition of components to reaction vial

PREPARATION:

1) Before radiolabeling, bring refrigerated ibritumomab tiuxetan cold kit to room temperature (25°C); perform a visual inspection of all vials.
2) Clean the rubber stopper of all cold kit vials and the yttrium-[90] chloride vial with a suitable alcohol swab and allow to air dry.
3) Place the reaction vial in a suitable dispensing shield (plastic enclosed in lead, e.g. 1 cm lucite surrounded by 1 cm of lead).
4) In a 1 ml syringe, draw sodium acetate buffer that is 1.2 times the starting volume of yttrium-[90] chloride (see below).
5) In a 2 - 3 ml syringe, draw 1.3 ml of ibritumomab tiuxetan.

[^{90}Y]-LABELING OF IBRITUMOMAB TIUXETAN:

Step 1: Transfer sodium acetate solution to the reaction vial
Using a 1-ml sterile syringe, transfer sodium acetate solution to reaction vial. The volume of sodium acetate solution added is equivalent to 1.2 times the volume of radioisotope to be transferred in step 2.

Step 2: Transfer yttrium-[90] chloride to the reaction vial.
Aseptically transfer 40 mCi (1480 MBq) of yttrium-[90] chloride with a 1-ml sterile syringe to the reaction vial containing the sodium acetate solution transferred in step 1. Mix completely by coating the entire inner surface of the reaction vial. Mix by inversion, rolling the container, avoid foaming or agitating the solution.

Step 3: Transfer ibritumomab tiuxetan solution to the reaction vial
Using a 2-3-ml sterile syringe, transfer 1.3 ml ibritumomab tiuxetan solution to the reaction vial. Mix completely by coating the entire inner surface of the reaction vial. Mix by inversion, rolling the container, avoid foaming or agitating the solution.

Incubate the yttrium-90 chloride/acetate/ibritumomab tiuxetan solution at room temperature for five minutes. Labeling time longer than six minutes, or shorter than four minutes will result in inadequate radioincorporation.

Step 4: Add the formulation buffer to the reaction vial
Using a 10-ml syringe with a large bore needle (18-20 G), draw formulation buffer that will result in a combined total volume of 10 ml.

Step 5: Assay the [^{90}Y]-labeled ibritumomab tiuxetan reaction vial for its specific radioactivity.
The percent radioincorporation of the prepared [^{90}Y]-labeled ibritumomab tiuxetan must be checked before administration to the patient according to the procedure outlined below.
Assay the reaction vial in a suitably calibrated dose calibrator.
The percent radiochemical purity of the prepared ^{90}Y-ibritumomab tiuxetan should be determined before administration to the patient.
If not immediately administered to the patient, store the reaction vial containing ^{90}Y-ibritumomab tiuxetan at 2° to 8° C and use within eight hours.
Calculate patient dose at 0.4 mCi/kg (max. 32 mCi/kg). Do not exceed the maximum allowed dose of 1184 MBq (32 mCi) of ^{90}Y-ibritumomab tiuxetan.

E <u>Initial determination of dose calibrator calibration, settings corrected for different geometries:</u>

1) <u>Calibration settings:</u> It is highly recommended that a range of different volumes from the 10 ml reaction vial and 10 ml syringe (Calibration Settings #B and #C) be checked. A calibration setting should be recorded for each volume frequently used.The establishment of calibration settings with ^{90}Y can be done with NIST traceable Radioactivity Standard Reference Materials (SRM's).
2) <u>Geometry changes:</u> It is highly recommended that every geometry configuration change be checked and a new calibration setting established. This would apply to a change in needle size, a change to a different syringe type or volume, or a change in the position of the container within the dose calibrator. Changing a container in the dose calibrator from a side reading, to an upright reading, or to an upside-down reading will all change the geometry and therefore the display readout with beta nuclides.
3) <u>Use of worksheet:</u> The worksheet represents only the determination of the initial calibration settings. Once initial calibration settings are established, steps can be eliminated. Using calibration setting #A

should be eliminated after the initial set-up. Dial in settings determined in calibration settings #B and #C are applied to the 10-ml reaction vial, and 10-ml syringe respectively.

4) Daily calibration check: It is highly recommended that a daily channel check for each frequently used calibration setting be done with a long lived dose calibrator source. Suggested isotopes are ^{137}Cs, ^{60}Co, or ^{133}Ba. Consult your health physicist.
5) Dose calibrator manufacturers: It is highly recommended that the dose calibrator manufacturer be contacted for the initial isotope calibration number when working with ^{90}Y.

