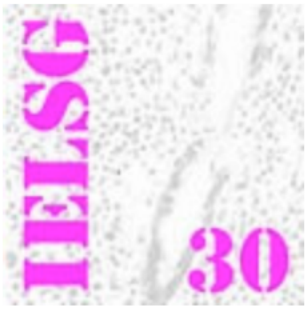

INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

A phase II study of R-CHOP with intensive CNS prophylaxis and scrotal irradiation in patients with primary testicular diffuse large B-cell lymphoma

EudraCT Number 2009-011789-26

INVESTIGATOR SPONSOR

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Protocol version 1.2 May 10, 2010

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A PHASE II STUDY OF R-CHOP WITH INTENSIVE CNS PROPHYLAXIS AND SCROTAL IRRADIATION IN PATIENTS WITH PRIMARY TESTICULAR DIFFUSE LARGE B-CELL LYMPHOMA

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

.....	.....	.....
Investigator (printed name)	Signature	Date

Institution, Address, Phone Number * .....

.....

On behalf of the IELSG: December 2, 2008
Prof. Dr. med. Franco Cavalli

.....	.....	.....
Sponsor representative	Signature	Date

* If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s).

PROTOCOL SYNOPSIS

TITLE: A PHASE II STUDY OF R-CHOP WITH INTENSIVE CNS PROPHYLAXIS AND SCROTAL IRRADIATION IN PATIENTS WITH PRIMARY TESTICULAR DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

AIM

To assess the feasibility, activity and safety of a therapeutic program in which patients with testicular large cell lymphoma receive state-of-the-art chemo-immunotherapy plus both intrathecal (with liposomal cytarabine) and systemic CNS prophylaxis (with intermediate-dose methotrexate), followed by locoregional radiotherapy.

PATIENT POPULATION

- Primary testicular DLBCL
- Ann Arbor stage I-II at presentation (including bilateral testis involvement)
- untreated disease
- bidimensionally measurable, evaluable or no evidence of disease
- age 18-80 years
- ECOG performance status ≤ 2

STUDY DESIGN AND STATISTICAL RATIONALE

Phase II non comparative study aimed to determine the feasibility and toxicity of the R-CHOP regimen in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional radiotherapy. The previous IELSG 5 retrospective analysis on 373 patients with testis lymphoma, showed a PFS of 48% at 5 years in the entire population, regardless of the type of treatment. The IELSG 10 prospective clinical study was designed with a sample size of 50 patients defined to reject the null hypothesis of a PFS of 50% under the alternative hypothesis that the true PFS is 70% with a 5% significance level (two-sided) and 80% power.

The early results of IELSG 10 study seem to suggest that Rituximab-CHOP regimen plus intrathecal prophylaxis with methotrexate may reduce the incidence of CNS relapses and, therefore, improve the outcome. However, the follow up is not yet adequate to allow any sound conclusion and, at present, it is unclear on which estimation of PFS should a sample size be calculated. According to the recruitment rate of the previous IELSG 10, assuming a similar number of participating centers, we may expect to enroll approximately 35 cases in 4 years. At that point, the feasibility of the design should be adequately evaluated and the follow up data from the previous IELSG 10 study should be mature enough for a careful calculation of the sample size in order to transform this pilot study in a formal phase II trial.

TREATMENT PROGRAM

WEEKS 1-15	- 6 cycles of CHOP on days 1 to 5, to be repeated q 21 days - Rituximab on day 0 or day 1 - IT chemotherapy: Depocyte®, 50 mg on day 0 of cycles 2, 3, 4, 5 of CHOP
WEEKS 18-22	- Methotrexate 1.5 g/m2 q 14 days x 2
FROM WEEKS 24	- Scrotal prophylactic radiotherapy or involved field radiotherapy (but can be planned concomitantly to R-CHOP in patients with bilateral disease)

SAFETY PARAMETERS

Clinical laboratory data, physical exams, observations for adverse events

TIME PERIOD AND NUMBER OF PATIENTS

Starting Date of Study	March 2009
Completion Date	March 2013
Trial sample	35 patients will be enrolled over 36 months

1. INTRODUCTION

1.1. Background

1.1.1. Primary testicular lymphoma background

PTL is a rare disease that represents 1% to 2% of all non-Hodgkin's lymphomas, with an estimated incidence of 0.26/100,000 per year. 1 PTLs account for no more than 5% of all testicular malignancies, however they represent the most frequent testicular cancer in men older than 50 years of age. 2 PTL is a typically disease of elderly, 85% of PTLs are diagnosed in men over 60 years of age. 3 Histologically, 90% or more of PTLs are of diffuse large-cell type (DLBCL) with B cell phenotype.

PTL has a propensity to disseminate systematically to several extranodal sites including the contralateral testis, central nervous system (CNS 6% - 16%), skin (0% - 35%), Waldeyer's ring (5%), lung, pleura and soft tissue. Mainly, the portion of patients showing CNS involvement at diagnosis, 2% to 16%, is higher than in nodal lymphomas.3,6,7

Primary testicular lymphomas (PTL) are very aggressive malignancies with poor prognosis. Five year survival ranged from 16% to 50% and median survival has been reported of only 12-24 months according to the different series of patients.2,8,7 The use of anthracycline-based chemotherapy has been associated with a 5-yr survival of 30-60% in different series, nevertheless there is a continuous relapse pattern with no evidence of plateau in the survival curve.9,10,11,12,7 Doxorubicin-containing regimens has allowed an improvement in the relapse-free survival comparing orchiectomy ± radiotherapy, however the advantage on survival time varied a lot among the different series published so far.13,11,7 In the largest series of patients reported so far by the IELSG (373 patents), the outcome of patients was extremely poor with an actuarial 5- and 10-years OS of 48% and 27% and an actuarial 5- and 10-years progression free survival of 48% and 33% respectively. The survival and PFS curves showed no clear evidence of a plateau, suggesting no cure for patients affecting by primary testicular lymphoma, even for those presenting with stage I/II (5 and 10 yrs OS in stage I 58% and 29%, stage II 46% and 29%7, respectively). The majority of patients with PTL relapse despite complete response to initial treatment. When radiation is given to the retroperitoneal lymph nodes, failures are systemic. Very few cases of in-field relapses have been reported. After chemotherapy both systemic and regional relapses are seen. Most relapses occurred in the first two years, but late relapses have also been described.14,7 One of the peculiar feature of PTL is a contralateral testis relapse occurring in 5-35% of the patients.5 In the retrospective series of 373 patients reported by IELSG, the commonest sites of relapse were: CNS (5 and 10-years risk of CNS relapse 20% and 35%) and contralateral testis (15% at 3 years, 40% at 15 years) occurring in patients not receiving prophylactic scrotal radiotherapy.7 Prophylactic irradiation of the contralateral testis has been proved to successfully prevent testicular recurrences in some studies.13,7 In the IELSG study prophylactic radiotherapy to contralateral testis was also associated with better PFS (5-year PFS 36% vs 70%) and OS (5-year OS 38% vs 66%). Moreover, CNS relapses are definitely more common than in other aggressive lymphomas and they have been reported up to 30% of the patients within 1-2 years from diagnosis. However, late relapse have also been described, sometimes as CNS relapse alone.12,11 The high rate of CNS recurrence is troublesome and has led to a recommendation for routine CNS prophylaxis. Although the use of prophylactic intrathecal chemotherapy has been advocated, its value is controversial because CNS relapses occur more frequently in brain parenchyma than in meninges and also in patients who had received intrathecal chemotherapy.6,7 The best strategy to prevent CNS relapse is still a matter of debate.

As well demonstrated in nodal diffuse large B-cell lymphoma (DLBCL) , the addition of Rituximab to CHOP chemotherapy may be useful in PTL as suggested by preliminary data of IELSG10 study recently reported.16 In this study 45 patients with stage I-II PTL were treated with CHOP - Rituximab and CNS prophylaxis with 4 administrations of intrathecal methotrexate and scrotal radiotherapy ± loco-regional radiotherapy for stage II. The preliminary results suggest an improvement in the outcome with a 3-year OS and EFS of 88% and 78%, no contralateral testis relapse and 2.5% actuarial risk of CNS relapse at three years. However the median follow-up is still short and systemic and CNS recurrence rate might increase with a longer follow-up. Perhaps the incorporation of chemotherapy agents that have a better penetration into the CNS, as intermediate/high-

dose methotrexate and/or intrathecal liposomal cytarabine, would allow a more effective control of the disease and may prevent CNS recurrence. A new prospective phase II study has been outlined aimed to further reduce systemic and CNS recurrence and, possibly, better define the standard treatment for PTL. Patients will receive state-of-the-art chemoimmunotherapy plus both intrathecal and systemic CNS prophylaxis.

1.1.2. Liposomal cytarabine (Depocyte) background

Potential risks of depocyte.
The following adverse event occurring in two or more patients receiving DepoCyte in the phase III/IV clinical studies were associated with patient outcomes categorized as serious. The events are listed by descending order of frequency within body system.
Body as a Whole: headache, fever, asthenia, back pain, hydrocephalus, pain, sepsis, neoplasm, injection site reaction, infection, mucous membrane disorder, abdominal pain, chills, accidental injury
Nervous system: seizure, psychosis (hallucinations/delusions), confusion, arachnoiditis, intracranial hypertension, somnolence, meningitis, agitation, neuropathy, hypoesthesia, liquor alterations, dizziness, gait disorders, coma, subdural haematoma, meningism, facial paralysis.
Digestive system: nausea, vomiting, gastrointestinal haemorrhage, intestinal occlusion, diarrhoea, anorexia
Cardiovascular system: cardiac arrest, pulmonary embolus, hypotension, syncope, deep thrombophlebitis.
Hemic and Lymphatic system: neutropenia, thrombopenia, anaemia.
Metabolic and Nutritional Disorder: dehydration, hyperglycaemia, hyponatremia, alkalosis
Respiratory system: pneumonia, apnoea, dyspnoea, bronchitis
Special senses: deafness
Urogenital system: urinary tract infection
Skin and Appendages: sweating

