Clinical Protocol

A multicenter, phase III, randomized study to evaluate the efficacy of a response-adapted strategy to define maintenance after standard chemoimmunotherapy in patients with advanced-stage Follicular Lymphoma

Study ID: FIL_FOLL12
VERSION DATE: VERSION 1.0 - 02 JULY 2012
EUDRACT NUMBER 2012-003170-60

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Version 1.0- 02 July 2012
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3.0 INVESTIGATOR AGREEMENT

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’s Signature Date

______________________________________________
Name of Investigator (Typed or Printed)

______________________________________________
Institution, Address*

______________________________________________
Phone Number*

______________________________________________
Investigator-Sponsor Signature* Date
(where required)

______________________________________________
Name of Coordinating Investigator (Typed or Printed)

______________________________________________
Institution

* 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).
# 4.0 PROTOCOL SYNOPSIS

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>A multicenter, phase III, randomized study to evaluate the efficacy of a response-adapted strategy to define maintenance after standard chemoimmunotherapy in patients with advanced-stage Follicular Lymphoma.</th>
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<tbody>
<tr>
<td><strong>Eudract number</strong></td>
<td>2012-003170-60</td>
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<tr>
<td><strong>Phase</strong></td>
<td>III</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Previously untreated intermediate-high risk according to the FLIPI2 stage II-IV follicular lymphoma requiring therapeutic intervention.</td>
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<tr>
<td><strong>Primary objective</strong></td>
<td>To evaluate whether a FDG-PET and MRD response-based maintenance therapy is more effective in terms of Progression-Free Survival (PFS) than a standard maintenance therapy with Rituximab in patients with untreated, advanced, follicular lymphoma.</td>
</tr>
<tr>
<td><strong>Secondary objectives</strong></td>
<td>To evaluate the efficacy of maintenance with observation or pre-emptive Rituximab therapy administered on the basis of MRD status and the efficacy of a standard maintenance for 2 years in patients at low risk of progression after induction chemoimmunotherapy.</td>
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<tr>
<td></td>
<td>To evaluate the efficacy of intensified maintenance with (90)Y Ibritumomab Tiuxetan followed by Rituximab maintenance therapy and the efficacy of a standard maintenance for 2 years in patients at high risk of progression after induction chemoimmunotherapy.</td>
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<td>To compare a response-based maintenance therapy with a standard maintenance therapy in terms of toxicity.</td>
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<td>To verify the predictive value of MRD detection (assessed by both nested PCR and real time PCR conducted according to Euro-MRD guidelines and FIL-MRD network SOPs) in the two study arms, in both bone marrow (BM) and peripheral blood (PB) and to assess whether delivery of pre-emptive Rituximab therapy is able to induce molecular remission and prevent clinical relapse.</td>
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<tr>
<td></td>
<td>To perform a cross evaluation of the predictive value of MRD analysis and FDG-PET.</td>
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<tr>
<td><strong>Study design</strong></td>
<td>This is a multicenter, randomized, phase III, superiority study comparing standard vs response driven approach to maintenance. Adult patients (age ≥ 18 years) with naïve, untreated follicular lymphoma, stage II-IV, FLIPI2&gt;0 requiring a therapeutic</td>
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</table>
intervention will be recruited and randomly assigned in a 1:1 ratio to either standard or experimental arm. All patients will receive the same induction therapy with 6 cycles of R-CHOP and 2 additional doses of Rituximab. At baseline patients will be assessed for molecular status and staged by means of CT scan. A baseline FDG-PET scan should also be performed.

At the end of chemoimmunotherapy all patients will be assessed for disease response by common clinical and laboratory examination, CT scan and FDG-PET. An intermediate assessment of response with CT scan and FDG-PET will also be performed after the first four courses of R-CHOP.

At the end of induction therapy the status of minimal residual disease will be also evaluated. After induction treatment all responding patients in the standard arm will receive standard maintenance therapy with Rituximab (every 2 months for 2 years), while patients in the experimental arm will be subdivided into two risk groups and assigned to different post induction treatments based on FDG-PET and MRD results.

In both arms, patients with stable or progressive disease (PET positive and less than PR on CT scan) will be addressed to salvage treatment chosen at physician discretion.

In the experimental arm, risk group allocation will be performed primarily on the basis of FDG-PET results:
- Group 1 (low risk): negative FDG-PET
- Group 2 (high risk): positive FDG-PET

Patients at low risk (FDG-PET negative) will receive maintenance therapy according to their MRD status, particularly:
- Group 1a (MRD negative): observation
- Group 1b (MRD positive): pre-emptive Rituximab therapy

Patients at high risk (FDG-PET positive) will receive maintenance regardless of their MRD status:
- Group 2: intensified maintenance ((90)Y Ibritumomab Tiuxetan + Rituximab maintenance)

Sample size
602 patients will be enrolled in order to have 546 evaluable patients considering an approximate 10% drop out rate.

Estimated study duration
Four years for the accrual phase and 3 years from the accrual of the last patient for the follow-up phase.

