Treatment protocol R-DHAOx

PHASE II STUDY OF RITUXIMAB, DEXAMETHASONE, HIGH-DOSE CYTARABINE, AND OXALIPLATIN (R-DHAOx) FOR TREATMENT OF PATIENTS WITH B-CELL LYMPHOMA EXPRESSING CD-20, WHO HAD BEEN PREVIOUSLY TREATED

SPONSOR:

Fax:

STUDY COORDINATOR

Name

E-Mail address

ADDRESS

telephone:

Fax:

DATA ANALYSIS

Address
# STUDY SYNOPSIS

<table>
<thead>
<tr>
<th>Title</th>
<th>PHASE II STUDY OF RITUXIMAB, DEXAMETHASONE, HIGH-DOSE CYTARABINE, AND OXALIPLATIN (R-DHAOx) FOR TREATMENT OF PATIENTS WITH B-CELL LYMPHOMA EXPRESSING CD-20, WHO HAD BEEN PREVIOUSLY TREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>To be determined</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>To be determined</td>
</tr>
<tr>
<td>Investigators</td>
<td>To be determined</td>
</tr>
<tr>
<td>Objectives</td>
<td><strong>To evaluate</strong> the efficacy and the safety of R-DHAOx in refractory and/or relapsed patients with CD20-positive B-cell lymphomas</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td><strong>Overall Response Rate</strong> (ORR; <em>i.e.</em>, Complete Response, CR; Unconfirmed Complete Response, CRu; and Partial Response, PR) achieved with R-DHAOx at completion of the treatment</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td><strong>Event free survival</strong> (EFS): events being (a) death from any cause, (b) relapse occurring in complete responders and unconfirmed complete responders, (c) progression during and after treatment, and (d) change for a new treatment.</td>
</tr>
<tr>
<td>Analysis of the Molecular response: in patients whose bone marrow and/or peripheral blood carry genetic molecular markers</td>
<td></td>
</tr>
<tr>
<td>Safety of R-DHAOx in this patient population.</td>
<td></td>
</tr>
<tr>
<td>Overall survival (OS), time to disease progression (TTDP), and disease-free survival (DFS) for patients who attain a CR.</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Phase II, non-randomized, open, monocentric (one single center) study</td>
</tr>
<tr>
<td>Number of patients</td>
<td>25 patients. Inclusions can stop earlier after interim analysis at the end of the first stage according to Simon’s design which calls for 16 patients evaluable for response</td>
</tr>
<tr>
<td>Study Population</td>
<td>- Patients diagnosed with histologically proven, CD 20-positive B-Cell Lymphoma, of follicular, mantle cell, marginal zone, and diffuse large cell subtypes (WHO Classification)</td>
</tr>
<tr>
<td>- (a) Patients in relapse after CR, (b) patients who attain only a partial response or a minor reduction of the tumor with any line of treatment, and (c) patients with tumor progression with any line of treatment</td>
<td></td>
</tr>
<tr>
<td>- Aged 18 - 80 years</td>
<td></td>
</tr>
<tr>
<td>- Previously treated with chemotherapy containing anthracyclins, with or without rituximab</td>
<td></td>
</tr>
<tr>
<td>- ECOG performance status 0 to 2</td>
<td></td>
</tr>
<tr>
<td>- patients with a minimum life expectancy of 3 months</td>
<td></td>
</tr>
<tr>
<td>- Having informed consent prior to enrolment</td>
<td></td>
</tr>
</tbody>
</table>
### Exclusion criteria
- Burkitt’s lymphoma; small lymphocytic, and lymphoplasmacytic lymphoma subtypes
- CD20-negative B-cell lymphoma
- HIV-related disease
- Central nervous system or meningeal involvement by the lymphoma
- Patients who previously treated with anthracycline-containing regimens
- Contraindication to any drug contained in the R-DHAOx chemotherapy regimen,
- Any serious active disease or co-morbid medical condition (according to the investigator’s decision)
- Creatinin level above 200 mol/l, and altered hepatic function (total bilirubin level >30mmol/l, transaminases >2.5 upper normal level) unless these abnormalities are related to organ involvement by the lymphoma
- Poor bone marrow reserve as defined by neutrophils <1.5 G/l and/or platelets <100G/l, unless these abnormalities are related to bone marrow involvement
- Any history of cancer during the last 5 years, with the exception of non-melanoma skin tumors or in situ cervical carcinoma
- Treatment with any investigational drug within 30 days before initiation of the first cycle of R-DHAOx
- Pregnant or lactating woman,
- Adult patient unable to give informed consent because of intellectual impairment.

### Treatment
R-DHAOx consists of four-day courses repeated every 21 days

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>375 mg/m²/d</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dexamethasone</td>
<td>40 mg/d</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>oxaliplatin</td>
<td>130 mg/m²/d</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cytarabine</td>
<td>2,000 mg/m²/12hr</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

G-CSF, 5 g/d, from Day 3 until recovery of PMN counts to above 500 cells/μL

R-DHAOx consists of dexamethasone, 40 mg/day iv, from day 1 to day 4; rituximab, 375 mg/m² on day 1; L-OHP, 130 mg/m² infused iv over 2 hr on day 1; and ara-C, 2,000 mg/m² infused iv over 3 hr every 12 hr on day two. Granulocyte-colony-stimulating factor (G-CSF) at a dose of 5 g/kg/day is administered from day 3 until recovery of PMN counts to above 500 cells/μL. Treatment is repeated every 21 days. The dose of L-OHP is reduced by 30 mg/m² in subsequent courses in cases of grades 1-2 peripheral neuropathy according to the scale presented in Appendix Z. Treatment is stopped when a tumor shrinkage is not observed after 3 courses of therapy, when a response can not be attained after 6 courses, and at any time in cases of peripheral neuropathy of grades ≥ 3. In responding patients, courses of R-DHAOx are repeated until a CR is attained. Complete responders subsequently receive additional courses of R-DHAOx, until a maximum total number of 8 courses, followed by additional rituximab at 375 mg/m² every two weeks for a total of four injections, then have their treatment terminated.