1.1.3. Rituximab background

Potential risks of rituximab.
The most serious adverse reactions with rituximab include: infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias, angina, and renal failure. The incidence of clinically significant abdominal pain, anemia, dyspnea, hypotension and neutropenia was higher in subjects with bulky disease (lesions > 10 cm) vs subjects with lesions < 10 cm. During retreatment with rituximab the incidence of grade 3 and 4 adverse events was similar to the experience of patients receiving the first treatment (58% and 57% respectively).
Mild to moderate infusion reactions consisting of fever and chill/rigors occurred in the majority of patients during the first infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the rituximab infusion and with supportive care.
Rituximab induced B-cell depletion in 70-80%of patients and was associated with decrease serum immunoglobulins in a minority of subjects, infections events occurred in 31% of patients. Grade 3 and 4 infectious events including sepsis occurred in 25 of patients. Grade 3 and 4 cytopenia were reported in 485 of subjects, a single occurrence of transient aplastic anemia and 2 occurrence of hemolytic anemia were reported. In addition, there have been a limited number of postmarketing reports of pancytopenia, marrow hypoplasia and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematological malignancies. Grade 3 and 4 cardiac events including hypotension and rare fatal cardiac failure with symptomatic onset after rituximab administration have been reported. Pulmonary events were experienced by 38% of patients. The most common respiratory adverse events were increased cough, rhinitis, bronchospasm, dyspnea and sinusitis. In addition, immune/autoimmune events have been reported including uveitis, optic neuritis (in a subject with systemic vasculitis), pleuritis in a subject with lupus-like syndrome, serum sickness with with polyarticular arthritis and vasculitis with rash.
Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure and death has been reported in some patients with hematological malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was

approximately 4 months after the beginning of rituximab and approximately 1 month after the last dose. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following rituximab therapy. In patients who develop viral hepatitis, rituximab and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral drugs should be initiated.
Two patients have died after being treated with rituxan for systemic lupus erythematosus (SLE). The cause of death was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated JC virus. Latent JC virus is present in about 80 percent of adults. Rituxan is prescribed off-label for other serious disease and conditions such as SLE. The sponsor estimates that approximately 10,000 patients with SLE have been treated with Rituxan. Reactivation or exacerbation of viral infections including JC virus leading to PML may occur when patients receive Rituxan for any reason. Patients who have been treated with Rituxan and present or develop new neurological signs or symptoms should be evaluated for PML.
Less common adverse events (>1% and <5%) reported from clinical studies included agitation anorexia, hypokinesia, hyperstesia, hypoglicemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo and weight decrease.

1.2. Overall rationale for the study

A previous IELSG large retrospective analysis on 373 patients with testis lymphoma, showed a PFS of 48% at 5 years in the entire population, regardless of the type of treatment. A more recent IELSG prospective study has suggested that systemic doxorubicin regimens with rituximab and intrathecal prophylaxis with short acting methotrexate may improve the outcome but long term results are available only for a few patients and this approach reduces but does not eliminate CNS relapses. The incorporation of chemotherapy agents that have a better penetration into the CNS, as intermediate-dose methotrexate and intrathecal liposomal cytarabine which maintains cytotoxic concentrations of ara-C in the CSF for at least 14 days, would allow a more effective control of the disease and may prevent CNS recurrence.

2. OBJECTIVES

2.1. Primary objective

To demonstrate safety and feasibility of the R-CHOP regimen in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional radiotherapy in untreated patient with stage I and II Primary Testicular Lymphoma

2.2. Secondary objectives

To evaluate the efficacy of the R-CHOP regimen in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional radiotherapy in prolonging 3-year Progression-Free Survival (PFS) and 3-year Event-Free-Survival (EFS) rate compared to historical standard treatment.
To evaluate 3-year overall survival of the patients treated with R-CHOP in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional radiotherapy.

3. OVERVIEW OF STUDY DESIGN

This is an open label, non randomized, phase II, multicenter, prospective trial to evaluate the safety and feasibility of the R-CHOP regimen in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional radiotherapy in patients with stage I and II PTL.

3.1. Statistical plan and rationale

The previous IELSG 5 retrospective analysis on 373 patients with testis lymphoma, showed a PFS of 48% at 5 years in the entire population, regardless of the type of treatment.
The IELSG 10 prospective clinical study was designed with a sample size of 50 patients defined to reject the null hypothesis of a PFS of 50% under the alternative hypothesis that the true PFS is 70% with a 5% significance level (two-sided) and 80% power.
The early results of IELSG 10 study seem to suggest that Rituximab-CHOP regimen plus intrathecal prophylaxis with methotrexate may reduce the incidence of CNS relapses and, therefore, improve the outcome. However, the follow up is not yet adequate to allow any sound conclusion and, at present, it is unclear on which estimation of PFS should a sample size be calculated. According to the recruitment rate of the previous IELSG 10, assuming a similar number of participating centers, we may expect to enroll approximately 35 cases in 3 years. At that point, the feasibility of the design should be adequately evaluated and the follow up data from the previous IELSG 10 study should be mature enough for a careful calculation of the sample size in order to transform this pilot study in a formal phase II trial.

3.2. Study design

The study is divided in 4 phases.

1. Pretreatment (screening) phase of approximately 28 days. Patients will be evaluated, according to the protocol, before to be enrolled in the study by means of the conventional procedures.

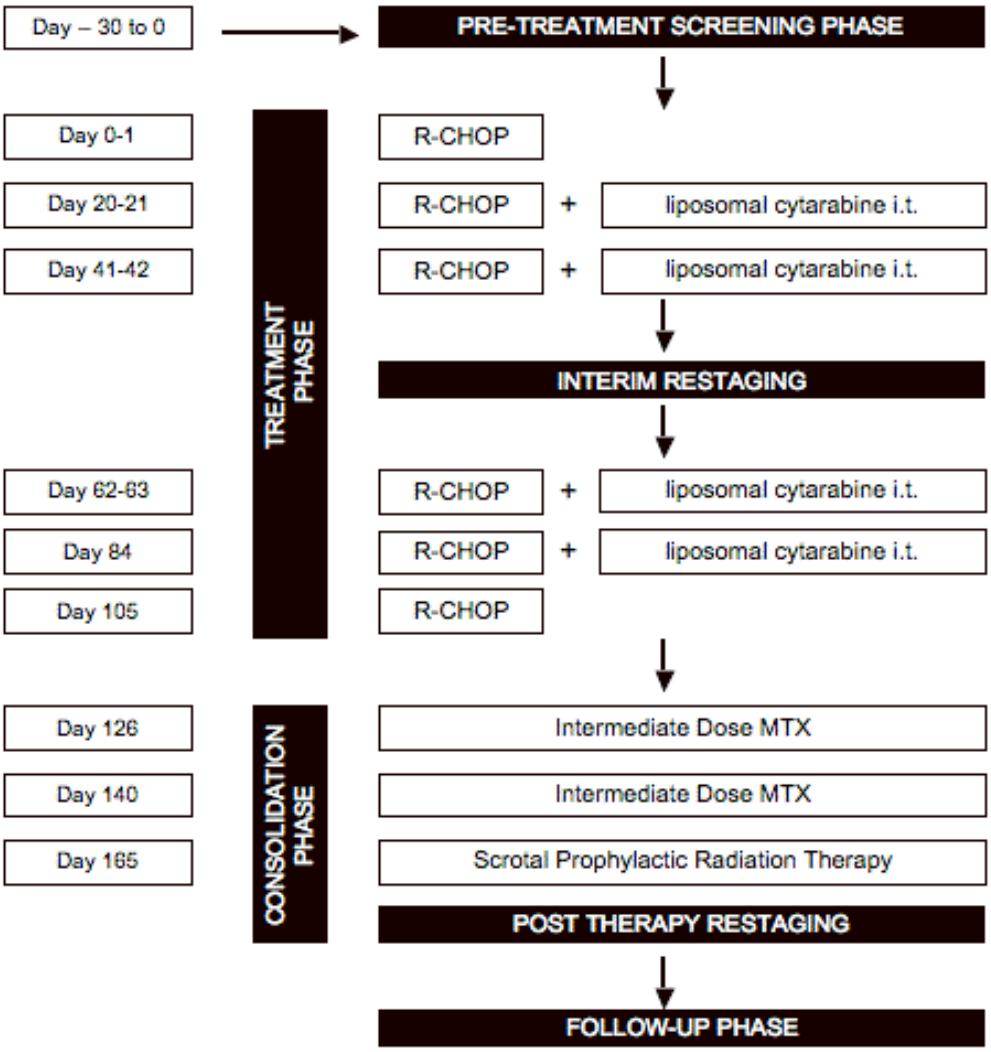
2. Open label non randomized multicenter treatment phase. The investigator will assess patient response to therapy using efficacy measurements and disease response criteria. Patients will be evaluated through this phase for possible toxicities and delays in dosing. Dose modifications will be made as required according to dose modification rules. Patients will be treated with six courses of R-CHOP chemotherapy with a twenty-one day rest period between them. Courses 2,3,4 and 5 will be scheduled with the association of intrathecal chemotherapy with Depocyte®.

Patients with progressive disease at any time will be withdrawn from the study.

3. Consolidation phase. Three weeks after the 6th course of R-CHOP chemotherapy, patients will receive two courses of intermediate-dose Methotrexate therapy every two weeks followed, two weeks later, by scrotal prophylactic radiotherapy or involved field radiotherapy (but can be planned concomitantly to R-CHOP in patients with bilateral disease).

4. Follow-up phase. Patients will be followed for disease progression and survival until the end of the study which is expected to be 36 months after the last patients enrolled into the study completed the treatment. For OS determination information will be required up to 5 years.

The study design is presented in the figure below.



4. STUDY POPULATION

4.1. General considerations

Patients 18-80 years old are eligible for this clinical trial if they have stage I and II Primary Testicular Lymphoma at diagnosis untreated.
Specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

4.2. Inclusion criteria

Patients must satisfy the following criteria to be enrolled in the study.