Subject inclusion criteria
- Histological diagnosis of B-Cell CD20+ Follicular Lymphoma (FL), grade I, II, IIIa according to the
WHO 2008 classification
- ECOG performance status 0-2
- Age ≥ 18 years
- Ann Arbor stage II-IV
- FLIPI2>0
- Presence of evaluable/measurable disease after diagnostic biopsy
- At least one of the following criteria for defining active disease:
  - systemic symptoms
  - cytopenia due to bone marrow involvement
  - LDH > upper normal value
  - any nodal or extranodal tumor mass with a diameter >7cm
  - involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3cm
  - extranodal disease
  - rapidly progressive disease
- Life expectancy > 6 months
- Left ventricular ejection fraction (LVEF) ≥ 50%
- Serum negativity for HIV
- Serum negativity for HBsAg; HBcAb positive but HBV-DNA negative patients are allowed with mandatory Lamivudine prophylaxis.
- Serum negativity for HCV, except for those patients without signs of active viral replication assessed by HCV-RNA copies
- Serum creatinine < 2mg/dl, serum bilirubin < 1.5mg/dl, aspartate amino-transferase (AST/GOT) ≤ 2.5xUNV, alanine amino-transferase (ALT/GPT) ≤ 2.5xUNV, and alkaline phosphatase ≤ 4 times the upper limit of normal (unless the increase is attributed directly to the presence of tumour by the Investigator)
- Patients with no previous treatment for the lymphoma with the exception of locoregional radiotherapy (IF-RT)
- Adequate measure adoption to avoid pregnancy
- Written informed consent given at time of registration
- Patient must be accessible for treatment and follow up

**Subject exclusion criteria**
- Histological diagnosis of:
  - any lymphoma other than follicular lymphoma and all CD20 negative B-cell lymphomas
  - grade III b follicular lymphoma
  - evidence of transformation to high grade lymphoma
- Ann Arbor stage I
- Suspect or clinical evidence of CNS involvement by lymphoma
- History of other malignancies within 5 years prior to
study entry except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer, low grade, early stage localized prostate cancer treated surgically with curative intent, good prognosis DCIS of the breast treated with lumpectomy alone with curative intent
• Evidence of any severe active acute or chronic infection
• Concurrent co-morbid medical condition which might exclude administration of full dose chemotherapy
• Severe chronic obstructive pulmonary disease with hypoxemia
• Severe diabetes mellitus difficult to control with adequate insulin therapy
• Myocardial infarction within 6 months before study entry
• Clinically significant secondary cardiovascular disease e.g. uncontrolled hypertension, (resting diastolic blood pressure >115 mmHg), uncontrolled multifocal cardiac arrhythmias, symptomatic angina pectoris or congestive cardiac failure NYHA class III-IV
• HbsAg-positive, HIV-positive, or HCVAb-positive patients
• Known hypersensitivity or anaphylactic reactions to murine antibodies or proteins
• Any other co-existing medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent
• Follicular lymphoma, showing a negative baseline PET scan

**Induction treatment**
As induction therapy all patients will receive 6 courses of:
- Rituximab: 375 mg/m² day 1 iv
- Cyclophosphamide: 750 mg/m² day 1 iv
- Doxorubicin: 50 mg/m² day 1 iv
- Vincristine: 1.4 mg/m² day 1 iv (max dose 2mg)
- Prednisone: 100 mg day 1-5 os

To allow administration of all drugs on the same day, Rituximab rapid infusion is permitted starting from cycle 2. Cycles are to be repeated every 21 days.

After the sixth R-CHOP course patients will receive 2 additional doses of Rituximab (375 mg/m²) with a 21-days interval.

**Maintenance**
*Standard arm*
Patients in the standard arm will receive Rituximab
Maintenance will have to be started no more than 12 weeks after the last induction chemoimmunotherapy infusion.

**Experimental arm – FDG-PET negative patients (Low risk, group 1)**

Patients in the experimental arm with a negative end-therapy FDG-PET and MRD negative (group 1a) will not receive maintenance therapy and will be followed-up with MRD monitoring. Only patients changing from MRD negative to positive and without radiological progression will receive a therapy with four weekly doses of Rituximab (375 mg/m²). If this will turn MRD back to negative, patients will continue with observation and regular follow-up. Rituximab could be repeated for MRD positive for a maximum of three courses (12 total doses).

Patients with a negative end-therapy FDG-PET and MRD positive (group 1b) will receive four weekly doses of Rituximab (375 mg/m²). If this will turn MRD back to negative, patients will continue with observation and regular follow-up. Rituximab could be repeated for MRD positive for a maximum of three courses (12 total doses). Patients still MRD positive after 12 doses will continue follow-up until progression.

**Experimental arm – FDG-PET positive patients (High risk, group 2)**

Patients in the experimental arm with a positive FDG-PET will receive a single dose of (90)Y Ibritumomab Tiuxetan (0.4 mCi/kg). Radioimmunotherapy should start no later than 12 weeks after the last induction chemoimmunotherapy infusion. Following RIT patients will continue maintenance with Rituximab (375 mg/m² every 2 months) for a total of 11 infusions. The first R maintenance infusion will be administered two months after day 1 of RIT.

If required, before (90)Y Ibritumomab Tiuxetan administration peripheral blood stem cells will be collected. For the harvest, only growth factors-based mobilizing protocols will be accepted.