No dose reductions are planned, except for peripheral neuropathy. Any other grade 4 toxic effect requires to delay further courses until recovery occurs.
| **Statistical analysis** | The primary endpoint of **Overall Response Rate** (ORR) was used to determine the sample size. In our own original study with DHAOx, as well as in studies performed by other investigators, for treatment of patients with relapsed or refractory non-Hodgkin’s lymphoma (refs), the ORR varied from 50% to 73%. Therefore, in this study testing for an additional benefit of the adjunction of rituximab to DHAOx for treatment of patients with relapsed or refractory CD20-positive non-Hodgkin’s lymphoma, a response rate in excess of 70% will be considered of clinical interest, and a response rate of 90% or greater will be considered of strong clinical interest. The Simon design will test the null hypothesis that the true response rate ≤ 70% versus the alternative that the true response rate > 70%. The study will have a significance level of 10% and will have 90% power to reject the null hypothesis if the true response rate is 90%. The Simon design in this case calls for 16 patients evaluable for response at the end of the first stage. If there are 11 or fewer responders at the end of the first stage, the study will be terminated and it will be concluded that the treatment is not of clinical interest (the probability of stopping the study at the end of the first stage when the true response rate is 70% or greater is less than 10%). Otherwise, an additional 9 response evaluable patients will be enrolled. The treatment will be considered of clinical interest (response rate greater than 70%) only if there are 21 or more responders (out of the 25 response evaluable patients) at the end of the second stage. |
| **Primary endpoint** | |
| **Secondary endpoints** | Categorical variables will be compared using chi-square test or Fisher exact test. Continuous variables will be compared using T-test. Survival data will be studied using the Log-rank test. |
| **Planned start/end of recruitment** | March 2005 /March 2006 |
TABLE OF CONTENTS

1 RESPONSABILITIES ..................................................................................................................8

1.1 TITLE OF THE TRIAL ..............................................................................................................8

1.2 STUDY COORDINATION CENTER .........................................................................................8

1.2.1 Sponsor: ..........................................................................................................................8

1.2.2 Study coordination center: Bureau d’Etudes Cliniques, FSMST, Hôpital Paul-Brousse ........8

1.3 INVESTIGATORS ....................................................................................................................8

2 RATIONALE ...............................................................................................................................8

3 STUDY OBJECTIVES ..................................................................................................................10

3.1 PRIMARY ENDPOINT ............................................................................................................10

3.2 SECONDARY ENDPOINTS .....................................................................................................10

4 STUDY DESIGN ........................................................................................................................10

4.1 SUMMARY OF STUDY DESIGN ..........................................................................................10

4.2 LABORATORIES ....................................................................................................................11

4.3 NUMBER OF PATIENTS ..........................................................................................................11

4.4 DURATION OF THE STUDY AND FOLLOW-UP FOR EACH SUBJECT ......................................11

5 STUDY POPULATION ...............................................................................................................11

5.1 PATIENTS ...............................................................................................................................11

5.2 INCLUSION CRITERIA .............................................................................................................11

5.3 EXCLUSION CRITERIA .............................................................................................................12

6 SCHEDULE OF ASSESSMENTS AND PROCEDURES ................................................................12

6.1 INFORMED CONSENT .........................................................................................................12

6.2 REGISTRATION PROCEDURE .............................................................................................12

6.3 STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS ...............................................13

6.3.1 Study flow chart ...............................................................................................................13

6.3.2 Screening examination and selection procedures (Appendix 15.6.1) ................................13

6.3.3 Evaluation during each induction and consolidation cycle ..............................................13

6.3.4 Periodic assessment of antitumor response (after the 3rd, 6th, and 8th cycles of R-DHAOx, and at the end of therapy) .................................................................14

6.3.5 Assessment during five years following treatment .........................................................14

6.3.6 Subsequent yearly assessment ........................................................................................14
7 TREATMENT ......................................................................................................................... 15

7.1 INDUCTION AND CONSOLIDATION REGIMEN ................................................................. 15

7.1.1 R-DHAOX ......................................................................................................................... 15

Part I: Induction and consolidation phases: ........................................................................... 15

Patients are treated every 3 weeks with the following treatment for a maximum number of 8 courses: .... 15

7.1.2 Dose adjustments ............................................................................................................. 16

(1) Hematologic toxicity ........................................................................................................... 16

Doses which have been reduced because of toxicity cannot be re-escalated to the starting level ........... 17

7.1.3 Stopping rules .................................................................................................................. 17

7.2 DRUGS .................................................................................................................................. 18

7.3 SUPPLIES ............................................................................................................................ 18

7.3.1 Drug supply ....................................................................................................................... 18

7.4 RESTRICTIONS FOR CONCOMITANT TREATMENTS ....................................................... 18

8 ADVERSE EVENTS ................................................................................................................. 19

8.1 ADVERSE EVENTS .............................................................................................................. 19

8.2 SERIOUS ADVERSE EVENTS (SAE) .................................................................................... 19

8.2.1 Definition ........................................................................................................................ 19

8.3 FOLLOW-UP OF ADVERSE EVENTS .................................................................................. 20

9 CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY ................................... 20

9.1 PREMATURE WITHDRAWAL OF SUBJECT ........................................................................ 20

10 ANALYSIS OF STUDY DATA .............................................................................................. 21

10.1 CRITERIA FOR EVALUATION, ENDPOINTS .................................................................... 21

10.1.1 Primary endpoint ............................................................................................................. 21

10.1.2 Secondary endpoints ...................................................................................................... 22

10.2 STATISTICAL ANALYSIS ................................................................................................. 23

10.2.1 Primary endpoint, early stopping rules, and sample size calculation ......................... 23

10.2.2 Secondary endpoints: Safety analysis ............................................................................. 24

11 STUDY MONITORING .......................................................................................................... 24

11.1 RESPONSABILITIES OF THE INVESTIGATORS ................................................................. 24

11.2 RESPONSABILITIES OF THE SPONSOR .......................................................................... 24

11.3 SOURCE DOCUMENT REQUIREMENTS ............................................................................. 25

11.4 USE AND COMPLETION OF THE CASE REPORT FORMS (CRF) ...................................... 25
12 ETHICAL AND REGULATORY STANDARDS ............................................................................. 25

12.1 Ethical Principles ............................................................................................................. 25
12.2 Laws and Regulations ...................................................................................................... 26
12.3 Informed Consent ............................................................................................................ 26
12.4 Ethics Review Committee (ERC) .................................................................................... 26

13 ADMINISTRATIVE PROCEDURES .................................................................................... 26

13.1 Curriculum Vitae ........................................................................................................... 26
13.2 Secrecy Agreement ......................................................................................................... 27
13.3 Record Retention in Investigating Centre(s) .................................................................. 27
13.4 Ownership of Data and Use of the Study Results ............................................................. 27
13.5 Publication ...................................................................................................................... 27
13.6 Insurance Compensation ................................................................................................. 28
13.7 Audits and Inspections by Regulatory Agencies ............................................................... 28
13.8 Clinical Study Report ..................................................................................................... 28
13.9 Protocol Amendments ..................................................................................................... 28