^{90}Y Decay Constant Tables

Hours Before Calibration										
	0	2	4	6	8	10	12	14	16	18
0	1.00	1.02	1.04	1.07	1.09	1.11	1.14	1.16	1.19	1.21
20	1.24	1.27	1.30	1.32	1.35	1.38	1.41	1.44	1.48	1.51
40	1.54	1.57	1.61	1.64	1.68	1.72	1.75	1.79	1.83	1.87
60	1.91	1.95	2.00	2.04	2.08	2.13	2.18	2.22	2.27	2.32
80	2.37	2.42	2.48	2.53	2.59	2.64	2.70	2.76	2.82	2.88
100	2.94	3.01	3.07	3.14	3.21	3.28	3.35	3.43	3.50	3.58
Hours After Calibration										
	0	2	4	6	8	10	12	14	16	18
0	1.00	0.979	0.958	0.937	0.917	0.898	0.787	0.860	0.841	0.823
20	0.806	0.788	0.771	0.755	0.739	0.723	0.707	0.692	0.678	0.663
40	0.649	0.635	0.621	0.608	0.595	0.582	0.570	0.558	0.546	0.534
60	0.523	0.511	0.501	0.490	0.479	0.469	0.459	0.449	0.440	0.430
80	0.421	0.412	0.403	0.395	0.386	0.378	0.370	0.362	0.354	0.347
100	0.399	0.332	0.325	0.318	0.311	0.304	0.298	0.291	0.285	0.279

To use the decay table, find the number of hours in the top and left-hand columns of the grids, then find the corresponding decay factor.

Worksheet

1. Consult concentration found on **Certificate of Analysis**. Use decay table for the determination of concentration, adjust for time zone changes (example: ^{90}Y at 22 hours pre-calibration [PST] = 1.27 x 1850 MBq/ml = 2349.5 MBq/ml). (Note: 1.27 = decay factor, 1850 MBq/ml = concentration on certificate of analysis) _____MBq/ml

2. Calculate the volume of activity for 1480 MBq (example: 1480 MBq ÷ 2349.5 MBq/ml = 0.63 ml) (Note: concentration is taken from calculation in Step 1) _____ml
3. In a 1 ml syringe, draw up the required volume (calculated in Step 2).
4. Place 1 ml syringe in dose calibrator. Change the "pot-setting/calibration number" to equal a 1480 MBq readout. **CAUTION: Do not leave ^{90}Y in syringe for extended period of time.** _____MBq
5. Record 1 ml syringe "pot-setting/calibration number." Calibration Setting (A): _____
6. Immediately transfer activity from 1 ml syringe to 10 ml reaction vial. Follow instructions for preparation of ^{90}Y-ibritumomab tiuxetan. While the five minute incubation time is taking place, assay residual activity in syringe (after *C Preparation of ^{90}Y- and ^{111}In-ibritumomab tiuxetan, Step* #6). _____MBq
7. Determine activity added to reaction vial (Step 4 – Step 6, example: 1480 MBq – 29.6 MBq = 1450.4 MBq). _____MBq
8. After incubation is complete, qs with **formulation buffer** in the 10 ml reaction vial (according to instructions in C, Step 9), place reaction vial in dose calibrator. Change the "pot-setting/ calibration number" to read the activity recorded in Step 7.
9. Record 10 ml reaction vial "pot-setting/calibration number." Calibration Setting (B): _____
10. Based on the activity determined in Step 7, draw up the "prescribed" activity by volume into a 10 ml syringe [example: ("prescribed" dose x 10 ml ÷ Step 7 MBq) = "prescribed" volume]. _____MBq "prescribed"

    Place the 10 ml syringe in the dose calibrator. Change the "pot-setting/ calibration number" to reflect the "prescribed" activity in a 10 ml syringe in this step. (**Caution: the "prescribed" activity should not exceed 1184 MBq for ^{90}Y**). If ^{90}Y-/^{111}In-ibritumomab tiuxetan is not being used immediately, see instructions in C, Step 11 for storage. _____mL
11. Record the 10 ml syringe "pot-setting/calibration number." Calibration Setting (C): _____

CALIBRATION SETTINGS

***A* = 1 ml Syringe Geometry**

***B* = 10 ml Reaction Vial Geometry**

***C* = 10 ml Syringe Geometry**

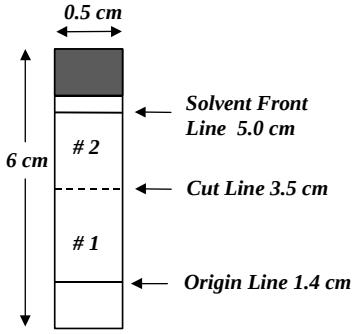
II. Clinical release testing for ^{90}Y-ibritumomab tiuxetan

Release assay is performed at the clinical site for 90Y-ibritumomab tiuxetan.

Radiochemical Purity: This assay insures that an acceptable percentage of the radioisotope is chelated by the antibody conjugate. An instant thin-layer chromatographic assay using a commercial kit (Biodex) is available for use. In this assay, conjugated antibody remains at the origin whereas tiuxetan or DTPA-chelated yttrium advances with the solvent front. The amount of radioactivity remaining at the origin bound to the antibody conjugate is expressed as a percentage of the total amount of radioactivity applied to the strip. See instructions below Steps #1 - #8.