After induction immunochemotherapy all patients will be monitored with CT scan and MRD analysis at the following timepoints or until disease progression: month +6,+12,+18,+24,+30,+36.

FDG-PET scan is not indicated for patient follow-up.

<table>
<thead>
<tr>
<th>Procedures required at different timepoints</th>
<th>General assessments:</th>
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<tbody>
<tr>
<td></td>
<td>• Demographics (date of birth, gender, height, weight,</td>
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Version 1.0- 02 July 2012
<table>
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<tr>
<th>Criteria for evaluation</th>
<th>Efficacy</th>
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<td><strong>Efficacy</strong> Primary endpoint: Progression free survival (PFS) defined as the time from entry onto the study until lymphoma progression or death as a result of any cause. Secondary endpoints: overall survival (OS), overall response rate (ORR), duration of remission (DR) and event free survival (EFS). Molecular response evaluated by PCR assessment of Bcl2/IgH rearrangement.</td>
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<tr>
<th>Laboratory</th>
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<td></td>
<td><strong>Laboratory</strong> • Complete blood count • Complete biochemistry: ESR, Na, K, SGOT, SGPT, GGT, AP, bilirubin, creatinine, serum glucose, BUN/urea, uric acid, total serum protein with serum protein electrophoresis, serum albumin • LDH, Beta2 microglobulin • Urine analysis • Serology for HIV, B and C Hepatitis • Serum policlonal IgG, IgM, IgA</td>
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<tr>
<th>Tumour assessment</th>
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<td><strong>Tumour assessment</strong> • Total body CT-scan with iodine contrast • FDG-PET/CT • Bone marrow biopsy with immunohistochemistry • Bone marrow aspirate with PCR assessment of translocation (14;18) • Adequate diagnostic surgical biopsy of lymph node or any available tissue sample • Biopsy of suspicious extranodal sites, if clinically indicated • Peripheral blood immunophenotyping in case of suspicious leukemic dissemination</td>
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<th>Cardiac function</th>
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<td></td>
<td><strong>Cardiac function</strong> • ECG • LVEF by either bi-dimensional echocardiogram or cardiac scintigraphy (MUGA)</td>
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- Relevant clinical history (general and disease-specific, including concurrent illnesses and therapies at the time of study entry)
- Complete physical examination (including peripheral lymph nodes, Waldeyer ring, size of liver and spleen)
- Orientating physical examination (changes compared to previous examination)
- ECOG status

- Orientating physical examination (changes compared to previous examination)

- Laboratory

- Tumour assessment

- Cardiac function

- Criteria for evaluation

- Efficacy

- Primary endpoint: Progression free survival (PFS) defined as the time from entry onto the study until lymphoma progression or death as a result of any cause.

- Secondary endpoints: overall survival (OS), overall response rate (ORR), duration of remission (DR) and event free survival (EFS). Molecular response evaluated by PCR assessment of Bcl2/IgH rearrangement.
<table>
<thead>
<tr>
<th><strong>Safety</strong></th>
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<tr>
<td>Acute events during chemoimmunotherapy and maintenance according to CTCAE (Version 4.03).</td>
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<tr>
<td>Long term toxicity:</td>
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<tr>
<td>- Secondary malignancies</td>
</tr>
<tr>
<td>- Cardiovascular events</td>
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<tr>
<td>- Pulmonary events</td>
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</table>
5.0 Trial design

**Randomization**
- Standard arm
  - 4x R-CHOP
  - 2x R-CHOP + 2R
- Experimental arm
  - PET
  - MRD

**Salvage**
- <PR

**R Maintenance**
- CR, PR
- <PR

**Patients with no molecular markers**
- Observation
  - PET-
  - MRD
  - Pos
    - Observation
    - Rituximab weekly x 4
  - Neg
    - PET+
      - (90)Y Ibritumomab Tiuxetan + R Maintenance
        - every 2 months x 2yrs

**Final Outcome**
- <PR
  - Salvage
6.0 BACKGROUND

6.1 Disease Background
Follicular lymphoma (FL) is one of the most common subtypes of lymphoma in Western countries and accounts for 10-20% of all newly diagnosed non-Hodgkin’s lymphomas[1]. The median age at presentation ranges from 55 to 60 years, and the incidence increases with age. Despite enhancement in treatment for this disease, leading to substantial improvements in survival, FL is still an incurable, neoplasm [2, 3]. Clinical course of FL is typically indolent with impressive responses to initial treatments but with frequent relapses, with the need for recurrent therapeutic interventions [4, 5]. Responses to salvage treatment is of shorter duration after every relapse, and most patients ultimately die of their disease or of treatment-related toxicity, with a median survival of 6-10 years [6, 7].