14 REFERENCES .................................................................................................................... 29

15 APPENDIX .......................................................................................................................... 31

15.1 Appendix 1: Ann Arbor Staging ...................................................................................... 31
15.2 Appendix 2: International Prognostic Index .................................................................... 31
15.3 Appendix 3: WHO (ECOG) Performance Status .............................................................. 32
15.4 Appendix 4: International Common Toxicity Criteria ..................................................... 32
15.5 Appendix 5: Response Evaluation. Panel Expert Committee: International Working Group Response Criteria [From Cheson et al. (15)] .................................................. 32
15.6 Appendix 6: Study Flow Chart and Schedule of Assessments ....................................... 33
15.6.1 Schedule of assessments ............................................................................................. 33
15.7 Appendix 7: Drug Information: ...................................................................................... 34
15.7.1 Rituximab: MABTHERA® .......................................................................................... 34
   → Formulation, storage, reconstitution and dilution of MabThera ........................................ 34
   → Mabthera: Administration and precautions .................................................................... 34
15.7.3 Oxaliplatine: ELOXATINE® .................................................................................... 36

Oxaliplatin in Combination with 5-Fluorouracil ................................................................. 42
Plasma Ultra-filrate .............................................................................................................. 43
1 RESPONSABILITIES

1.1 Title of the trial

PHASE II STUDY OF RITUXIMAB, DEXAMETHASONE, HIGH-DOSE CYTARABINE, AND OXALIPLATIN (R-DHAOx) FOR TREATMENT OF PATIENTS WITH B-CELL LYMPHOMA EXPRESSING CD-20, WHO HAD BEEN PREVIOUSLY TREATED

1.2 Study coordination center

1.2.1 Sponsor:

1.2.2 Study coordination center:

1.3 Investigators

The medical teams of the Mediterranean Oncology Society (MOS)

2 RATIONALE

Patients with malignant lymphoma in relapse, and patients who do not achieve a complete response with initial (first-line), anthacycin-containing chemotherapy have a poor long-term outcome. High-dose chemotherapy regimens followed by autologous stem cell support is an established salvage treatment for chemosensitive relapses (Philip, 1). However not all patients are candidates for these types of treatments because of advanced age, previous transplantation, comorbidity, and frequent presence of tumor cells in peripheral blood and/or in the bone marrow despite induction chemotherapy, as frequently diagnosed by the persistence of tumor molecular markers. Therefore, effective and well tolerated salvage therapies with acceptable levels of toxicity are needed.

Our objective is to elaborate a salvage regimen with the combination of rituximab, dexamethasone, cytarabine and oxaliplatin for patients with B-cell non-Hodgkin’s lymphoma.

This schema was originally derived from the DHAP regimen that combines dexamethasone, cytarabine (ara-C) and cisplatin. Based upon laboratory and previously reported clinical data, we hypothesized that substitution of cisplatin by oxaliplatin, [trans-(L)-1,2-diaminocyclohexane] oxalatoplatinum (II) (L-OHP), in the DHAP schema could result in lesser toxicity and greater efficacy. L-OHP is a platinum coordination complex with an oxalato ligand as leaving group and a 1,2-diaminocyclohexane carrier. The drug possesses activity against a number of human and murine tumor cells in vitro and in vivo, including murine leukemia cell lines.[5,6] It has a higher cytotoxic potency on a molar basis than do cisplatin and paraplatin, and it is active on various cell lines that have been selected for resistance to cisplatin. The drug used as a single agent is active in several types of solid tumors,[7] and it was reported to achieve responses, mostly partial, in 40% of patients with non-Hodgkin’s lymphomas of various histologic types.[8] Toxic effects of oxaliplatin include dose-related peripheral neuropathy, vomiting, diarrhea, and mild myelosuppression. The drug is
devoid of renal toxicity.\cite{7} We, and, subsequently, other investigators have already studied the DHAOx schema, consisting in the substitution of the cisplatin in the DHAP schema by oxaliplatin, in patients with non-Hodgkin’s lymphoma who had been previously treated (Machover\cite{9}, Chau\cite{8}). In our previous study \cite{Machover9}, 69\% of patients with B-cell non-Hodgkin’s lymphoma had a response, and 46\% achieved a CR with DHAOx. Responses were achieved by patients with lymphomas of various histologies that included mainly the follicular subtype, and by patients with and without resistance to prior chemotherapy. CRs were of long duration, and disappearance of molecular markers was observed in all patients who achieved a CR and whose tumor cells carried molecular abnormalities. Other investigators have used DHAOx to treat patients with refractory or relapsed intermediate and high-grade B-cell non-Hodgkin’s lymphoma [Chau \cite{8}]. They reported an overall response rate of 55\%, including a CR rate of 18\%, which demonstrates that DHAOx is also active in lymphomas with aggressive histologies.

In recent years, evidence was obtained for a greater efficacy of various chemotherapy regimens in combination with the anti-CD20 chimeric mouse-human monoclonal antibody rituximab in most types of B-cell malignancies expressing the CD20 antigen, compared to the efficacy with chemotherapy alone \cite{5,6}. These findings prompted us to modify our salvage schema for patients who had B-cell non-Hodgkin’s lymphomas for whom we used DHAOx alone, and to design a new regimen with the addition of rituximab (R-DHAOx).

In vitro, the addition of rituximab to cytostatic drugs increases cell lysis even in chemoresistant cell lines (Demidem,\cite{2}; Ghetie,\cite{3}). This chemosensitizing effect was also demonstrated in patients by the results of the Groupe d’Etude des Lymphomes de l’Adulte (GELA) trial in elderly patients with diffuse large B-cell lymphoma (DLBCL) (Coiffier,\cite{5}). An improvement in response rate by fifteen percent was strongly suggested in a phase II study of the RICE regimen (rituximab plus ifosfamide, carboplatine and etoposide) for treatment of patients with relapsed DLBCL, in comparison with the results achieved in prior studies with the same chemotherapy regimen (ICE), in the absence of rituximab (Kewalramani, ASH 2001,\cite{6}). This retrospective comparison led the SWOG to stop an ongoing randomised trial comparing ICE vs RICE in patients with relapsed aggressive lymphoma.