1. Patients with primary testicular lymphoma at diagnosis. Histological subtype included into the study is only Diffuse Large B Cell Lymphoma (Attachment 2: WHO classification of lymphoma).
2. Orchiectomy is mandatory, before enrolment of the patient into the study.
3. Orchiectomy should be performed within 2 months before study entry.
4. Age 18-80
5. Untreated patients
6. Ann Arbor Stage IE and IIE. Bilateral testicular involvement at presentation will not be considered Stage IV. These patients may be included into the study and the final Ann Arbor stage (I or II) will be determined by the extent of nodal disease.
7. Bidimensionally measurable or evaluable disease. Patients who have had all disease removed by surgery are eligible.
8. Adequate haematological counts: ANC $>$ 1.0 x 109/L and PLTs count $>$ 75 x 109/L
9. Cardiac ejection fraction $\geq$ 45% by MUGA scan or echocardiography
10. Non peripheral neuropathy or any active non-neoplastic CNS disease.
11. No other major life-threatening illnesses that may preclude chemotherapy
12. Conjugated bilirubin $\leq$ 2 x ULN.
13. Alkaline phosphatase and transaminases $\leq$ 2 x ULN.
14. Creatinine clearance $\geq$ 45 ml/min.
15. HIV negativity
16. HBV negativity or patients with HBcAb +, HbsAg -, HBsAb+/- with HBV-DNA negative
17. HCV negativity with the exception of patients with no signs of active chronic hepatitis histologically confirmed
18. Life expectancy $>$ 6 months.
19. Performance status $<$ 2 according to ECOG scale.
20. No psychiatric illness that precludes understanding concepts of the trial or signing informed consent
21. Written informed Consent

4.3. Exclusion criteria

Potential patients who meet any of the following criteria will be excluded from participating in the study.

1. Has known or suspected hypersensitivity or intolerance to rituximab
2. History of clinically relevant liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances
3. Uncontrolled diabetes (if receiving antidiabetic agents, subjects must be on a stable dose for at least 3 months before first dose of study drug)
4. Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure (Attachment 5, NYHA Classification of Cardiac Disease), uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis
5. History of clinically relevant hypotension

6. CNS involvement (meningeal and/or brain involvement by lymphoma)
7. Evolving malignancy within 3 years with the exception of localized non-melanomatous skin cancer
8. HIV positivity
9. HBV positivity with the exception of patients with HBcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative
10. HCV positivity with the exception of patients with no signs of active chronic hepatitis histologically confirmed
11. Active opportunistic infection
12. Receipt of extensive radiation therapy, systemic chemotherapy, or other antineoplastic therapy
13. Exposure to Rituximab prior study entry
14. Have received an experimental drug or used an experimental medical device within 4 weeks before the planned start of treatment. Concurrent participation in non-treatment studies is allowed, if it will not interfere with participation in this study.
15. Any other co-existing medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent

5. REGISTRATION AND STUDY DRUG SUPPLY

Prior to registration the following steps have to be performed:

- check inclusion and exclusion criteria
- obtain informed consent
- complete pre-treatment screening procedures (see study evaluation 9.1.2)
- fill the registration form

Registration is done by faxing the completed Registration Form, dated and signed to the IELSG central office:

IELSG - Oncology Institute of Southern Switzerland - Ospedale San Giovanni - CH-6500 Bellinzona

[redacted]

The office is open from Monday to Friday 08:00 - 17:00 CET

A confirmation of registration (**Confirmed Registration / Drug Order Form**) will be faxed by the IELSG to the investigator, and if needed to the coordination office of any national group / intergroup participating to the study.
The same form, which contains the investigator address, to whom Depocyte® must be sent, is also faxed to Mundipharma International Limited, Cambridge, England.

Mundipharma will then supply the labelled study drug directly to the investigator.

6. DOSAGE AND ADMINISTRATION

6.1. Drug administration

The amount (in mg) of RITUXIMAB and of chemotherapeutic agent (CHOP) to be administered will be determined based on body surface area (BSA) using a standard formula provided in Attachment 8, (Suggested Body Surface Area Calculation).
Instructions including calculation of the subject's dose, preparation and handling of the RITUXIMAB infusion are provided in Attachment 4, (Instructions for the Preparation and Handling of RITUXIMAB Injections).
Instructions including preparation and handling of the DEPOCYTE administration, discarding of used study drug supplies, and precautions and care are provided in Attachment 3, (Instructions for the Preparation and Handling of DEPOCYTE Injections).
Study drug will be administered only to eligible subjects under the supervision of the investigator or identified sub-investigator(s).

6.1.1. Treatment schedule and doses

Treatment phase

R-CHOP		
Rituximab	375 mg/m^2	day 0 or day 1
Cyclophosphamide	750 mg/m^2	day 1
Doxorubicin	50 mg/m^2	day 1
Vincristine	1.4 mg/m^2 (2 mg dose max)	day 1
Prednisone	40 mg/m^2	day 1-5

IT CHEMOTHERAPY		
Depocyte®	50 mg	on day 0 of cycles 2, 3, 4 and 5 of R-CHOP

R-CHOP courses will be repeated every 3 weeks. The prophylactic intrathecal Depocyte will be given for a total of 4 times, during R-CHOP cycles.

Consolidation phase

Begins three weeks after the R-CHOP/IT therapy completion.

INTERMEDIATE-DOSE MTX	
Methotrexate	1.5 g/m^2

It will be administrated diluted in 500 ml of normal saline solution (NaCl 0.9%). A urine flow $\geq$ 125 ml/hr has to be recorded in the 12 hrs before the MTX administration.

For MTX handling and administration see Attachement 5.

Intermediate-dose Methotrexate courses will be repeated every 14 days for 2 cycles.

All patients will undergo interim restaging procedures after the 3rd course (and before the 4th) of R-CHOP. Clinical response will be re-assessed at the end of planned treatment, one-two month after the completion of the whole therapy, including radiotherapy. Additional imaging studies during the treatment phase will be done only if clinically indicated.
Patients with progressive disease at any time will be withdrawn from the study.

6.2. Dose modification and delay

Dose modifications may be made according to any observed toxicity during the previous cycle, as outlined below. Toxicities are to be assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE)
version 3.0, 12/12/2003, National Institute of Health (NIH) http://ctep.cancer.gov/reporting/ctc.html

6.2.1. CHOP dose modification

Patients will start R-CHOP every 21 days if neutrophils > 1.0 x 109/L and platelets > 75 x 109/L.

- If neutrophils are < 1.5 x 109/L and/or platelets < 75 x 109/L: R-CHOP must be delayed (after 7 days, on day +28)
- If Neutrophils ≥ 1.5 x 109/L and Platelets ≥ 75 x 109/L on Day +28 R-CHOP will be performed with no change in dose

In case of neutropenia Filgrastim or Peg-Filgastrim should be added in the following course of chemotherapy according to "2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline"(Journal Clinical Oncology 2006 24:3187-3205), and to primary physician judgment in order to avoid delay. Primary prophylaxis of neutropenia with filgastrim or peg-Figastrim is allowed in patients over 65 years of age according to the same guidelines.

- Dose modification for sensory neuropathy. No modification as long as neuropathy does not affect function. Any decrease of function (grade 3/4) would lead to dose reduction of vincristine by 50%. If grade 4 toxicity persists after reduction of vincristine by 50%, vincristine may be eliminated from subsequent cycles.
- Prednisone dose may be decreased by 50% or discontinued if patients have increase in serum glucose to > 300 mg/dl, or other psychological disturbances such as psychosis or anxiety attacks.

Just patients who have achieved PR/CR after three cycles of CHOP will continue therapy. All other patients will be removed from the study and will be considered for other possible therapies according to the local policy.

6.2.2. Rituximab dose modification

Rituximab administration and dose modification must follow labeling instructions and guidelines. Please refer to the approved product label for instructions.
Patients who develop severe infusion reactions should have rituximab infusion discontinued and supportive care measures as medically indicated (e.g. fluids, vasopressors, oxygen, bronchodilators, acetaminophen, etc.). In most cases, the infusion can be resumed at 50% reduction rate (e.g. from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events, and those with high numbers of circulating malignant cells (>25 x 109/l) with or without evidence of high tumor burden.

7. RADIOTHERAPY PORTS

Scrotal radiation therapy will be given to all patients.

Timing

Radiation therapy will begin three weeks after the completion of chemotherapy, provided that WBC is >3000/µl and platelets >100,000/µl.

Portal and treatment definition

PROPHYLACTIC SCROTAL RT
The clinical target volume (CTV) includes the contralateral testis.

Localization and simulation

Patients must be simulated in the treatment position on a dedicated treatment simulator or CT simulator.

Treatment technique

Patients should be treated in supine position.
Scrotal radiotherapy - CTV should be defined clinically by palpation. The contralateral testis should be treated with the direct anterior beam with electron beam 9 to 12 MeV or 6MV field bolus should be placed for patients who are treated with 6MV linear accelerator. Care should be taken to avoid unnecessary radiation to the perineum or the legs.

Dose definition and schedule

For prophylactic scrotal RT, the following dose fractionations schedules are acceptable:

- 25 Gy in 10-15 fractions
- 30 Gy in 10-20 daily fractions

8. CONCOMITANT THERAPY

During treatment are recommended as concomitant therapy:

- Pre-phase therapy is recommended in older patients (>65 years) with PDN 100 mg/die for 10 days and VCR 1.5 mg total dose
- G-CSF or Peg-Filgrastim as primary prophylaxis for the prevention of febrile neutropenia in older (>65 years) patients in according to 2006 Update of Recommendations for the use of white blood cell growth factors (SmithTJ, Khatcheressian J, Lyman GH, et al. 2006 Update of Recommendation for use of white blood cell growth factors: an evidenced-based clinical practice guideline. J Clin Oncol 2006; 24: 3187-3205)
- Cotrimoxazole BACTRIM 3 tablets/week (or 1 x 2/day for two days/week) or Pentamidine aerosol every 15 days in patients with Bactrim allergy or in patients with G6PD deficiency throughout the treatment and consolidation phase
- In patients with Ab antiHBcAg +, Ab antiHBsAg +/- prophylaxis against hepatitis B reactivation with Lamivudine 100 mg/die from the start of the treatment to one year after the end of the treatment

All concomitant medications for medical conditions other than B-NHL are permitted, as clinically indicated.
All supportive therapies other than anti-cancer treatment needed for the management of patients enrolled in this study are permitted.