Histologically, FL is composed by a population of centrocytes and centroblasts with nodular or diffuse growth. In the World Health Organization classification the histology of Follicular lymphoma is further classified into Grade 1, 2 or 3 depending on the percentage of large cells seen on high power field microscopy [8]. Grade 3 FL is further subdivided into 3a and 3b, where 3b may represent a distinct biological entity more similar to diffuse large B-cell lymphoma. Biologically, the neoplastic clone of the great majority (up to 80%) of FL patients bears the t(14;18) translocation in which the bcl-2 proto-oncogene on chromosome 18 is translocated to the immunoglobulin heavy chain (IgH) region on chromosome 14, thus creating a hybrid bcl-2/IgH gene[9]. The translocation causes an over expression of the bcl-2 protein, which inhibits apoptosis of lymphoid cancer cells[10]. The research of the hybrid bcl-2/IgH gene generated by the translocation could be used for confirming the diagnosis of FL, but for evaluating the quality of response to treatment as well.

6.2 Current therapies for Follicular Non-Hodgkin’s Lymphoma
Treatment options for treatment-naive or recurring follicular lymphoma patients are still controversial, ranging from “watch and wait” to hematopoietic stem-cell transplantation. However, none of these treatments has demonstrated the potential to eradicate the disease. When a treatment is indicated, chemotherapy is usually prescribed either as single or multi-agent regimen. For many years, alkilators have represented the backbone of chemotherapy for FL with promising but discordant results for anthracyclines and purine analogues. In most recent years, the advent of anti
CD20 monoclonal antibody Rituximab (R) has dramatically changed the approach to this disease, and R with chemotherapy is at present considered the standard of care for patients diagnosed with FL.

Currently, the open question is what is the best chemotherapy regimen to combine with R. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) is by far the most used combination [11]. However CVP (cyclophosphamide, vincristine, prednisone), and fludarabine-containing regimens are widely adopted. Recently, the Fondazione Italiana Linfomi (FIL) concluded the FOLL05 trial, comparing R-CVP, R-CHOP and R-FM for the initial treatment of stage II-/IV FL patients. The study enrolled more than 500 patients. The preliminary results were presented at the 11th International Conference on Malignant Lymphoma in Lugano and at the 2012 American Society of Clinical Oncology Annual meeting [12, 13]. The analysis showed that R-CVP was associated with an inferior 3-year TTF (46%) compared with R-FM (61%) and R-CHOP (64%). Moreover, OS was similar among study arms but R-FM showed a higher rate of acute and long term toxicity. Based on these results, R-CHOP may now be considered as the standard regimen for the treatment of patients with advanced FL.

6.3 Maintenance after induction therapy
The use of maintenance strategies after the first treatment in FL has been considered over a long time. The use of interferon was first evaluated, showing benefits in terms of duration of remission and survival; however the safety profile of the drug and the low manageability of treatment has led most physicians to abandon this treatment option [14]. The availability of R as an effective and low toxic single agent has suggested to explore the possibility to use it not only to improve efficacy of chemotherapy in first line therapy, but also to delay progression after initial treatment.

So far, in FL patients maintenance with R has been mostly considered after relapse, or in case of refractoriness to treatment. Recently, the results of the PRIMA trial have been published providing data on the use of maintenance after first line therapy [11]. The study included 1217 patients with previously untreated follicular lymphoma requiring systemic therapy. Patients received initial therapy on a non-randomized basis, by choosing among one of three chemoimmunotherapy induction regimens used in routine practice: R-CHOP, R-CVP and R-FCM (4%), that were adopted in 74%, 22% and 4% respectively. After induction therapy 1019 patients achieving a complete or partial response were randomly assigned to receive 2 years of R maintenance therapy (375 mg/m² every 8 weeks) or observation. The primary endpoint was progression-free survival (PFS). With a median follow-up of 36 months, PFS was 74.9% in the R maintenance group and 57.6% in the
observation group (218 progressed; hazard ratio [HR] 0.55, 95% CI 0.44–0.68, p<0.0001). Overall survival did not differ significantly between groups (HR 0.87, 95% CI 0.51-1.47)[11].

Recently, results of a meta-analysis performed on a series of electronic databases updated through December 31, 2010, and including nine trials and 2586 FL patients were published [15]. Patients with refractory or relapsed (i.e., previously treated) FL receiving rituximab maintenance showed both an improved overall and progression free survival if compared with those who were not administered maintenance (pooled HR of death = 0.72, 95% CI = 0.57-0.91). Moreover, from the same meta-analysis emerged that previously untreated patients did not benefit in terms of overall survival from rituximab maintenance (pooled HR of death = 0.86, 95% CI = 0.60 to 1.25)[15].

6.4 Minimal residual disease (MRD)

Notwithstanding the addition of the immunotherapy to the conventional therapies in the recent years, follicular lymphomas still relapse. Different observed rates of response and outcome are of course related to the new more effective regimens combining immuno- and chemotherapy, but they could be related as well to the persistence or not at the molecular level of a minimal residual disease (MRD) after treatment.

The study of MRD in FL is based on the use of t(14;18) chromosomal translocation as a very sensitive and predictive marker to assess quality of molecular response in different treatment phases. Currently available PCR techniques reach a sensitivity of $10^{-5}$ and allow to detect presence of minimal quantities of the hybrid bcl-2/IgH gene. The results of several clinical trials indicate that, regardless to the treatment administered, the absence in the bone marrow and peripheral blood of neoplastic cells bearing the bcl-2/IgH rearrangement during the follow-up is strongly associated with a reduced risk of recurrence, while on the other side the positivization of molecular markers during follow-up may anticipate clinical progression, clearly suggesting a need to improve the management of MRD [16-19].