Cisplatin plus cytarabine-containing regimens such as DHAP, ESHAP (Velasquez,\cite{7}) were developed in the 1980s based upon the demonstrated experimental synergism between ara-C and cisplatin [ref.]. These regimens are not cross resistant with frontline doxorubicin-containing combination chemotherapy. Oxaliplatin has been show to be active in relapsed or refractory NHL when used either as a single agent (German,\cite{10}) and in combination (Machover,\cite{9}; Chau,\cite{8}). Furthermore, the combination of rituximab, gemcitabine and oxaliplatin has shown to be effective in patients with NHLs (poster Hayoun, Reyes) which outlines the importance of oxaliplatin-containing regimens in patients with these diseases.

Our aim in the present study is to achieve an improvement of 20\% in overall response rate compared to that previously reported with DHAOx in patients with previously treated CD-20 positive NHLs who require salvage treatment, with a good safety profile.
3 STUDY OBJECTIVES

To evaluate the efficacy and the safety of R-DHAOx as salvage treatment for relapsed and/or refractory patients with CD20-positive B-cell lymphomas.

3.1 Primary endpoint

- Overall response rate (ORR; comprising complete response, CR; unconfirmed complete response, CRu; and partial response, PR) obtained with R-DHAOx.

3.2 Secondary endpoints

- Overall response rate (ORR; comprising complete response, CR; unconfirmed complete response, CRu; and partial response, PR) at completion of the planned treatment (8 courses of R-DHAOx as a maximum, followed by 4 injections of rituximab as a single agent)
- Time to disease progression (TTDP)
- Disease-free survival (DFS)
- Event free survival (EFS), events being defined as (1) death from any cause, (2) relapse for complete responders and unconfirmed complete responders, (3) progression during or after treatment for partial responders, and (4) institution of any subsequent therapy for treatment of the lymphoma.
- Overall survival
- Safety
- Analysis of the genetic molecular response in the peripheral blood, and in the bone marrow

4 STUDY DESIGN

4.1 Summary of study design

This study is an open, non-randomized, single center, phase II trial for evaluation of the efficacy and safety of R-DHAOx in relapsed and/or refractory patients aged 18-80 years with previously treated CD20-positive B-cell lymphoma who require salvage treatment.

Part I: Induction and consolidation phases: Four-day courses of R-DHAOx are repeated every 21 days (Day 1, Day 22, Day 43 etc), and tumor mass evaluations are performed at regular intervals. Treatment is stopped when a tumor shrinkage is not observed after 3 courses of therapy, or when a response can not be attained after 6 courses. In responding patients (i.e., in patients with a PR), courses of R-DHAOx are repeated until a CR is attained. Complete responders (i.e., in patients with
a CR, or a CRu) subsequently receive additional courses of R-DHAOx, until a maximum total number of 8 courses.

**Part II: Additional rituximab as a single agent**: 4 injections of rituximab at the end of the induction and consolidation phases

**4.2 Laboratories**

All laboratories used for hematological and biochemical tests and assays must provide their normal values.

**4.3 Number of patients**

A total number of 25 patients with previously treated CD20-positive Large B-Cell lymphoma will be enrolled in the study.

**4.4 Duration of the study and follow-up for each subject**

Patients will be recruited over 1 year and followed indefinitely at regular intervals. The duration of the treatment period for each patient is approximately 28 weeks.

**5 STUDY POPULATION**

**5.1 Patients**

Adult patients aged 18 to 80 years with previously treated CD20-positive B-cell non-Hodgkin’s lymphoma in relapse or with disease progression at any time during the treatment of their disease, with no contraindication to any of the drugs included in the R-DHAOx regimen.

**5.2 Inclusion criteria**

- Patients with CD20-positive B-cell non-Hodgkin’s lymphoma. The disease must be histologically proven.
- Patients aged 18 - 70 years
- (a) Patients in relapse after CR, (b) patients who attain only a partial response or a minor reduction of the tumor with any previous line of treatment (*i.e.*, first or subsequent), and (c) patients with tumor progression with any line of treatment
- Patients not eligible for intensive chemotherapy followed by autologous stem cell transplantation
- Patients previously treated with chemotherapy containing an anthracycline, with or without rituximab.
- ECOG performance status 0 to 2.
- Signed written informed consent.
5.3 Exclusion criteria

- Burkitt’s, small lymphocytic, and lymphoplasmacytic B-cell lymphoma subtypes, and T-cell lymphomas
- CD20-negative B-cell lymphoma
- Patients with documented infection with HIV
- Central nervous system or meningeal involvement by the lymphoma.
- Patients not previously treated with at least one anthracycline-containing regimen
- Contraindication to any drug contained in the R-DHAOx regimen
- Any serious active disease or co-morbid medical condition (according to the investigator’s decision).
- Altered renal function (creatinine level >200 mol/l), altered hepatic function (total bilirubin level >30 mmol/l, transaminases >3 x upper normal level) unless these abnormalities are related to organ infiltration by the lymphoma.
- Altered baseline myelopoiesis as defined by neutrophils <1.5 G/l or platelets <80,000 G/l, unless related to bone marrow infiltration.
- Any history of cancer during the last 5 years with the exception of non-melanoma skin tumors or stage 0 (in situ) cervical carcinoma.
- Treatment with any investigational drug within 30 days before the beginning of the first cycle of R-DHAOx, and during the study.
- Pregnant or lactating woman
- Adult patient unable to provide informed consent because of intellectual impairment.

6 SCHEDULE OF ASSESSMENTS AND PROCEDURES

6.1 Informed consent

Written informed consent will be obtained from each subject prior inclusion.

The investigator shall provide one copy of the signed consent to the study subject, another copy shall be maintained in the subject’s medical record and a third copy will be kept in the patient's clinical research files that pertain to this study. The patient and the investigator will date and sign the informed consent form. The investigator may then register the subject for the study.