8.1. Permitted therapy

The following medications and support therapies that may be used if needed during this study:

- Antiviral prophylaxis with acyclovir 800-1200 mg at day since the beginning of therapy is strongly recommended in patients with herpes virus infection reactivation Additional prophylaxis with levofloxacin or ciprofloxacin will be administered in case of neutropenia <1.0 x 109/l.
- G-CSF or Peg-Filgastrim is allowed and will be given according to primary physician decision in presence of neutropenia < 1.0 x 109/L.
- Platelets and red blood cell transfusion are allowed, if needed with filtered and irradiated products in case of Hb < 8 g/dL or Plts < 10 x 109/L.
- Erythropoietin therapy is allowed according to ASH/ASCO guidelines
- Immunoglobulin assay is advisable once a month during the therapy with immunoglobulin replacement in case of IgG level < 0.3-0.5 gr/dl and frequent infectious events.
- Laxatives and other prebiotics and probiotics are recommended to prevent constipation and should be administered according to standard practice
- Antiemetic agents
- Premedication for rituximab infusion with paracetamol and diphenhydramine is mandatory before each infusion of rituximab, because it may reduce infusion reactions.
- Use of corticosteroids is allowed in emergency or as pre-medication for rituximab infusion

8.2. Prohibited therapy

The following medications and supportive therapies are prohibited at all times:

- Any antineoplastic agent other than those planned by the study program.
- Any experimental agent

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

Patients participation will include:

1. The pretreatment (screening) phase will be 30 days for all laboratory tests and radiographic imaging phase and up to 60 days for orchiectomy and bone marrow evaluation.
2. The open label treatment phase will extend from the first day of the first course of R-CHOP to a maximum of 6 courses.
3. The consolidation phase will extend from the first day of the first course of Intermediate-dose MTX to the end of radiotherapy.
4. The follow-up phase will begin after the completion of the consolidation phase. Follow-up will continue until disease progression (PD), patient withdrawal, death or the study completion (expected to be 36 months from the date of the last patient's end of therapy).

Hematology results must be available and reviewed by the investigator to evaluate for possible hematological toxicity.
All subjects will be monitored for adverse events throughout the study and for 30 days after the end of treatment.

9.1.2. Pretreatment (screening) phase

All patients must satisfy all the inclusion criteria and none of exclusion criteria listed in section 4.2 and 4.3 and sign informed consent before the first dose of study drug can be administered. Results of procedures performed as part of standard medical care before signing the informed consent may be used as part of the screening evaluation if performed within 30 days of beginning of therapy for laboratory tests and imaging studies, within 60 days for orchiectomy and bone marrow biopsy and aspirate.

- Complete medical history
- Concomitant diseases and treatment
- Recent clinical history (B symptoms)
- Physical examination (size of lymph nodes, sign of organ involvement)
- ECOG performance status
- ECG and echocardiogram or blood pool cardioscintigraphy
- Bone marrow biopsy and aspirate
- Orchiectomy
- Chest and abdomen computer tomography; CT of the head and neck at the discretion of the treating physician
- Testicular ultrasound
- CT-PET scan (if possible, recommended but not mandatory)
- Hematology (hemoglobin, WBC and differential, Platelets)
- Blood chemistry (AST, ALT, ALP, total bilirubin, creatinine, albumin, serum LDH)
- Clearance creatinine
- Beta-2-microglobulin
- IgA, IgG, IgM
- HIV
- HBsAg, HBsAb, HBcAb and HBV-DNA, HBV-DNA in case of HBcAb+
- HCVAb, HCV-RNA in case of HCVAb+
- Lumbar puncture for determination of cell count, differential, cytologic and flow cytometry examination in patients with neurologic symptoms and/or clinical suspicion of meningeal lymphoma involvement
- Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.
- Written informed consent.

9.1.3. Treatment phase

Before each course the following parameters will be evaluated:

- Physical examination
- Hematology (Whole blood cell counts and differential)
- Blood chemistry (AST, ALT, ALP, LDH, total bilirubin, creatinine, albumin).
- determination of cell count, differential, cytologic and flow cytometry examination of CNS fluid (during the planned 4 IT therapies)

9.1.4. Intermediate evaluations (after third course of R-CHOP)

- Physical examination (size of lymph nodes, signs of organ involvement)
- ECOG performance status
- Hematology (hemoglobin, WBC and differential, Platelets)
- Blood chemistry (AST, ALT, ALP, total bilirubin, creatinine, albumin, serum LDH)
- Chest and abdomen computer tomography; CT of the head and neck at the discretion of the treating physician
- Testicular ultrasound
- Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.
- Interim CT-PET scan is advisable, if previously positive, according to local policy but it is not mandatory.

All patients with disease in CR, PR will continue the trial.
All patients in SD/PD will be withdrawn from the study and evaluated as treatment failure

9.1.5. Consolidation phase

Before each course the following parameters will be evaluated:

- Physical examination
- Hematology (Whole blood cell counts and differential)
- Blood chemistry (AST, ALT, ALP, LDH, total bilirubin, creatinine, albumin)
- Clearance creatinine

9.1.6. End of treatment restaging

Response to the treatment will be evaluated 1-2 months after the end of the whole treatment and includes the following tests and evaluation:

- Recent clinical history
- Physical examination (size of lymph nodes, sign of organ involvement)
- ECOG performance status
- Chest and abdomen computer tomography; CT of the head and neck at the discretion of the treating physician
- Testicular ultrasound
- CT-PET scan (to be performed three months after radiotherapy) is mandatory according to recent international criteria of response (Cheson et al 2007)
- Hematology (hemoglobin, WBC and differential, Platelets)

- Blood chemistry (AST, ALT, ALP, total bilirubin, creatinine, albumin, serum LDH)
- Clearance creatinine
- Beta-2-microglobulin
- IgA, IgG, IgM
- Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.

9.1.7. Follow-up phase

After the completion of the end of treatment evaluation all patients will enter in the follow up phase.
The follow up phase will end in case of dead or progressive disease.
During the follow-up phase the following parameters will be evaluated:

Minimal evaluations at months 3, 9, 15, 21 and 30

- Physical examination
- Recent clinical history
- ECOG performance status
- Hematology (hemoglobin, WBC and differential, Platelets)
- Blood chemistry (AST, ALT, ALP, creatinine, serum LDH, total bilirubin, albumin)
- Additional assessments if clinically indicated

Extensive evaluations at months 6, 12, 18, 24 and 36

- Recent clinical history
- Physical examination (size of lymph nodes, sign of organ involvement)
- ECOG performance status
- Chest and abdomen computer tomography; CT of the head and neck at the discretion of the treating physician
- Testicular ultrasound
- Hematology (hemoglobin, WBC and differential, Platelets)
- Blood chemistry (AST, ALT, ALP, total bilirubin, creatinine, albumin)
- Clearance creatinine
- Serum LDH
- Beta-2-microglobulin
- IgA, IgG, IgM
- Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician

9.2. Pathology review

The work of the pathologist is essential for the success of this study and includes diagnosis and classification of the lymphoma according to the WHO classification criteria.
The local pathlogist of each center participating in this trial has to be informed by the local investigator about the trial protocol, particularly about data and sample processing. The IESLG Lymphoma Review Center will review all cases.
After examination by the local pathologist, paraffin block shold be sent for central pathology review and additional pathological studies to the lELSG Lymphoma Review Center (LRC) at the IELSG Coordinating Center.
In addition, a copy of original report(s) including diagnosis, classification and immunophenotyping by the local pathologist will be sent by fax or e-mail to the IELSG coordinating center. If possible, diagnostically relevant clinical data (i.e., peripheral blood examination, bone marrow aspiration cytology, immunoelectrophoresis) should be added. In case of doubt the LRC may request paraffin embedded material to complement the analysis.

9.3. Endpoint definitions

Overall Response Rate (ORR): Complete Remission, Complete Remission Unconfirmed, Partial Remission.
A patient is defined as a responder if he has a complete or partial response. Patients without response assessment (due to whatever reason) will be considered as non-responder.

9.3.1. Criteria for evaluation

The recently published recommendations of an International Workshop to Standardise Response Criteria for Non-Hodgkin´s Lymphomas [Cheson et al., 2007 Journal Clinical Oncology 25: 579-586] will be applied.

Response criteria will be determined as follows:

Complete response (CR) is required:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
2. (a) Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan is positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

   (b) Variably FDG-avid lymphomas /FDG avidity unknown: in patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size ($\leq$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 long axis and more than 1.0 cm in their short axis before treatment must have decreased to $\leq$1.0 cm in their short axis after treatment.
3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvements not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of $>$ 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that

demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Remission (PR) is required:

1. At least a 50% decrease in sum of the product of the diameters (SPD)of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g. large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

Stable Disease (SD) is required:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfil those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease[after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR) / Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes ≤1.0x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymphnode with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems(< 1.5 cm in its long axis by CT).
5. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g. pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.
6. In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g. a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Overall survival will be determined from the date of enrollment into the study to the date of death from any cause. Patients who have not died at the time of the final analysis will be censored at the date of the last contact.

Event-free survival (time to treatment failure) is measured from the time from study entry to any treatment failure including disease progression, or discontinuation of treatment for any reason (e.g. disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death). It may be useful in the evaluation of some therapies such as those that are highly toxic.

Progression-free survival PFS is defined as the time from entry onto a study until lymphoma progression or death as a result of any cause. PFS is the preferred end point in lymphoma involving incurable histologic subtypes clinical trials (e.g. follicular, other low-grade lymphoma, or mantle cell lymphoma). In studies in which failure to respond without progression is considered an indication for another therapy, such patients should be censored at that point for the progression analysis.

Disease-Free Survival is measured from the time of occurrence of disease-free state or attainment of a CR to disease recurrence or death as a result of lymphoma or acute toxicity of treatment. This definition may be complicated by deaths that occur during the follow-up period that are unrelated to the lymphoma, and there is controversy about whether such deaths should be considered as events or censored at the time of occurrence. Although it is often possible to identify those deaths related to the lymphoma, there is the potential for bias in the attribution of deaths.

Lymphoma-Specific Survival is defined as time from study entry to death as a result of lymphoma. This end point is potentially subject to bias because the exact cause of death is not always easy to ascertain. To minimize the risk of bias, the event should be recorded as death as a result of lymphoma, or as a result of toxicity from the drug. Death as a result of unknown causes should be attributed to the therapy.

9.4. Safety evaluations

The study will include the following evaluations of safety and tolerability:

Adverse Events
Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study.

Clinical Laboratory Tests
All laboratory tests should be performed at the laboratory of the investigational site: laboratory certificates or accreditation and normal ranges must be submitted before the patient's enrollment.

Electrocardiogram
Vital Signs (pulse, temperature, blood pressure, respiration rate)

Physical Examination
Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Safety and feasibility of treatment: severe hematological toxicities (grade 3-4) expected.
Grading of toxicity will be defined according to the International Common Toxicity Criteria, version 3.0 (12/12/2003)

10. SUBJECT COMPLETION / WITHDRAWAL

10.1. Completion

A subject will be considered as having completed the study if he/she has completed all assessments at week 30 of the [open label] treatment phase.] [Subjects who discontinue study treatment due to lack of efficacy are also considered to have completed the study.]