Several studies have confirmed the major predictive value of MRD detection in FL[20, 21]. When multivariate analysis was employed, the lack of MRD emerged as an independent outcome predictor in most studies[22].

6.5 FDG-PET in Follicular Lymphoma

[18F]fluorodeoxyglucose - Positron Emission Tomography (FDG-PET) has recently emerged as a useful functional imaging tool to study lymphoma and its use in staging and restaging patients with Hodgkin lymphoma and with Diffuse Large B-Cell Lymphoma is well established[23, 24].
Despite FL is accounted among FDG-avid lymphoma, few studies have been performed to investigate how FDG-PET can be used in patients with such indolent lymphoma. The accuracy of PET/CT for assessment of response was higher than that of CT, especially due to its ability to identify inactive residual masses [25]. PET negativity can be achieved in high proportion of cases with conventional chemotherapy, 70-80% after first line [26] and 45% in relapsed refractory[27]. Compared with CT, PET has a similar sensitivity (100%) but higher specificity (97% vs 51%) for residual disease detection. In a recent report on a study performed on 124 patients enrolled in the PRIMA trial whose response to initial chemoimmunotherapy was also assessed with PET, the achievement of PET negativity was an independent prognostic factor for PFS [28].

In 2007 PET scan has been incorporated in the new criteria for end-therapy assessment of treatment response [29]. The proposed criteria for end-therapy PET interpretation have been defined in the International Harmonization Project (IHP) using both anatomical volumetric criteria on CT and qualitative assessment with mediastinal blood pool structure as reference organ for residual FDG uptake quantification [30]. However, IHP criteria have never been validated; moreover, using different background reference for residual FDG-avid lesion lower or greater than 2 centimeters could overestimate the residual activity in small residual nodes and consequently yield a number of false-positive results [31].

Quite recently, the Deauville 5-point scale has been proposed to graduate residual FDG uptake in interim PET scan in Hodgkin lymphoma using two different organs as background reference: the mediastinal blood pool structures (MBPS) and the liver [32, 33]. The same score has been successfully employed in the GELA prospective protocol in bulky FL to assess the interim and final response to treatment with R-CHOP-21 followed by two consolidation administration of Rituximab[34].

In the present study PET scan will be performed at baseline, after 4 courses of R-CHOP-21 (not mandatory) and at the end of treatment, after 2 doses of Rituximab consolidation (see the below sketch). PET-4 will be a classic interim PET scan and no decision will be taken based on PET-4 results. By contrast, PET-end is made at the end of treatment with decisional aim: therapy will be modulated based on MRD detection and PET-end results.
7.0 STUDY RATIONALE

Recently, the availability of R has substantially changed therapeutic approach to FL patients, since its combination with chemotherapy has improved response rates, progression free survival (PFS) and overall survival (OS). Based on the results of recently completed randomized studies the standard treatment for patients with FL should consist of an initial therapy with R-CHOP combination followed by two-year maintenance with R. Although results of randomized trials confirmed that this approach results in an improved patients’ outcome and made a step forward in the management of patients with FL, one important question that can be raised is if this approach is really needed for all patients with FL or if some of them could benefit from a reduced intensity treatment achieving the same results in terms of outcome and survival. This question is of particular interest for newly diagnosed patients for whom maintenance does not affect OS.

More recent data demonstrated that the outcome of patients with FL can be further predicted by evaluating the quality of response to therapy studying minimal residual disease (MRD). This project addresses the objective of evaluating if combining clinical response assessed on FDG-PET scan and molecular response measured through MRD detection could permit to single out groups of patients at different risk of progression and to consequently modulate maintenance therapies, with the aim to provide clinicians a more rational use of the available diagnostic and therapeutic resources.
8.0 STUDY OBJECTIVES

8.1 Primary Objective

- To evaluate whether a FDG-PET and MRD response-based maintenance therapy is more effective in terms of Progression-Free Survival (PFS) than a standard maintenance therapy with Rituximab in patients with untreated, advanced, follicular lymphoma.

8.2 Secondary objectives

- To evaluate the efficacy of maintenance with observation or pre-emptive Rituximab therapy administered on the basis of MRD status and the efficacy of a standard maintenance for 2 years in patients at low risk of progression after induction chemoimmunotherapy.

- To evaluate the efficacy of intensified maintenance with (90)Y Ibritumomab Tiuxetan followed by Rituximab maintenance therapy and the efficacy of a standard maintenance for 2 years in patients at high risk of progression after induction chemoimmunotherapy.

- To compare a response-based maintenance therapy with a standard maintenance therapy in terms of toxicity.

- To verify the predictive value of MRD detection (assessed by both nested PCR and real time PCR conducted according to Euro-MRD guidelines and FIL-MRD network SOPs) in the two study arms, in both bone marrow (BM) and peripheral blood (PB) and to assess whether delivery of pre-emptive Rituximab therapy is able to induce molecular remission and prevent clinical relapse.