6.2 Registration procedure

Patients will be registered in the study at the Address…., telephone …………., fax……………..
6.3 Study flow chart and Schedule of assessments

6.3.1 Study flow chart

See Appendix 15.6.2

6.3.2 Screening examination and selection procedures (Appendix 15.6.1)

The subject will be evaluated for eligibility during the baseline period prior administration of the first cycle of chemotherapy. Assessments are to be conducted within 2 weeks before administration of the treatment. Assessments are:

- Age, gender, weight, height
- Relevant medical history
- History of the lymphoma
- Clinical examination
- Determination of stage and extent of the disease
- Head and neck, thoracic and abdominal plus pelvic CT scans without and with contrast
- Bone marrow biopsy and bone marrow smears
- Genetic molecular assays in peripheral blood and bone marrow including (a) PCR amplification of the rearranged VH-J region of the immunoglobulin heavy chain genes, for determination of B-cell clonality; and (b) PCR amplification of the BCL2-IgH fusion gene (MBR and mcr) which results from the t(14;18) in B-cell lymphomas, and of the BCL1-IgH fusion gene from the t(11;14) in mantle cell lymphoma.
- Lactate deshydrogenase (LDH) and 2 microglobuline plasma levels
- Biochemical tests: serum creatinine, ASAT, ALAT, total bilirubin, alkaline phosphatase, calcium, phosphorus, uric acid, electrolytes.
- Serum electrophoresis: total protein, albumin, globulins
- Complete blood cell counts
- Echocardiographic and / or isotopic determination the LVEF at rest
- EKG
- HIV, HBV and HCV serologies
- CSF examination by lumbar puncture if clinically indicated
- Brain CT scan if clinically indicated
- Any additional examination clinically indicated. (e.g., endoscopy, ultrasound imaging, H & N examination …..)

6.3.3 Evaluation during each induction and consolidation cycle

- Clinical examination prior administration of the cycle
- Blood cell counts prior administration, and on days 5, then every three days or more frequently when indicated
- Adverse events (symptoms / toxicity)
6.3.4 Periodic assessment of antitumor response (after the 3rd, 6th, and 8th cycles of R-DHAOx, and at the end of therapy)

- Clinical examination
- Head and neck, thoracic and abdominal/pelvis CT scan with and without contrast
- Complete (full) blood cell counts
- LDH plasma levels
- Bone marrow biopsy if initially involved
- Genetic molecular assays in peripheral blood and bone marrow if markers were present initially
- Adverse events (symptoms / toxicity)
- 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan is performed at the end of the treatment (in principle, 4 weeks after the 8th course of R-DHAOx) in patients who attain a CR or a CRu.
- Additional tests to explore previously involved sites (e.g., endoscopy, H & N examination …)

6.3.5 Assessment during five years following treatment

- Every 3 months
  - Clinical examination
  - Blood cell counts
  - LDH plasma level

- Every 6 months
  - Head and neck, thoracic and abdominal/pelvis CT scan without and with contrast
  - Genetic molecular assays in peripheral blood and bone marrow if markers were present initially

6.3.6 Subsequent yearly assessment

- Clinical examination
- Blood cell counts
- LDH plasma levels
- CT scan

6.4 Pathological review

A central review of the histological diagnosis will be performed for each patient enrolled in the trial. The goal is to confirm the diagnosis of CD20-positive diffuse large B-cell lymphoma and to define the subtype of the lymphoma according to the WHO classification. Expression of biological markers will be studied by immunohistochemistry, according to the type of lymphoma. DNA extraction may be performed in selected cases for genetic molecular studies, as described above (6.3.2.). It will be ensured that material will be available for review. Pathologic material will be examined at:
7 TREATMENT

7.1 Induction and consolidation regimen

7.1.1 R-DHAOx

Part I: Induction and consolidation phases:

Patients are treated every 3 weeks with the following treatment for a maximum number of 8 courses:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m²/day</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dexamethasone</td>
<td>40 mg/day</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>oxaliplatin</td>
<td>130 mg/m²/day</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cytarabine</td>
<td>2,000 mg/m²/12 hr</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Rituximab is infused iv at 375 mg/m² on Day 1 (see Appendix 15.7.1).
(2) Dexamethasone at 40 mg per day during 4 days is administered iv or orally, on days 1 to 4.
(3) Oxaliplatin at 130 mg/m² is injected iv in 2 hours, on Day 1. It is diluted in 250 ml of D5W).
(4) Cytarabine is injected iv in 3 hours at 2,000 mg/m² every 12 hours, on Day 2 for a total dose of 4,000 mg/m²
(5) G-CSF, 5 g/d iv or subcutaneously is administered from Day 3 until recovery of PMN counts to above 500 cells/L

Four-day courses of R-DHAOx are repeated every 21 days (Day 1, Day 22, Day 43 etc), and tumor mass evaluations are performed at regular intervals. Treatment is stopped when a tumor shrinkage is not observed after 3 courses of therapy, or when a response can not be attained after 6 courses (i.e., in patients with less than a PR). In responding patients (i.e., in patients with a PR), courses of R-DHAOx are repeated until a CR is attained. Patients who achieve a complete response (i.e., in patients with a CR or a CRu) receive subsequently additional consolidation courses of R-DHAOx, until a maximum total number of 8 courses.
Part II: Additional rituximab as a single agent:

This phase consists of 4 injections of rituximab at the end of the induction and consolidation phases. After this phase, treatment is terminated.

Patients who do not achieve a response, and responding patients who do not attain a CR or a CRu with R-DHAOx, will receive further treatment according to the decision of the investigator.

7.1.2 Dose adjustments

(1) Hematologic toxicity

There is no dose adjustment related to hematological toxicity. However, subsequent courses of R-DHAOx will be postponed until neutrophil counts are > 1.0 x 10^9 cells/l and platelet counts 100 x 10^9 cells/l. G-CSF at 5 g/kg/day is administered in all patients from Day 3 until recovery of PMN counts to above 500 cells/ L.

(2) Neuropathy

Peripheral neuropathy is graded according to a specific scale which takes in account the duration of the symptoms and their intensity: Grade 1: mild dysesthesia and / or paresthesia, transient, ≤ 7 days; grade 2: dysesthesia and / or paresthesia, transient, < 14 days; grade 3: dysesthesia and / or paresthesia persisting during the drug-free interval between courses with complaint (i.e., for more than 14 days); grade 4: permanent severe dysesthesia and / or hypoesthesia with functional impairment.

In cases of grades 1-2 peripheral neuropathy graded according to the specific scale described above, the dose of oxaliplatin is reduced by 30 mg/m² in subsequent courses, until a maximum of two consecutive dose reductions. In cases of neuropathy ≥ grade 3, the treatment is stopped. In cases of pharyngolaryngeal dysesthesia, the duration of the infusion of oxaliplatin is prolonged to 4-6 hours in subsequent courses.

Table for adjustments of the dose of oxaliplatin in subsequent courses in case of neuropathy according to type of symptoms and duration. These indications are especially useful in cases of neuropathy of borderline grade.