10.2. Discontinuation of Treatment

A patient should be discontinued from study treatment based on:

- Investigator discretion based on safety issues
- Progressive disease
- No response after the third course of therapy
- Any $\geq$ grade 3 toxicity for $>$ 2 weeks

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost at follow-up
- Consent withdrawal
- Discontinuation of study treatment (final assessments will be obtained) if applicable

When a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

11. ADVERSE EVENT(AE) AND SERIOUS ADVERSE EVENT (SAE) REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and are mandated by regulatory agencies worldwide.

11.1. Definitions

11.1.1. Adverse Events definition and classification

Adverse Event (AE)
An adverse event is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (Definition per International Conference on Harmonization [ICH]).
This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious Adverse Event (SAE)
A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability / incapacity
- Is a congenital anomaly / birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (unexpected) Adverse Event
The nature or severity of the adverse event is not consistent with the applicable product information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Associated with the use of the drug
An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 11.1.2.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
A SUSAR is a serious adverse drug reaction (SADR), the nature or severity of which is not consistent with the applicable product information.
A serious event or drug reaction is not defined as a SUSAR when:

- it is serious but expected
- it does not fit the definition of a SAE o SADR, whether expected or not

11.1.2. Attribution definitions

Intensity (severity) reporting and attribution

For both serious and non-serious adverse events, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Intensity for each adverse event will be determined by using Version 3.0 of the National Cancer Institute Common Toxicity Criteria (NCI CTC) as a guideline, wherever possible. The criteria will be provided to the investigator as a separate document. In those cases where the NCI CTC do not apply, intensity should be defined according to the following criteria:

- mild awareness of sign or symptom, but easily tolerated
- moderate discomfort enough to cause interference with normal daily activities
- severe inability to perform normal daily activities
- life threatening immediate risk of death from the reaction as it occurred
- death

Relationship to study drug administration will be determined as follows

Not related	An adverse event which is not related to the use of the drug.
Unlikely/doubtful	An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
Possible	An adverse event which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probable	An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s).
Definite/very likely	An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

11.2. Procedures

11.2.1. All Adverse Events

All adverse events other than disease progression will be reported from the time a signed and dated informed consent form is obtained until 30 days after the lst dose of study drug. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

All grade 3 and 4 adverse events, considered related, must be followed until resolution of the event, or the event improves to a grade 2 or better. The events of interest in the table above of grade 2 or higher will be followed until grade 1 or better. The unresolved aforementioned events will be followed for a maximum of 6 months.

Sections of the CRFs containing adverse event information will be submitted by the investigator to a representative of the sponsor. Serious adverse event reports will be submitted as described in Section 11.2.2, Serious Adverse Events.

The investigator-Sponsor must report adverse events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. The Investigator-Sponsor assumes responsibility for appropriate reporting of adverse events to regulatory authorities. The Investigator-Sponsor shall also report all serious adverse events to the pharmaceutical companies providing the study medication.

11.2.2. Serious Adverse Events and SUSAR

Reporting of SAE

All serious adverse events occurring during clinical studies must be reported **by fax** to the sponsor IELSG (IELSG Coordinating Center, CH-6500 Bellinzona – Switzerland; Phone: ++41 91 811 90 40 – Fax: ++41 91 811 91 82; E-mail: ielsg@ticino.com) by investigational staff **within 24 hours** of their knowledge of the event, using the **SAE Report Forms**, which must be signed by a member of the investigational staff.

The SAE outcome must be reported within 14 days, using the **SAE Follow up Form**. In case the SAE is still ongoing after 14 days, additional SAE Follow up Forms must be sent again to report the final outcome.

The cause of **death** of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring **hospitalization** (or prolongation of hospitalization) that occurs during the course of a subject's participation in the clinical study must be reported as a serious adverse event, except hospitalizations for:

- a standard procedure for protocol therapy administration
- social reasons in absence of an adverse event
- surgery or procedure planned before entry into the study (must be documented in the CRF)
- study drug administration
- study related procedures defined in the protocol

Reporting of SUSAR

All relevant information about suspected unexpected serious adverse reactions (SUSAR's) are recorded and reported in an expedited fashion.
Events that fall into this category must be reported **within 24 hours** of occurrence **using the SAE Report Form** (see above).
It is the legal requirement of the sponsor to report SUSARs to the Competent Authorities and Ethics Committees (fatal or life-threatening within 7 days, nonfatal and non life-threatening within 15 days)

12. STUDY DRUG INFORMATION

12.1. Physical description of study drug(s)

DepoCyte® (Cytarabine Liposomal Injection) is a sterile sustained –release formulation of cytarabine that is manufactured by encapsulating an aqueous solution of cytarabine (ARA-C) in spherical multivesicular lipid-based particles (DepoFoam drug delivery system).
DepoCyte®injection contains cytarabine (also called cytosine arabinoside, ara-C, 4-amino-1-1-β-D-arabinofuranosynol-2(1H)-pyrimidine ($C_9H_{13}N_3O_5$, molecular weight 243.22).), which is an analogue of the nucleosides cytidine and deoxycytidine, but contains arabinose in place of the usual ribose or deoxyribose. Cytarabine is an odourless white powder that is freely soluble in water and slightly soluble in alcohol.
Cytarabine enters cells by a facilitated diffusion mechanism. Once inside the cell, cytarabine must be metabolised to a nucleotide, ara-CTP, before it can exert its effects.
Ara-CTP inhibits DNA polymerase and terminates DNA chain elongation. The cytotoxic effects are therefore specific to the S-phase of the cell cycle. This means that the cytotoxic effects are a function of concentration and duration of exposure, and prolonged exposure of cells to the drug is vital to achieve maximum activity.
The half-life of free cytarabine in the CSF is only 3.4 hours, so cytotoxic levels are maintained for less than 24 hours. Because the drug is cleared rapidly relative to flow rates within the CSF, it often does not spread well throughout the neuraxis. In contrast, DepoCyte®injection distributes well throughout the neuraxis and increases the half-life of cytarabine in the CSF over 40-fold, as shown in the pharmacokinetic study by Chamberlain et al. The concentration of cytarabine after administration of DepoCyte®injection is maintained for at least 14 days.

DepoCyte® is formulated as a sterile non- pyrogenic white to off- white suspension of cytarabine in sodium chloride 0, 9% w/v in Water for Injection. DepoCyte® is preservative free. Inactive ingredient at the respective approximate concentrations are cholesterol, 4.1 mg/mL; triolein, 1.2 mg/mL; 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 5.7 mg/mL; and 1,2-dipalmitoyl-sn-glycero-3-phospho-rac-(1-glycerol) (DPPG), 1.0 mg/mL. The pH of the product falls within the range from 5.5 to 8.5.
The lipid-encapsulated aqueous chambers form spherical particles of approximately 20 μm in diameter. The particles are suspended in 5 mL of sterile NaCl, 0 9% at a concentration of 10mg/mL and stored ready to use without further dilution. DepoCyte® has the consistency and appearance of skim milk. When stored in sterile normal saline at 2° - 8° C the particles are stable for 12 months. When the particles are injected into the CSF they spread throughout the neuraxis and slowly release the cytarabine. The particles gradually degrade and disappear from the CSF, and the lipids enter the normal lipid metabolic pathways for triglycerides, phospholipids and cholesterol in the body. .As a single injection of 50 mg, DepoCyte® maintains cytotoxic concentration of cytarabine in the CSF for ≥14 days in most patients, thus, IT administration of DepoCyte® is required just once every two weeks

12.2. Packaging

DepoCyte® suspension is provided in a 5 mL ready-to-use single-use glass vials containing 50 mg (10mg/mL) of cytarabine.

12.3. Labeling

The study drug label contains information to meet the applicable regulatory requirements. The label text in English/Italian is provided in Attachment 11.

12.4. Preparation and handling

12.4.1. DepoCyte

For additional information refer to the package insert for liposomal cytarabine (DepoCyte®). See also Attachment 3.

12.4.2. Rituximab

For additional information refer to the package insert for rituximab. See also Attachment 4.

12.5. Drug accountability

After patient's registration, the study drug will directly be supplied to the clinical investigator by Mundipharma (see 5. Registration)
The clinical investigator is responsible for ensuring that all study drug (i.e., Deppocyte®) received at the site is inventoried and accounted for throughout the study. Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area and under locked conditions.

Study drug should be dispensed under the supervision of investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug form, nor store it at any site other than study sites agreed upon the sponsor.

13. ETHICAL ASPECTS

13.1. Regulatory Ethics Compliance

13.1.1. Investigator responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.
GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

13.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator will provide the IEC/IRB with current and complete copies of the following documents:

- final protocol and, if applicable, amendments
- informed consent form (and any other written materials to be provided to the subjects)

- Investigator's Brochure (or equivalent information) and amendments
- information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- information regarding funding, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- any other documents that the IEC/IRB requests to fulfil its obligation

If study drug is being provided, it will not be shipped until after IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the Investigator-sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved.

During the study the investigator will send the following documents to the IEC/IRB for their review and approval, where appropriate:

- protocol amendments
- revision(s) to informed consent form and any other written materials to be provided to subjects
- if applicable, new or revised subject recruiting materials approved by the sponsor
- revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)
- summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC/IRB)
- reports of adverse events that are serious, unlisted, and associated with the investigational drug
- new information that may affect adversely the safety of the subjects or the conduct of the study
- deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- report of deaths of subjects under the investigator's care
- notification if a new investigator is responsible for the study at the site
- any other requirements of the IEC/IRB

For protocol amendments that increase subject risk, the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).
At least once a year, the IEC/IRB will be informed about the clinical ongoing of this clinical study. This request should be documented in writing.
At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

13.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by IELSG and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.
Before entry into the study, the investigator or an authorized member of the investigational staff must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated

benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.
The subject or legally acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry to the study, consent should be appropriately recorded by means of either the subject's or his/her legally acceptable representative's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.
Subjects will also be asked to consent to participate in a genetic research component of the study. Refusal to participate will not result in ineligibility for the rest of the clinical study unless participation in genetic testing is required as an inclusion criterion. After informed consent is appropriately obtained, the subject or his/her legally acceptable representative will sign and personally date a separate DNA informed consent form indicating agreement or refusal to participate in the genetic testing. A copy of this informed consent form will be given to the subject.
If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and personally date and sign the informed consent form after the oral consent of the subject or legally acceptable representative is obtained.