- To perform a cross evaluation of the predictive value of MRD analysis and FDG-PET

9 STUDY DESIGN

9.1 Study overview

This is a multi-centre, randomized, phase III, superiority study comparing a standard versus a response driven approach maintenance for patients with untreated stage II-IV Follicular NHL and FLIPI2 score > 0.

Patients aged 18 years or older with an histological proven naïve diagnosis of follicular lymphoma, stage II-IV, FLIPI2>0, with previously untreated disease and a requirement for therapeutic
intervention will be recruited and randomly assigned in a 1:1 ratio to either standard arm or experimental arm.

All patients will receive the same induction therapy with 6 cycles of R-CHOP and 2 additional doses of Rituximab.

At the end of chemoimmunotherapy all patients will be assessed for disease response by common practice clinical and laboratory examination, CT scan and FDG-PET. An intermediate assessment of response with CT scan and FDG-PET (not mandatory) will also be performed after the fourth course of R-CHOP.

At the end of induction therapy the status of minimal residual disease will be also evaluated. Treatment response will be assessed by traditional IWC criteria and PET/CT. PET scan will be uploaded to a dedicated website and centrally reviewed. Five expert reviewers will be asked to take part to the review panel (see Appendix D). The scans will be reported using the qualitative criteria for residual FDG uptake of the Deauville score [35]. According to the GELA experience, PET scan with an attributed score 1-3 will be considered negative; scans with a score 4 or 5, positive [34]. All responding patients in the standard arm will receive standard maintenance therapy with Rituximab (every 2 months for 2 years), while patients in the experimental arm will be subdivided into two risk groups and assigned to different post induction treatment.

In both arms, patients with stable or progressive disease (PET positive and less than PR on CT-scan) will be addressed to salvage therapy according to physician discretion.

In the experimental arm, risk group allocation will be performed primarily on the basis of FDG-PET results:

- Group 1 (low risk): negative FDG-PET (Score 1-3 see Appendix D)
- Group 2 (high risk): positive FDG-PET (Score 4-5 see Appendix D)

Patients at low risk (FDG-PET negative) will received maintenance therapy according to their MRD status. PCR negativity will be defined according to the FIL-MRD network SOPs and will take into account both nested-PCR and real-time quantitative PCR results.

- Group 1a (MRD negative): observation
- Group 1b (MRD positive): pre-emptive [36] Rituximab therapy

Patient at high risk (FDG-PET positive) will receive maintenance regardless of their MRD status:

- Group 2: intensified maintenance ((90)Y Ibritumomab Tiuxetan + Rituximab)
9.2 Study duration

The study period will consist of five phases: screening, registration and randomization, induction therapy, maintenance and follow-up.

Six-hundred and two (602) patients satisfying inclusion and exclusion criteria will be enrolled in a planned period of 4 years from different Italian Centers. Patients registered will be administered the induction treatment and then followed-up for disease evaluation for at least three years or until disease progression, death, withdrawal of consent, or study end.

Considering four years for accrual completion and 3 years of follow up, the overall duration of the study is planned to be approximately 7 years.

Screening

All patients must sign informed consent prior to registration.

Once informed consent is obtained, patient can be assessed for eligibility to the trial.

For all screening procedures patient will be assigned a Unique Subject Identifier (SID) number that will be used to identify the subject during the screening period and throughout all subsequent study phases.

Screening procedures to evaluate subject eligibility for the study have to be performed within 6 weeks prior to study Day 1 (day induction treatment is started).

Registration and randomization

Patients will be evaluated for all inclusion and exclusion criteria listed in section 10 before registration. After confirmation of eligibility, patients will be registered online at www.filinf.it, in the protocol dedicated section.

Subjects registered into the study will be randomly assigned to standard or experimental arm.

Registration and randomization have to be performed within 72 hours prior to study day 1.

Induction therapy

Subjects will receive induction treatment according to study schedule.

At the end of the fourth R-CHOP cycle patients will be addressed to an intermediate evaluation of disease status. Intermediate evaluation will consider size changes of the target lesions assessed by CT scan.
Patients achieving complete and partial response will receive two additional treatment cycles followed by two Riuximab infusions; patients with stable disease (SD) or progressive disease (PD) will discontinue study treatment and will receive salvage treatment at physician discretion. Final response to induction therapy will be assessed within one month after last treatment infusion. Patients with PD or SD will be addressed to salvage treatment at physician discretion.

**Maintenance**

Responding patients will be addressed to maintenance according to study schedule. Patients allocated in the standard arm will receive standard Rituximab maintenance while patients allocated in the experimental arm will be administered maintenance on the basis of PET response and MRD status.

**Follow-up phase**

Subjects will regularly undergo follow up visits until month 36 from the end of induction therapy. During the follow-up phase, patients will be evaluated for tumor response according to study schedule. Patients who will show a clinical relapse or PD will be addressed to salvage treatment according to physician decision.