The Radiochemical Purity by Instant Thin Layer Chromatography (ITLC) shall be done according to the following procedure at room temperature:

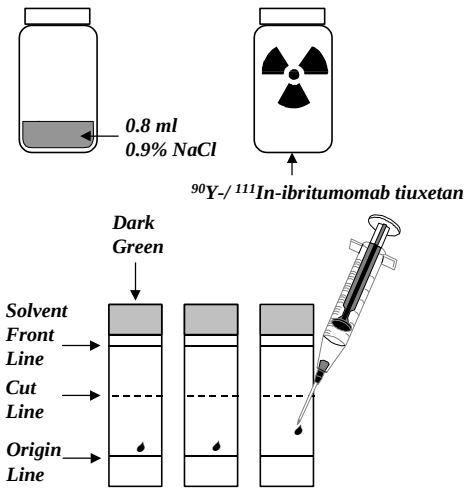
1. Required materials not supplied:
   - 1 ml insulin syringe with a 25 - 26 G needle
   - ITLC-SG, e.g., Biodex "Tec-Control" kit, part number 151-770
   - Single or multichannel analyzer



ITLC-SG Strip

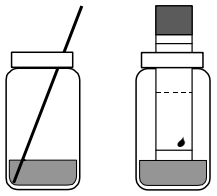
2. Set region of interest of single or multichannel analyzer to incorporate channels 140-1000 keV.

3. Using a 1 ml insulin syringe, place a hanging drop (7 - 10 µl) onto the ITLC-SG strip at its 1.4 cm mark "origin." Spot one strip at a time and run the procedure on three ITLC-SG strips. A 1:100 dilution may be necessary if the instrument deadtime is appreciable.

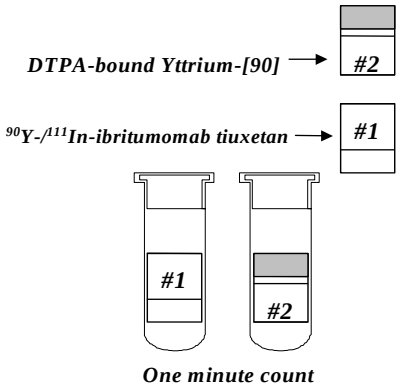


4. Fill developing chamber with 0.8 ml of bacteriostatic free 0.9% NaCl. The volume of 0.9% NaCl should not touch the 1.4 cm origin line.

5. Place ITLC-SG strip into developing chamber and allow the solution to migrate past the 5 cm "Solvent Front" line. Do not allow ITLC-SG strip to adhere to the side of the developing chamber. See illustration below.



6. Remove ITLC-SG strip and cut in half at the 3.5 cm "Cut-Line." Count each half of the ITLC-SG strip in a multi-channel or single channel analyzer counter for one-minute (cpm). Subtract background counts and use corrected counts.



7. Calculate the radiochemical purity % as follows:

$$\textit{(Radiochemical purity \%)} = \left(\frac{\textit{(cpm \#1)}}{\textit{(cpm \#1) + (cpm \#2)}} \right) \textit{x 100}$$

8. Repeat process three times and take the average percentage of the radiochemical purity (RCP).

The release specification for the average radiochemical purity is > 95% for ^{90}Y-ibritumomab tiuxetan.

III. Recommended handling and andministration of ^{90}Y- ibritumomab tiuxetan

1) Refer to the clinical study protocol for details about the dose and dose schedule. Patients will be treated with a 14.8 MBq/kg (0.4 mCi/kg) dose of yttrium-[90]. A 0.22 micron filter is required for the administration of the drug.

2) **Vials should be stored with proper shielding at 2 - 8°C**. Do not freeze or store at room temperature. The drug is a protein -- HANDLE GENTLY AND AVOID FOAMING. The avoidance of foaming during product handling, preparation and administration is important, as foaming may lead to the denaturing of the product proteins.
NOTE: Do not use evacuated glass containers which require vented administration sets because this causes foaming as air bubbles pass through the solution.

3) All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood.

4) ^{90}Y-ibritumomab tiuxetan may be directly infused by stopping the flow from the IV bag and injecting the radiolabeled antibody directly into the infusion port. A 0.22 micron filter must be on line between the syringe and the infusion port.

5) The administration of the radiolabeled drug will be accomplished by a 10 minute slow IV push and should be completed within the time specified in the protocol.CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS BOLUS. Flush the line with at least 10 ml of normal saline after the radiolabeled product has been infused.

6) IV pumps may be used with the ^{90}Y-ibritumomab tiuxetan infusion. Do not infuse concomitantly with another IV solution or IV medications.

7) If a delay in administration occurs after the ^{90}Y-ibritumomab tiuxetan have been prepared, the radiolabeled product must be kept refrigerated after preparation at 2 - 8°C and may be used for up to 8 and 12 hours, respectively. If not used soon after the calibration time, the actual dose activity will have decayed and therefore requires recalculation.