13.4. Privacy of personal data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.
These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The investigator-sponsor ensures that the personal data will be

- processed fairly and lawfully
- collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- adequate, relevant, and not excessive in relation to said purposes
- accurate and, where necessary, kept current

Explicit consent for the processing of personal data will be obtained from the participating subject (or his/her legally acceptable representative) before collection of data. Such consent should also address the transfer of the data to other entities and to other countries.
The subject has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

14. ADMINISTRATIVE REQUIREMENTS

14.1. Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples. CRF completion guidelines will be provided and reviewed with study personnel before the start of the study. The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate
Investigator will permit trial-related monitoring, providing direct access to source documents/data

14.2. Record retention

Once controlled for accuracy and completeness, copy of all CRFs will be kept at the IELSG coordination office, where the contained data will be transferred into an electronic study database.
The results of the study will be reported in a Clinical study Report generated by the investigator-sponsor and will contain all data from all investigational sites.

14.3. On-site audits

Investigator / institution will permit trial-related audits, providing direct access to source documents / data

15. REFERENCES

Duncan PR, Checa F, Gowing NF, McElwain TJ, Peckham MJ. Extranodal non-Hodgkin's lymphoma presenting in the testicle: a clinical and pathologic study of 24 cases. Cancer 1980; 45: 1578-1584.

Zucca E, Roggero E, Bertoni F and Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol. 1997; 8:727-737.

Doll DC, Weiss RB. Malignant lymphoma of the testis. American Journal of Medicine 1986; 81: 515-524.

Ferry JA, Harris NL, Young RH, Coen J, Zietman A, Scully RE. Malignant lymphoma of the testis, epididymis, and spermatic cord. A clinicopathologic study of 69 cases with immunophenotypic analysis. Am J Surg Pathol 1994; 18: 376-390.

Shahab N, Doll DC. Testicular Lymphoma. Semin Oncol, 1999; 26:259-269

Fonseca R, Habermann TM, Colgan JP, et al. Testicular lymphoma is associated with a high incidence of extranodal recurrence. Cancer 2000; 88: 154-161.

Zucca E, Conconi A, Mughal TI, et al: Patterns of outcome nd prognostic factors in primary larg-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. J Clin Oncol 2003; 21:20-27.

Moller MB, D'Amore F, Christensen BE. Testicular lymphoma: A population-based study of incidence, clinico-pathological correlations and prognosis. Eur J Cancer 1994; 30A: 1760-1764.

Crellin AM, Hudson BV, Bennett MH, Harland S, Hudson GV. Non-Hodgkin's lymphoma of the testis. Radiotherapy & Oncology 1993May; 27: 99-106.

Liang R, Chiu E, Loke SL. An analysis of 12 cases of non-Hodgkin's lymphomas involving the testis [letter]. Annals of Oncology 1990Sep; 1: 383-383.

Tondini C, Ferreri AJ, Siracusano L, Valagussa P, Giardini R, Rampinelli I, et al. Diffuse large-cell lymphoma of the testis. J Clin Oncol 1999; 17: 2854-2858.

Touroutoglou N, Dimopoulos MA, Younes A, Hess M, Pugh W, Cox J, et al. Testicular lymphoma: late relapses and poor outcome despite doxorubicin- based therapy. J Clin Oncol 1995; 13: 1361-1367.

Connors JM, Klimo P, Voss N, Fairey RN, Jackson S. Testicular lymphoma: improved outcome with early brief chemotherapy. J Clin Oncol 1988; 6: 776-781.

Ikeda Y, Nakazawa S, Kudo M. Intracranial malignant lymphoma developing 20 years after total removal of testicular malignant lymphoma--case report. Neurol Med Chir (Tokyo) 1986; 26: 68-70.

Zietman AL, Coen JJ, Ferry JA, et al. The management and outcome of stage IAE non Hodgkin's lymphoma of the testis. J Urol 1996; 155: 943-946.

Vitolo U, Zucca E, Martelli M, et al. Primary Diffuse Large B-Cell Lymphoma Of The Testis (PTL): A Prospective Study Of Rituximab (R)-CHOP With CNS And Contralateral Testis Prophylaxis. Results Of The IELSG 10 Study. Blood 2006; 108 (11): 208 (Abs).

P. McLaughlin, F.B. Hagemeister and A. J. Grillo-Lopez " Rituximab in indolent lymphoma: the single agent Pivotal trial " Seminars in Oncology vol 26, n5 suppl 14, 79-87, 1999

Mor V, Laliberte L, Morris JN, et al. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer 1984;53:2002-2007.

Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. Int J Gynecol Cancer 2003;13:7416

The Criteria Committee of the New York Heart Association, Inc.: Diseases of the heart and blood vessels; Nomenclature and criteria for diagnosis, 6th Ed. Boston: Little, Brown; 1964.

Cheson, Pfistner, et al. Revised Response Criteria for Malignant Lymphoma. Journal of Clinical Oncology 2007; 25:579-586

Smith, Khatcheressian et al. 2006 Update of Recommendation for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline 2006 ; 24:3187-3205

ATTACHMENT 1

Performance Status scales

The following table presents the Karnofsky performance status scale.
Which of the following descriptions best describes the subject's level of performance at this time:

Eastern Cooperative Oncology Group (Zubrod-ECOG)[1,2]		KARNOFSKY SCORE	
Description	Grade	Scale	Description
Fully active, able to carry on all pre-disease activities without restriction.	0	100 90	Normal, no complaints, no evidence of disease. Able to carry on normal activity, minor symptoms or signs of disease.
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work, office work)	1	80 70	Normal activity with effort, some signs or symptoms of disease. Cares for self, unable to carry on normal activity or to do active work.
Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	60 50	Requires occasional assistance, but is able to care for most of his needs. Requires considerable assistance and frequent medical care.
Capable of only limited self care, confirmed to bed or chair more than 50% of waking hours.	3	40 30	Disabled, requires special care and assistance. Severely disabled, hospitalization is indicated although death is not imminent.
Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.	4	20 10 0	Hospitalization necessary, very sick, active supportive treatment necessary. Moribund, fatal processes progressing rapidly. Dead

1 Zubrod, C.G., et al. Appraisal of Methods for the Study of Chemotherapy of Cancer in Man. Journal of Chronic Diseases, 11:7-33, 1960.
2 Oken, M.M., et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol (CCT) 5: 649-655, 1982
3 Karnofsky, D.A., Abelmann, W.H., Craver, L.F., and Burchenal, J.H., The use of the nitrogen mustards in the palliative treatment of carcinoma. Cancer (Philad.) 1:634, 1948.
4 Schag, C.C., Heinrich, R.L., Ganz, P.A., Karnofsky Performance Status Revisited : Reliability, Validity, and Guidelines, Clinical Oncology. 2:187-193, 1984.
5 Mor V, Laliberte L, Morris JN, et al. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer 1984;53:2002-2007.

ATTACHMENT 2

WHO classification for lymphoma

Swerdlow SH, Campo E, Harris NL et al (Eds.). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th Ed. IARC Lyon 2008

MYELOPROLIFERATIVE NEOPLASMS

Chronic myelogenous leukaemia, *BCR-ABL1* positive	9875/3
Chronic neutrophilic leukaemia	9963/3
Polycythaemia vera	9950/3
Primary myelofibrosis	9961/3
Essential thrombocythaemia	9962/3
Chronic eosinophilic leukaemia, NOS	9964/3
Mastocytosis	
Cutaneous mastocytosis	9740/1
Systemic mastocytosis	9741/3
Mast cell Leukaemia	9742/3
Mast cell sarcoma	9740/3
Extracutaneous mastocytoma	9740/1
Myeloproliferative neoplasm, unclassifiable	9975/3

MYELOID AND LYMPHOID NEOPOLASMS WITH EOSINOPHILIA AND ABNORMALITIES OF *PDGFRA, PDGRFB OR FGFR1*

Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement	*9965/3*
Myeloid neoplasms with *PDGFRB* rearrangement	*9966/3*
Myeloid and lymphoid neoplasms with *FGFR1* abnormalities	*9967/3*

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

Chronic myelomonocytic leukaemia	9945/3
Atypical chronic myeloid leukaemia, *BCR-ABL1* negative	9876/3
Juvenile myelomonocytic leukaemia	9946/3
Myelodysplastic/Myeloproliferative neoplasm, Unclassifiable	9975/3
Refractory anaemia with ring sideroblasts associated with marked thombocytosis	9982/3

MYELODISPLASTIC SYNDROMES

Refractory cytopenia with unilineage dysplasia	
Refractory anaemia	9980/3
Refractory neutropenia	*9991/3*
Refractory thrombocytopenia	*9992/3*
Refractory anaemia with ring sideroblasts	9982/3
Refractory cytopenia with multilineage dysplasia	9985/3
Refractory anaemia with excess blasts	9983/3
Myelodysplastic syndrome associated with isolated del(5q)	9986/3
Myelodysplastic syndrome, unclassifiable	9989/3
Childhood myelodisplastic syndrome	
Refractory cytopenia of childhood	9985/3

ACUTE MYELOID LEUKAEMIA (AML) AND RELATED PRECURSOR NEOPLASMS

AML with recurrent genetic abnormalities

AML with t(8;21)(q22 ;q22); *RUNX1-RUNX1T1*	9896/3
AML with inv(16)(p13.1q22) or t(16 ;16)(p13.1 ;q22) ; *CBFB-MYH11*	9871/3
Acute promyelocytic leukaemia with t(15 ;17)(q22 ;q12) ; *PML-RARA*	9866/3
AML with t(9 ;11)(p22 ;q23) ; *MLLT3-MLL*	9897/3
AML with t(6 ;9)(p23 ;q34) ; *DEK-NUP214*	*9865/3*
AML with inv(3)(q21q26.2) or t(3 ;3)(q21 ;q26.2) ; *RPN1-EVI1*	*9869/3*
AML (megakaryoblastic) with t(1 ;22)(p13 ;q13) ; *RMB15-MKL1*	*9911/3*
AML with mutated NPM1	9861/3
AML with mutated CEBPA	9861/3
AML with myelodysplasia-rel. changes	9895/3
Therapy-related myeoloid neoplasms	9920/3
Acute myeloid leukaemia, NOS	9861/3
AML with minimal differentiation	9872/3
AML without maturation	9873/3
AML with maturation	9874/3
Acute myelomonocytic leukaemia	9867/3
Acute monoblastic and monocytic leuk.	9891/3
Acute erythroid leukaemia	9840/3
Acute megakaryoblastic leukaemia	9910/3
Acute basophilic leukaemia	9870/3
Acute panmyelosis with myelofibrosis	9931/3
Myeloid sarcoma	9930/3