**10 SELECTION CRITERIA**

**10.1 Inclusion Criteria**

- Histological diagnosis of B-Cell, CD20+ Follicular Lymphoma (FL), grade I, II, IIIa according to WHO 2008 classification
- ECOG performance status 0-2 (Appendix A)
- Age ≥18 years
- Ann Arbor stage II-IV (Appendix B)
- FLIPI2>0
- Presence of evaluable/measurable disease after diagnostic biopsy
- At least one of the following criteria for defining active disease:
  - systemic symptoms
  - cytopenia due to bone marrow involvement
  - LDH> upper normal value
  - any nodal or extranodal tumor mass with a diameter >7cm
  - involvement of ≥ nodal sites, each with a diameter of ≥ 3cm
- extranodal disease
- rapidly progressive disease

- Life expectancy > 6 months
- Left ventricular ejection fraction (LVEF) ≥ 50%
- Serum negativity for HIV
- Serum negativity for HBsAg. Patients HBcAb positive but HBV-DNA negative patients are allowed but Lamivudine prophylaxis is mandatory
- Serum negativity HCV except for those without signs of active viral replication, assessed by HCV-RNA copies
- Serum creatinine < 2 mg/dl, serum bilirubin < 1.5 mg/dl, aspartate amino-transferase (AST/GOT) ≤ 2.5xUNV, alanine amino-transferase (ALT/GPT) ≤ 2.5xUNV, and alkaline phosphatase ≤ 4 times the upper limit of normal (unless the increase is attributed directly to the presence of tumor by the Investigator)
- Patients with no previous treatment for the lymphoma with the exception of locoregional radiotherapy (IF-RT)
- Adequate measure adoption to avoid Pregnancy (if applicable)
- Written informed consent given at time of registration
- Patient must be accessible for treatment and follow up

10.2 Exclusion Criteria

- Histological diagnosis of :
  - any lymphoma other than follicular lymphoma and all CD20 negative B-cell lymphomas
  - grade IIIb follicular lymphoma
  - evidence of transformation in high grade lymphoma
- Ann Arbor stage I
- Suspect or clinical evidence of CNS involvement by lymphoma
- History of other malignancies within 5 years prior to study entry except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer, low grade, early stage localized prostate cancer treated surgically with curative intent, good prognosis DCIS of the breast treated with lumpectomy alone with curative intent
- Evidence of any severe active acute or chronic infection
- Concurrent co-morbid medical condition which might exclude administration of full dose chemotherapy
• Severe chronic obstructive pulmonary disease with hypoxemia
• Severe diabetes mellitus difficult to control with adequate insulin therapy
• Myocardial infarction within 6 months of entry on study
• Clinically significant secondary cardiovascular disease e.g. uncontrolled hypertension, (resting diastolic blood pressure >115 mmHg), uncontrolled multifocal cardiac arrhythmias, symptomatic angina pectoris or congestive cardiac failure NYHA class III-IV
• HBV positivity with the exception of patients who are seropositive because of hepatitis B virus vaccination and patients HbcAb positive and HbsAg negative with undetectable serum HBV-DNA.
• HIV-positive
• HCV positivity with elevated transaminases or INR or APTT or active virus replication
• Known hypersensitivity or anaphylactic reactions to murine antibodies or proteins
• Non FDG-avid Follicular Lymphoma
• Any other co-existing medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent

11.0 STUDY PROCEDURES (Appendix H)

Only patients with local histological diagnosis of B-Cell, CD20 + Follicular Lymphoma (FL), grade I, II, IIIa can be enrolled. The diagnosis should have been performed on lymph node or tissue biopsy with immunohistochemistry study.

A new tissue biopsy is not required for patients with FL progressing from a watch & wait approach unless there is a suspect of transformation into high grade NHL.

11.1 Screening period

All subject will be screened for study eligibility including:

Within 6 weeks prior to Study Day 1

• A bone marrow biopsy with immunohistochemical evaluation and bone marrow aspirate;
• Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement (sample to be centralized) (Appendix C);
• Measurable lesion assessment on CT scan;
• FDG-PET/CT scan (Appendix D);
• Complete medical history;
• LVEF by either bi-dimensional echocardiogram or cardiac scintigraphy (MUGA);
• Biopsy of suspicious extranodal sites if clinically indicated;
• Peripheral blood immunophenotyping in case of suspicious leukemic dissemination.

Within 2 weeks prior to Study Day 1

• Physical examination;
• Vital sign measurements (temperature, pulse, systolic and diastolic blood pressure and respiratory rate);
• Height, weight and body surface area;
• ECOG Performance Status;
• Disease related signs and symptoms;
• Serious pre-treatment event evaluation and recording;
• ECG;
• Hematology: hemoglobin, ANC and WBC count, platelets;
• Blood chemistry: serum glucose, AST, ALT, total bilirubin, creatinine, Na, K, uric acid, total protein with serum protein electrophoresis, albumin;
• Serum LDH;
• Serum beta2 microglobulin;
• 1st hour ESR;
• Urine analysis;
• Serum polyclonal IgA, IgG, IgM;
• Serology test for HIV, HCV, and HBV (including HBsAg, antiHBsAb, antiHBCAb);
• HBV-DNA, HCV RNA for patients with positive serology for HBV or HCV respectively;
• Pregnancy test (if applicable)

11.2 Induction therapy period

Before each course of chemioimmunotherapy:

- Physical examination (weight, BSA);
- Hematology :hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, creatinine, uric acid, LDH.