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th>Transient, ≤ 7 days</th>
<th>Transient, &gt; 7 and &lt; 14 days</th>
<th>Persistent between courses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R-DHAOx, le 12-02-2005
<table>
<thead>
<tr>
<th>Type</th>
<th>Dose reduction of oxaliplatin in mg/m²/course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold-related dysesthesia only</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>30 mg/m²</td>
</tr>
<tr>
<td></td>
<td>30 mg/m²</td>
</tr>
<tr>
<td>Mild paresthesia or dysesthesia</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>30 mg/m²</td>
</tr>
<tr>
<td></td>
<td>30 mg/m²</td>
</tr>
<tr>
<td>Paresthesia associated with pain or complaint</td>
<td>30 mg/m²</td>
</tr>
<tr>
<td></td>
<td>30 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Stop the treatment</td>
</tr>
<tr>
<td>Paresthesia associated with functional impairment</td>
<td>30 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Stop the treatment</td>
</tr>
<tr>
<td></td>
<td>Stop the treatment</td>
</tr>
</tbody>
</table>

Doses which have been reduced because of toxicity cannot be re-escalated to the starting level.
Doses can be reduced until a maximum of 2 dose reductions.
Presence of a Lhermitte sign requires one dose reduction.

Rituximab treatment will be postponed or stopped if DHAOx is postponed or stopped. The dose of rituximab will not be adjusted otherwise.

### 7.1.3 Stopping rules

This study will utilize a Simon minimax two-stage design (Réf. Simon 1989) to test whether the objective response rate in this study is of clinical interest. This design minimizes the expected number of patients who receive the study treatment when the true response rate is not of clinical interest.

In this study testing for an additional benefit of the adjunction of rituximab to DHAOx for the treatment of patients with relapsed or refractory CD20-positive non-Hodgkin’s lymphoma, a response rate in excess of 70% will be considered of clinical interest, and a response rate of 90% or greater will be considered of strong clinical interest. The Simon design will test the null hypothesis that the true response rate \( \leq 70\% \) versus the alternative that the true response rate \( > 70\% \). The study will have a significance level of 10% and will have 90% power to reject the null hypothesis if the true response rate is 90%. The Simon design in this case calls for 16 patients evaluable for response at the end of the first stage. If there are 11 or fewer responders at the end of the first stage, the study will be terminated and it will be concluded that the treatment is not of clinical interest (the probability of stopping the study at the end of the first stage when the true response rate is 70% or greater is less than 10%). Otherwise, an additional 9 response evaluable patients will be enrolled. The treatment will
be considered of clinical interest (response rate greater than 70%) only if there are 21 or more responders (out of the 25 response evaluable patients) at the end of the second stage.

- **IMPORTANT NOTE:**

  If a patient does not respond to treatment, relapses, or has progressive disease, further treatment or therapeutic options are left to the investigator’s decision. The patient is then dropped out from the study and the investigator continues collecting follow-up information regarding relapse, progression, and survival time.

7.2 **Drugs**

Details on products: *see appendix 15-7.*

7.3 **Supplies**

  7.3.1 **Drug supply**

  The drugs which compose the R-DHAOx regimen are available at the pharmacy of the hospital. Rituximab (Mabthera®) is purchased from Laboratoires Roche. Oxaliplatin (Eloxatin®) is purchased from Sanofi-Synthélabo; and cytarabine and dexamethasone are generic drugs.

  In accordance with the requirements of national regulatory agencies, the pharmacist attached to the investigator’s department is responsible for proper storage, dispensation, and disposal of the drugs.

7.4 **Restrictions for concomitant treatments**

- Supportive treatments will be administered according to the standard use in each center regarding hydratation, antiemetics, antimicrobials, blood component therapy, erythropoietin, prophylaxis of tumor lysis syndrome, and nutritional supportive care. Concomitant administration of any other chemotherapy agents or regimens during treatment with R-DHAOx is not allowed.

- Concomitant treatment with any investigational drug within 30 days before initiation of the first cycle of R-DHAOx and during the study is not allowed.
8 ADVERSE EVENTS

8.1 Adverse Events

Definition: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject given a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

→ Due to the expected toxicity of these treatments, only grade 3 and 4 toxicities (NCIC Common Toxicity Criteria grading system – version 2) or grade 2 for infections, and toxicities (grade 1 to 4) related to a Serious Adverse Event as described below, must be reported as “Adverse Event”.

→ All “Alopecia” toxicity and hematologic toxicities without fever is not recorded as “Adverse Event”.

All Adverse Events (AE) occurring from the signing of the Informed Consent and until 30 days after the end of the last cycle of treatment will be recorded on the patient’s file.

The intensity of this event will be graded according to the NCIC Common Toxicity Criteria grading system (see Appendix 4) in the toxicity categories that have recommended gradings. Adverse events not listed on this grading system will be graded according to the four-point system below:

→ Mild (grade 1) : Discomfort noticed but no disruption of normal daily activity
→ Moderate (grade 2) : Discomfort sufficient to reduce or affect normal daily activity
→ Severe (grade 3) : Incapacitating with inability to work or perform normal daily activity
→ Life-threatening (grade 4) : Self-explanatory.

The investigator should specify the date of onset, corrective therapies given, outcome of all severe adverse events and his opinion as to whether the adverse event can be related to study drug.

8.2 Serious adverse events (SAE)

8.2.1 Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

• Results in death or
• Is life-threatening or
Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires in-patient hospitalization or prolongation of existing hospitalization or
- Results in persistent or significant disability / incapacity.

All such defined SAEs encountered 30 days after the last cycle of chemotherapy, whether or not ascribed to the study, will be recorded. Medical and scientific judgement should be exercised in deciding whether other important medical events should be considered serious.

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

8.3 Follow-up of adverse events

Any additional information known after the event has been initially reported should be reported as information becomes available.

Subjects withdrawn from the study treatment due to any adverse event will be followed at least until the outcome is determined or resolves and even if it implies that the follow-up continues after the patient has left the trial.

In the case of a serious adverse event, the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. It may imply that this follow-up will continue after the patient has left the trial.

9 CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

9.1 Premature withdrawal of subject

Circumstances that lead to premature withdrawal of a subject from the trial must be clearly reported by the investigator on the patient’s file.

Criteria for subject withdrawal include (but are not limited to) death, toxicity, an intercurrent illness, noncompliance (including loss of subject to follow-up), voluntary withdrawal, and failure to meet the eligibility criteria.

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the
patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time there must be documented attempts to contact the patient either by phone or letter.