Myeloid proliferations related to Down syndrome

Transient abnormal myelopoiesis	*9898/1*
Myeloid leukaemia associated with Down syndrome	*9898/3*
Blastic plasmacytoid dendritic cell neoplasm	9727/3

ACUTE LEUKAEMIAS OF AMBIGUOUS LINEAGE

Acute undifferentiated leukaemia	9801/3
Mixed phenotype acute leukaemia with t(9 ;22)(q34 ;q11.2) ; *BCT-ABL1*	*9806/3*
Mixed phenotype acute leukaemia with t(v ;11q23) ; *MLL* rearranged	*9807/3*
Mixed phenotype acute leukaemia, B/myeloid, NOS	*9808/3*
Mixed phenotype acute leukaemia, T/myeloid, NOS	*9809/3*
Natural killer (NK) cell lymphoblastic Leukaemia/lymphoma	

PRECURSOR LYMPHOID NEOPLASMS

B lymphoblastic leukaemia/lymphoma

B lymphoblastic leukaemia/lymphoma, NOS	*9811/3*

B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukaemia/lymphoma with t(9 ;22)(q34 ;q11.2) ; *BCR-ABL1* *9812/3*
B lymphoblastic leukaemia/lymphoma with t(v ;11q23) ; *MLL* rearranged *9813/3*
B lymphoblastic leukaemia/lymphoma with t(12 ;21)(p13 ;q22) ; *TEL-AML1 (ETV6-RUNX1)* *9814/3*
B lymphoblastic leukaemia/lymphoma with hyperdiploidy *9815/3*
B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL) *9816/3*
B lymphoblastic leukaemia/lymphoma with t(5 ;14)(q31 ;q32) ; *IL3-IGH* *9817/3*
B lymphoblastic leukaemia/lymphoma with T(1 ;19)(q23 ;p13.3) ; *E2AA-PBX1 (TCF3-PBX1)* *9818/3*

T lymphoblastic leukaemia/lymphoma *9837/3*

MATURE B-CELL NEOPLASMS

Chronic lymphocytic leukaemia/ Small lymphocytic lymphoma 9823/3
B-cell prolymphocytic leukaemia 9833/3
Splenic B-cell marginal zone lymphoma 9689/3
Hairy cell leukaemia 9940/3
Splenic B-cell lymphoma/leukaemia, unclass 9591/3
Splenic diffuse red pulp small B-cell lym 9591/3
Hairy cell leukaemia-variant 9591/3
Lymphoplasmacytic lymphoma 9671/3
Waldenström macroglobulinemia 9761/3
Heavy chain diseases 9762/3
Alpha heavy chain disease 9762/3
Gamma heavy chain disease 9762/3
Mu heavy chain disease 9762/3
Plasma cell myeloma 9732/3
Solitary plasmacytoma of bone 9731/3
Extraosseous plasmacytoma 9734/3
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) 9699/3
Nodal marginal zone lymphoma 9699/3
Paediatric nodal marginal zone lymph 9699/3
Follicular lymphoma 9690/3
Paediatric follicular lymphoma 9690/3
Primary cutaneous follicle centre lymphoma *9597/3*
Mantle cell lymphoma 9673/3
Diffuse large B-cell lymphoma (DLBCL), NOS 9680/3
T-cell/histiocyte rich large B-cell lymph 9688/3
Primary DLBCL of the CNS 9680/3
Primary cutaneous DLBCL, leg type 9680/3
EBV positive DLBCL of the elderly 9680/3
DLBCL associated with chronic inflammation 9680/3
Lymphomatoid granulomatosis 9766/1
Primary mediastinal (thymic) large B-cell lymphoma 9679/3
Intravascular large B-cell lymphoma 9712/3
ALK positive large B-cell lymphoma 9737/3
Plasmablastic lymphoma 9735/3
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman dis. *9738/3*
Primary effusion lymphoma 9678/3
Burkitt lymphoma 9687/3
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma 9680/3
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell Lymphoma and classical Hodgkin lymph. 9596/3

MATURE T-CELL AND NK-CELL NEOPLASMS

T-cell prolymphocytic leukaemia 9834/3
T-cell large granular lymphocytic leukaemia 9831/3
Chronic lymphoprolifer. disorder of NK-cells 9831/3
Aggressive NK cell leukaemia 9948/3
Systemic EBV positive T-cell lymphoproliferative disease of childhood *9724/3*
Hydroa vacciniforme-like lymphoma *9725/3*
Adult T-cell leukaemia/lymphoma 9827/3
Extranodal NK/T cell lymphoma, nasal type 9719/3
Enteropathy-associated T-cell lymphoma 9717/3
Hepatosplenic T-cell lymphoma 9716/3
Subcutaneous panniculitis-like T-cell lymphoma 9708/3
Mycosis fungoides 9700/3
Sézary syndrome 9701/3
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
Lymphomatoid papulosis 9718/1
Primary cutaneous anaplastic large cell lymphoma 9718/3
Primary cutaneous gamma-delta T-cell lymphoma *9762/3*
Primary cutaneous CD8 positive aggressive Epidermotropic cytotoxic T-cell lymph. 9709/3
Primary cutaneous CD4 positive small/medium T-cell lymphoma 9709/3
Peripheral T-cell lymphoma, NOS 9702/3
Angioimmunoblastic T-cell lymphoma 9705/3
Anaplastic large cell lymphoma, ALK positive 9714/3
Anaplastic large cell lymph., ALK negative 9702/3

HODGKIN LYMPHOMA

Nodular lymphocyte predominant Hodgkin lymphoma 9659/3
Classical Hodgkin lymphoma 9650/3
Nodular sclerosis classical Hodgkin lymphoma 9663/3
Lymphocyte-rich classical Hodgkin lymphoma 9651/3
Mixed cellularity classical Hodgkin lymphoma 9652/3
Lymphocyte-depleted classical Hodgkin lymphoma 9653/3

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

Histiocytic sarcoma	9755/3
Langerhans cell histiocytosis	9751/3
Langerhans cell sarcoma	9756/3
Interdigitating dendritic cell sarcoma	9757/3
Follicular dendritic cell sarcoma	9758/3
Fibroblastic reticular cell tumour	9759/3
Indeterminate dendritic cell tumour	9757/3
Disseminated juvenile xanthogranuloma	

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

Early lesions	
Plasmacytic hyperplasia	9971/1
Infectious mononucleosis-like PTLD	9971/1
Polymorphic PTLD	9971/3
Monomorphic PTLD (B- andT/NK-cell types)*	
Classical Hodgkin lymphoma type PTLD*	

NOS, not otherwise specified.

The italicized numbers are provisional codes for the 4th edition of ICD-O. While they are expected to be incorporated in the next ICD-O edition, they currently remain subject to changes.

The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

* These lesions are classified according to the leukaemia or lymphoma to which they correspond, and are assigned the respective ICD-O code.

ATTACHMENT 3

Instructions for the preparation and handling of DEPOCYTE injections

DepoCyte® should be stored in a refrigerator between 2° to 8°C (DO NOT FREEZE).

The principal investigator has to authorize those personnel having access to and the ability to administer the investigational medicinal product. This will be documented on a so called "authorised personnel form" provided by the monitor. Only qualified personnel who are familiar with procedures which minimize undue exposure to themselves and to the environment shall undertake, in a self-contained protective environment, the preparation, handling and safe disposal of DepoCyte®.

The vial must be at room temperature prior to performing the following procedures. Immediately prior to withdrawing a dose of DepoCyte®, the vial should be gently agitated by rolling the vial between the palms. Avoid excessive agitation (DO NOT SHAKE). No filtering, reconstitution or dilution is required prior to withdrawing drug. DepoCyte®must be used within 4 hours of withdrawal from the single-dose vial. Since DepoCyte®does not contain any preservatives, unused portions of each vial should be properly discarded. Do not mix DepoCyte®with any other medications.

Concurrent steroid administration is important for the prevention of drug-related arachnoiditis.
Therefore the patients should receive dexamethasone 4mg po (or iv) b.i.d. on the day of intrathecal injection.
Steroid medication should be continued for 5 days after Depocyte® injection as standard part of the R-CHOP regimen (i.e., Prednisone 40mg/m^2 d 1-5)

ATTACHMENT 4

Dispensing information for Rituximab

DESCRIPTION
Rituximab is a mouse/human chimeric antibody. The rituximab antibody is produced by a Chinese hamster ovary transfectoma. Rituximab will be provided in l00 mg (l0 mL) and 500 mg (50 mL) pharmaceutical grade vials at a concentration of l0.0 mg of protein per mL (actual concentration should be noted on the product label).

RECOMMENDED PREPARATION AND ADMINISTRATION

1. Refer to the clinical trial protocol for details about the dose and dose schedule.
2. Rituximab should be stored at 2-8°C. Do not freeze or store at room temperature. The product 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 de-naturing of the product proteins.
3. All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood.
4. Prepare the rituximab infusion solution as follows:
   (a) Refrigerate (2-8°C) all materials and solutions prior to use.
   (b) Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks and transfer tubing, etc.
   (c) Transfer of the rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle.
   (d) Transfer the appropriate amount of rituximab from the graduated syringe, into a partially filled IV pack containing sterile pyrogen-free 0.9% sodium chloride solution, USP (saline solution). **The final concentration of rituximab in saline solution should be a maximum of 1 mg/ml**. Mix by inverting the bag gently. DO NOT USE A VACUUM APPARATUS to transfer the product from the syringe to the plastic bag.
   (e) Place an IV administration into the outflow port of the bag containing the infusion solution.
   (f) NOTE: DO NOT USE evacuated glass containers which require vented administration sets because this causes foaming as air bubbles pass through the solution.
5. The administration of rituximab will be accomplished by slow IV infusion.CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.
6. IV pumps such as the IMED 960 may be used with the rituximab infusion. DO NOT INFUSE CONCOMITANTLY with another IV solution or IV medications. Prime the line with the rituximab solution such that approximately 30 mL are delivered
7. Administration of rituximab

Pre-administration of allopurinol (or suitable alternative)
Patients thought to be at risk of tumor lysis syndrome should be well-hydrated and treated with allopurinol (300 mg p.o.) or suitable alternative treatment for 12-24 hours before prior to the first dose of therapy with rituximab.