10 ANALYSIS OF STUDY DATA

10.1 Criteria for evaluation, endpoints

10.1.1 Primary endpoint

Overall response rate (ORR; i.e., Complete Response, CR; Unconfirmed Complete Response, CRu and Partial Response, PR) achieved with R-DHAOx at completion of the treatment. The responses are defined, according to Cheson (Appendix 5, 15). Response to treatment may also be subjected to evaluation by an external panel. The definition of antitumor response is:

- **Complete response (CR):** complete disappearance of all detectable clinical and radiologic evidence of disease: all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest orthogonal diameters (SPD). Normalization of biological abnormalities assignable to lymphoma at diagnosis and no new lesion is required. 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 on physical examination. If the bone marrow was involved before treatment, the infiltrate must be cleared on repeat biopsy.

- **Unconfirmed CR (CRu):** as above but with one or more of the following features: A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD and or indeterminate bone marrow with normalization of all biologic abnormalities, and normalization of the PS.

In case of persistence of lymphoma cells proven by histologic or cytologic analysis, the response is classified as a PR.
Partial response (PR): regression by more than 50% (in the sum of the products of the greatest orthogonal diameters) of all measurable lesions and disappearance of non-measurable lesions and no new lesion.

Stable disease (SD): no response to the treatment; regression by less than 50% (in the sum of the products of the greatest diameters) of all measurable lesions; regression of more than 50% but with the persistence of clinical symptoms; or no change for the non-measurable lesions. Stable disease is considered as treatment failure.

Progressive disease (PD) for partial responders and non-responding patients: appearance of any new lesion or any growth of more than 25% (in the sum of the products of the greatest diameters) of a measurable lesion.

Relapsed disease for patients in CR or CRu: appearance of any new lesion or increase by more than 25% (in the sum of the products of the greatest diameters) of any residual site or node that was considered "normal" by the IWG guidelines and definitions of normal lymph node size.

10.1.2 Secondary endpoints

Event-free survival (EFS):
Events are defined as follows:
- Progression of the lymphoma during or after treatment for partial responders,
- Relapse for CR and CRu patients,
- Institution of a new treatment for the lymphoma,
- Death from any cause, without progression.

Event-free survival will be calculated as the duration from the start of R-DHAOx to the date of first event. Patients who have not experienced an event at the time of analysis will be censored at the most recent date of disease assessment.

Time to Progression (PFS):
Progression is defined as either a progression of the lymphoma in non-responding patients or PR patients, a relapse for CR patients, or death from lymphoma.

Progression-free survival is calculated as the time from registration to the date of first progression. The difference between EFS and PFS is that, in PFS, institution of a new treatment and unrelated deaths are not counted as progression. Any unrelated deaths prior to progression will be censored at the date of death.

Disease-free survival (DFS) for CR and CRu patients
DFS will be calculated as the duration from start of the treatment with R-DHAOx to the date of first event. Patients who have not experienced an event at the time of analysis will be censored at the most recent date of disease assessment.

Events are: Relapse after a CR or CRu. Death from a secondary cancer will be considered as an event. Death from unknown cause will be considered as an event. Unrelated death in a CR patient will not be considered as an event and the patient will be censored at the time of death for this analysis. Unrelated death is defined as death from a cause not related to the lymphoma, any examination done for the lymphoma, or any treatment for the lymphoma.

- **Overall survival:**
  Overall survival is measured from the date of initiation of the treatment with R-DHAOx to the date of death, irrespective of the cause. Patients who have not died at the time of analysis will be censored at the most recent date they were known to be alive or at the stopping date if the most recent date is later.

- **Safety:**
  A summary of adverse events will be presented.

### 10.2 Statistical analysis

**10.2.1 Primary endpoint, early stopping rules, and sample size calculation**

The primary endpoint of **Overall Response Rate** (ORR) was used to assess sample size. In our previous study [Machover9], sixty-nine percent of patients with B-cell non-Hodgkin’s lymphoma had a response, and forty-six percent of patients achieved a CR with DHAOx. Therefore, in this study testing for an additional benefit of the adjunction of rituximab to DHAOx for the treatment of patients with relapsed or refractory CD20-positive non-Hodgkin’s lymphoma, a response rate in excess of 70% will be considered of clinical interest, and a response rate of 90% or greater will be considered of strong clinical interest. The Simon design will test the null hypothesis that the true response rate \( \leq 70\% \) versus the alternative that the true response rate is \( > 70\% \). The study will have a significance level of 10% and a 90% power to reject the null hypothesis if the true response rate is 90%. The Simon design in this case calls for 16 patients evaluable for response at the end of the first stage. If there are 11 or fewer responders at the end of the first stage, the study will be terminated and it will be concluded that the treatment is not of clinical interest (the probability of stopping the study at the end of the first stage when the true response rate is 70% or greater is less than 10%). Otherwise, an additional 9 response evaluable patients will be enrolled. The treatment will be considered of clinical
interest (response rate greater than 70%) only if there are 21 or more responders (out of the 25 response evaluable patients) at the end of the second stage.

10.2.2 Secondary endpoints:

The duration of response, event free, progression free and overall survival will be also analyzed. A Kaplan-Meier plot of time to first event will be produced. The genetic molecular response will also be reported.

Categorical variables will be compared using chi-square test or Fisher exact test. Continuous variables will be compared using T-test. Survival data will be compared using the Log-rank test.

Safety analysis:
Adverse events will be described by individual listings and by summary tables broken by body system, intensity and relationship to trial treatment. Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges. Vital signs will be listed.

11 STUDY MONITORING

11.1 Responsibilities of the investigators

The investigator(s) undertake(s) to perform the study in accordance with the protocol, ICH, Good Clinical Practice (GCP) and specifically either good clinical practice for trials on medicinal products in the European Community (ISBN 92 - 825-9563-3) or 21 CFR - Part 312 subpart D and guidelines for the monitoring of clinical investigations.

The investigators are required to ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the protocol. The investigators agree to provide all information in an accurate and legible manner.

11.2 Responsibilities of the sponsor

The sponsor has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the project leader and of his clinical research support team is to help the investigator maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.
At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, by a representative of the monitoring team to review study progress, investigator and subject adherence to protocol requirements and any emergent problems.

During monitoring visits, the following points will be scrutinized with the investigator: subject informed consent, subject recruitment and follow-up, study drug allocation, subject compliance to the study treatment, study treatment accountability, concomitant therapy use, adverse event documentation and reporting, and quality of data. Sections of Case Report Forms may be collected on a visit per visit basis.

### 11.3 Source document requirements

According to the guidelines on Good Clinical Practice, the study monitor has to check the case report form entries against the source documents. The consent form will include a statement by which the subjects allow the sponsor's duly authorized personnel (trial monitoring team) to have direct access to source data which supports data on the case report forms (e.g. patient's medical file, appointment books, original laboratory records, etc…). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

### 11.4 Use and completion of the case report forms (CRF)

It is the responsibility of the investigator to prepare and maintain adequate and accurate CRF which have been designed by the sponsor to record all observations and other pertinent data to the clinical investigation. All CRF should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. CRF will be made on triplicate, one for the investigator, one for central data management and one for the group principal investigator.

A black ball point pen should be used to ensure the clarity of reproduced copy of all CRF.

Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed next to the previous value with the reason for the correction, initialed and dated by the authorized person.

### 12 Ethical and Regulatory Standards

#### 12.1 Ethical principles

This protocol is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983) and the 41st (Hong Kong, 1989) World Medical Assemblies.
12.2 Laws and regulations

This protocol is also in accordance with laws and regulations of the country, in which the trial is performed, as well as any applicable guidelines.

12.3 Informed consent

It is the responsibility of the investigator to obtain informed consent in compliance with national requirements from each subject prior to entering the trial or, where relevant, prior to evaluating the subject's suitability for the study.

The informed consent document used by the investigator for obtaining subject's informed consent must be approved by the Ethics Review Committee (CCPRRB).

The investigator must explain to potential patient the aims, methods, reasonable anticipated benefits and potential hazards of the trial and any discomfort it may entail. Patients will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.

The patient should receive a signed and dated copy of the informed consent form and patient information leaflet. The consent process will be documented in each patient’s medical records.

12.4 Ethics Review Committee (ERC)

The investigator must submit this protocol to an Ethics Review Committee, and he is required to forward a copy of the written approval / advice signed by the chairman to the sponsor.

On the approval / advice sheet, the trial (title, protocol number and version), the documents studied (protocol, informed consent material, advertisement when applicable) and the date of the review should be clearly stated.

13 Administrative Procedures

13.1 Curriculum vitae

An updated copy of the curriculum vitae of each investigator and co-investigator will be provided prior to the beginning of the study.
13.2 Secrecy agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this protocol, the patient case report forms are the exclusive property of MOS.

They may not be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of the MOS.

It is specified that the submission of this protocol and other necessary documentation to the Ethics Review Committee or a like body (IRB, CCPPRB...) is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

13.3 Record retention in investigating centre(s)

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice. However, national regulations should be taken into account, the longest time having to be considered.

For trials performed in the European Community, the investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

13.4 Ownership of data and use of the study results

The MOS (?) has the ownership of all data and results collected during this study. In consequence the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

13.5 Publication

The results of the trial will be published after complete data collection and evaluation. Partial or preliminary results can be published beforehand. Publication is to be initiated by the protocol coordinator.

Any publication in the form of a lecture, poster of publication of data must be basically approved by the coordinator investigator. Such publication should generally not occur before the joint publication of
the study group. Enquiries from the press and general public concerning study results may only be answered by the coordinator investigator.

13.6 Insurance compensation

The sponsor certifies having taken out a liability insurance policy which covers the investigator and his co-workers and which is in accordance with the local laws and requirements. Specific statements will be contained in appendix where is needed.

A certificate of insurance will be provided to the investigator in countries in which this document is required.

13.7 Audits and inspections by regulatory agencies

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines it may be necessary to conduct a site audit or an inspection. The investigator agrees to allow any regulatory agency to have direct access to his study records for review or inspection.

13.8 Clinical study report

A Clinical Study Report will be prepared under the responsibility of the principal investigator.

13.9 Protocol amendments

It is specified that the appendices attached to this protocol and referred to in the main text of this protocol, form an integral part of the protocol.

Any change or amendment to this protocol will be recorded in writing, the written amendment will be signed by the investigator and the signed amendment will be appended to this protocol.

Approval / advice of amendments by Ethics Review Committee or similar body (CCPPRB) is required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.

In some instances, an amendment may require a change to a consent form. The investigator must receive approval / advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.
Prior to initiating the changes, protocol amendment must be submitted to regulatory agencies, where applicable, except under emerging conditions.

14 References


15 APPENDIX

15.1 Appendix 1: Ann Arbor staging

**Stage I:** - I: Involvement of a single lymph node region.
- IE: Localized involvement of a single extralymphatic organ or site.

**Stage II:** - II Involvement of ≥ 2 lymph node regions on the same side of the diaphragm.
- IIE: Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm.

**Stage III:** - III: Involvement of lymph node regions on both sides of the diaphragm.
- IIE: Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site.
- IIIS: Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen.
- IIIS+E: Both IIIS+IIE.

**Stage IV:** - IV: Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non regional) nodal involvement.
- IVE: Extranodal lymphoid malignacies arise in tissues separate from, but near, the major lymphatic aggregates.

15.2 Appendix 2: International Prognostic Index


**Prognostic Factors:**

- **Age**
  - ≤ 60 years *versus* > 60 years

- **Lactate dehydrogenase (LDH) level**
  - Normal serum level *versus* elevated serum level

- **Ann Arbor stage**
  - I-II *versus* III-IV

- **Performance status (PS)**
  - 0-1 *versus* 2-4

- **Extranodal involvement**
  - ≤ 1 site *versus* > 1 site

Each of these features are independent prognostic factors.
15.3 Appendix 3: WHO (ECOG) performance status

15.4 Appendix 4: International Common Toxicity Criteria

In the present study, toxicities will be recorded according to the International Common Toxicity Criteria (CTC), version 2.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html)

Copies of this document are available at the Bureau d'Etudes Cliniques, FSMST, Hôpital Paul-Brousse.

15.5 Appendix 5: Response evaluation. Panel expert committee: International Working Group Response Criteria [from Cheson et al. (15)]

**Response Criteria for Non-Hodgkin's Lymphoma**

<table>
<thead>
<tr>
<th>Response category</th>
<th>Physical examination</th>
<th>Lymph nodes</th>
<th>Lymph nodes; masses</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Cru</td>
<td>Normal</td>
<td>Normal</td>
<td>Indeterminate</td>
<td>Normal or indeterminate</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>&gt; 75 % decrease</td>
<td>Normal or indeterminate</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>≥ 50 % decrease</td>
<td>≥ 50 % decrease</td>
<td>Irrelevant</td>
<td></td>
</tr>
<tr>
<td>Decrease in liver/spleen</td>
<td>≥ 50 % decrease</td>
<td>≥ 50 % decrease</td>
<td>Irrelevant</td>
<td></td>
</tr>
<tr>
<td>Relapse / Progression</td>
<td>Enlarging liver/spleen; new sites</td>
<td>New or increased</td>
<td>New or increased</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>