Caution: Do not administer rituximab as an intravenous push or bolus
Rituximab will be administered intravenously in an out- or in-patient setting. Oral premedication (1000 mg of paracethamole and 50-100 mg diphenhydramine hydrochloride) needs to be administered 30-60 minutes prior to starting each infusion of rituximab. Prednisone/prednisolone as part of the chemotherapy protocol will be administered in the prescribed dose before the infusion of rituximab, preferably as oral medication. A peripheral or central intravenous (iv) line will be established. Before starting the infusion, there should be a

ready supply of epinephrine for subcutaneous injection and diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for the emergency handling of anaphylactic reactions.
The infusion will be started at an initial rate of 50 mg/hour for the first hour. During the rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration and temperature) will be monitored every 15 minutes (4x) for one hour or until stable and then hourly until the infusion is discontinued. If no toxicity is seen during the first hour, the dose rate may be escalated gradually (by increments of 50 mg/hour at 30 minute intervals) to a maximum of 300 mg/hour. If the first dose of rituximab is well-tolerated, the starting flow rate for administration of the second and subsequent infusions will be 100 mg/hour and then increased gradually (by 100 mg/hour increments at 30 minute intervals) not to exceed 400 mg/hour. Patients may experience transient fever and rigors with infusion. If any of the effects below are noted, the antibody infusion should be temporarily discontinued, the patient should be observed, and when the symptoms improve, the infusion should be continued but at half the previous rate.

Dose Rate	Fever	Rigors/chills	Mucosal congestion Edema	Drop in Systolic Blood Pressure
Decrease to 1/2 If any of these Events seen:	> 38.5°C	Mild/Moderate	Mild/Moderate	> 30 mm Hg

Following the infusion the intravenous line should be kept open for medications, as needed. If there are no complications, the intravenous line may be discontinued after one hour of observation.

Dosage: 375 mg/m² body surface

body surface	total dose
1.4 m²	525.0 mg
1.5 m²	562.0 mg
1.6 m²	600.0 mg
1.7 m²	637.5 mg
1.8 m²	675.0 mg
1.9 m²	712.5 mg
2.0 m²	750.0 mg

	1st application		further applications	
Hours	mg/h *)	mg-total	mg/h *)	mg-total
0 – 1	50	50	100	100
1 – 1.5	100	100	150	175
1.5 – 2	150	175	200	275
2 – 2.5	200	275	250	400
2.5 – 3	250	400	300	550
3 – 3.5	300	550	350	725
3.5 – 4	300	700	400	925
4 – 4.5	300	850		

*) With a concentration of 1 mg/ml the values of mg/h are equal to ml/h

Suggested Rituximab Rapid infusion
If no adverse events occurred during first Rituximab infusion,with adeguate premedication, II-III and IV Rituximab infusion will be performed as follows:

rituximab 375 mg/m²	First dose of 100 mg in saline solution 100 ml
	Second dose (to total dose) mg in saline solution 250 ml

time	ml/h
0-60	100
61-180	125

ATTACHMENT 5

Methotrexate schedule (> 500 MG and ≤ 3000 MG)

Day	Date	Time	Treatment	Nurse Signature
0	../../….	16:00 – 24:00	1000 ml Gluc / NaCl 2:1	
		20:00	2 cp Hydrochlorothiazide® 250 mg p.os.	
1	../../….	24:00 – 08:00	100 ml Gluc / NaCl 2:1	
			500 ml NaHCO3 1,4%	
		06:00	2 cp Hydrochlorothiazide® 250 mg p.os.	
		08:00 – 12:00	1000 ml Gluc NaCl 2:1	
		08:00 – 14:00	500 ml NaHCO3 1,4%	
		11:30 – 11:45	20 mg Metroclopramide in 100 ml NaCl 0.9% i.v.	
		Attention! Before Methotrexate infusion: 1. Diuresis has to be al least 1500 ml in the last 12 hrs and 500 ml in the last 4 hrs 2. pH must be 8 in two assessments		
		12:00	2 cp Hydrochlorothiazide® 250 mg p.os.	
		12:00 – 14:00	…. mg Methotrexate in 500 ml NaCl 0,9%	
		14:00 – 22:00	1000 ml Gluc / Nacl 2:1	
		14:00 – 02:00	500 ml NaHCO3 1,4 %	
		…..	…….	
		18:00	2 cp Hydrochlorothiazide® 250 mg p.os.	
		22:00 – 06:00	1000 ml Gluc / NaCl 2:1	
		24:00	2 cp Hydrochlorothiazide® 250 mg p.os.	
2	../../….	02:00 – 14:00	500 ml NaHCO3 1,4%	
		…..	…….	
		06:00	2 cp Hydrochlorothiazide® 250 mg p.os.	
		06:00-14:00	1000 ml Gluc / NaCl 2:1	
		12:00	30 mg Calciumfolinate® i.v. bolus	
			2 cp Hydrochlorothiazide® 250 mg p.os.	
		14:00 – 22:00	1000 ml Gluc NaCl 2:1	
		14:00 – 02:00	500 ml NaHCO3 1,4%	
		…..	……	
		18:00	1 cp 15 mg Calciumfolinate® p.os.	
			2 cp Hydrochlorothiazide® 250 mg p.os.	
		22:00 – 06:00	1000 ml Gluc / NaCl 2:1	
		24:00	1 cp 15 mg Calciumfolinate® p.os. .	
			2 cp Hydrochlorothiazide® 250 mg p.os.	
3	../../….	02:00 – 14:00	500 ml NaHCO3 1,4%	
		06:00	1 cp 15 mg Calciumfolinate® p.os.	
			2 cp Hydrochlorothiazide® 250 mg p.os.	
		06:00 – 14:00	1000 ml Gluc / NaCl 2:1	
			1 cp 15 mg Calciumfolinate® p.os.	
		12:00	2 cp Hydrochlorothiazide® 250 mg p.os. then stop if MTX level is normal.	
		14:00 - …..	**Upon clinical judgement:** **1000 ml Glucose 5%** **(according to MTX levels post-48 hours)**	
		14:00 - …..	**Upon clinical judgement:** **500 ml NaHCO3 1,4%** **(according to MTX levels post-48 hours)**	
		…..	……	
		18:00	1 cp 15 mg Calciumfolinate® p.os.	

Day	Date	Time	Treatment	Nurse Signature
3 (cont.)	../../…. (continued)	24:00	1 cp 15 mg Calciumfolinate® p.os.	
4	../../….	15 mg Calciumfolinate® p.os. must be administered every 6 hours up to 72 hours after MTX infusion start time.		

Hydric balance and wight: D1-3: every 12 hours (06:00 + 18:00)
After MTX infusion urinary pH must be > 8:

- if pH = 8, must be assessed every 6 hours
- if pH < 8, must be assessed each urine sample

Never administer Lasix during urine alkalinisation time.
For 6 hours after MTX diuresis must be > 1000ml. If under this value upon clinical judgement enhance hydric intake or diuresis. 24 hours diuresis must be at least 3000 ml.
MTX levels will be assessed 24 and 48 hours after the MTX start infusion time.

ATTACHMENT 6

Creatinine clearance calculation

Creatinine clearance for men and women will be calculated according to the Cockcroft-Gault formula as follows:

In men: $$\frac{\left[(140 - age) \times weight(kg)\right]}{\left[72 \times creatinine(mg/dL)\right]}$$

In women: $$\frac{\left[(140 - age) \times weight(kg)\right]}{\left[72 \times creatinine(mg/dL)\right]} \times 0.85$$

Note:
Age (in years), weight (in kg), serum-creatinine (in mg/dL)
72 (normalized to 72 kg body weight and a body surface of 1.72 m2)

ATTACHMENT 7

New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
II	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association, Inc.: Diseases of the heart and blood vessels; Nomenclature and criteria for diagnosis, 6th Ed. Boston: Little, Brown; 1964

ATTACHMENT 8

Suggested Body Surface Area Calculation

BSA should be determined using the Mosteller formula as follows:

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

OR

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Source: NEJM 1987; 317: 1098

ATTACHMENT 9

Timing of treatment and investigations

	PRE-TREATMENT PHASE	TREATMENT PHASE							CONSOLIDATION PHASE					FOLLOW UP PHASE	
		I	II	III	INTERIM RESTAGING	IV	V	VI					POST THERAPY RESTAGING	MINIMAL EVALUATION	EXTENSIVE EVALUATION
DAY	-28	0	21	42		63	84	105	126	140	150	165			
COURSES		1	2	3		4	5	6							
CHOP		X	X	X		X	X	X							
RITUXIMAB		X	X	X		X	X	X							
IT CHEMOTHERAPY			X	X		X	X								
METHOTREXATE									X	X					
RADIOTHERAPY												X			
History, physical examination	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Orchiectomy (1)	X														
Testicular ultrasound	X				X								X		X
CT chest, abdomen	X				X								X		X
CT-PET (2)	X												X		
Blood counts + differential	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Bone marrow aspirate+biopsy (3)	X														
Lumbar puncture (4)	X														
ß2-microglobulin IgA, IgG, IgM	X												X		X
HIV, HBV, HCV (5)	X														
Biochemistry (6)	X								X	X	X		X		X
Biochemistry (7)		X	X	X	X	X	X	X						X	
MUGA or cardiac echo	X														

(1) Orchiectomy should be performed witin 2 months before study entry
(2) CT-PET mandatory only at final evaluation
(3) Bone marrow mandatory at baseline. Will be repeated only if clinically indicated
(4) Lumbar Puncture for determination of cell count, differential, cytologic and cytoflussimetry examination of CNS liquor
(5) Patients HCV+ with no signs of active chronic hepatitis histologically confirmed: HCV-RNA once a month; Patients HBcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative: HbsAg once a month
(6) Biochemistry including serum Creatinine, clearance Creatinine AST, ALT, ALP, total Bilirubin, albumin, LDH
(7) Biochemistry comprises: AST, ALT, ALP, LDH, Creatinine, total bilirubin, albumin