At days 7 and 14 during each course (not mandatory):
- Physical examination;
- Hematology: hemoglobin, ANC and WBC count, platelets.

**Intermediate evaluation after four courses of chemioimmunotherapy:**
- Physical examination;
- ECOG performance status;
- Total body computed tomography;
- FDG-PET/CT scan (not mandatory);
- Hematology: hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, creatinine, uric acid, total protein with serum protein electrophoresis, albumin;
- Serum LDH;
- Serum beta-2-microglobulin;
- 1st hour ESR.

**End of induction treatment: evaluation of response at one month after last treatment administration (eight rituximab):**
- Physical examination;
- ECOG performance status;
- Total body computed tomography;
- FDG-PET/CT scan (Appendix D);
- Hematology: hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, creatinine, total protein with serum protein electrophoresis, albumin;
- Serum LDH;
- Serum beta-2-microglobulin;
- 1st hour ESR;
- Serum polyclonal IgA, IgG, IgM;
- Serology test for HIV, HCV, and HBV (including HBsAg, antiHBsAb, antiHBeAb);
- HBV-DNA, HCV RNA for patients with positive serology for HBV or HCV respectively;
- Bone marrow biopsy (BMB), and immunohistochemical evaluation only if BM was involved at baseline;
- Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement only if baseline PCR was positive (sample to be centralized) (Appendix C).

11.3 Maintenance phase

**Standard arm, responding patients**

*Every 2 months for 2 years:*

- Physical examination;
- ECOG performance status;
- Hematology: hematocrit, hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, creatinine, total protein with serum protein electrophoresis, albumin;
- Serum LDH;
- Serum beta-2-microglobulin;
- 1st hour ESR;
- Serum polyclonal IgG, IgM, IgA.

*Every 6 months (months 6,12,18,24):*

- Total body CT scan
- Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement only if baseline PCR was positive (sample to be centralized) (Appendix C).

**Experimental arm PET negative**

*Every 2 months for 2 years:*

- Physical examination;
- ECOG performance status;
- Hematology: hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, creatinine, total protein with serum protein electrophoresis, albumin;
- Serum LDH;
- Serum beta-2-microglobulin;
- 1st hour ESR;
- Serum polyclonal IgG, IgM, IgA.

Every 6 months (months 6, 12, 18, 24):
- Total body CT scan
- Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement only if baseline PCR was positive (sample to be centralized) (Appendix C).

Before each Rituximab infusion (4 weekly infusions):
- Physical examination (weight, BSA);
- ECOG performance status;
- Hematology: hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, creatinine, total protein with serum protein electrophoresis, albumin;
- Serum LDH.

One month after last Rituximab infusion (after four weekly infusions):
- Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement only if baseline PCR was positive (sample to be centralized) (Appendix C).

Experimental arm PET positive

Before each Rituximab infusion:
- Physical examination;
- ECOG performance status;
- Hematology: hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, creatinine, total protein with serum protein electrophoresis, albumin;
- Serum LDH;
- Serum beta-2-microglobulin;
- 1 hour ESR;
- Serum polyclonal IgG, IgM, IgA.

**After (90)Y Ibritumomab Tiuxetan infusion:**

- FDG-PET/CT scan
- Every day until full haematological recovery (ANC>1.5x10^9L and PTLS> 75x10^9L):
  - Physical examination;
  - ECOG performance status;
  - Hematology: hemoglobin, ANC and WBC count, platelets.
- At full hematological recovery (2 months after (90)Y Ibritumomab Tiuxetan infusion)
  - Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement only if baseline PCR was positive (sample to be centralized) (Appendix C).

**Every 6 months (months 6,12,18,24):**

- Total body CT scan
- Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement only if baseline PCR was positive (sample to be centralized) (Appendix C).

**11.4 Follow-up phase**

*After maintenance phase patients will be followed for 1 year.*

**Every six months (months +6, +12):**

- Physical examination(weight, BSA);
- ECOG performance status;
- Hematology: hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, BUN/urea, creatinine, total protein with serum protein electrophoresis, albumin;
- Serum LDH;
- Serum beta-2-microglobulin;
- 1st hour ESR;
- Urine analysis;
- Serum polyclonal IgG, IgM, IgA.
- Total body CT scan;
- Bone marrow biopsy (BMB), and immunohistochemical evaluation only if BM was previously involved and examination is clinically indicated. BMB is mandatory at the end of follow up;
- Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement only if baseline PCR was positive (sample to be centralized) (Appendix C).

11.5 Early withdrawn (discontinuation from study treatment)

One month after last treatment administration:
- Physical examination;
- ECOG performance status;
- Total body computed tomography;
- FDG-PET/CT scan;
- Hematology: hemoglobin, ANC and WBC count, platelets;
- Blood chemistry: serum glucose, AST, ALT, total bilirubin, BUN/urea, creatinine, total protein with serum protein electrophoresis, albumin;
- Serum LDH;
- Serum beta-2-microglobulin;
- 1st hour ESR;
- Urine analysis;
- Serum polyclonal IgA, IgG, IgM;
- Bone marrow biopsy (BMB), and immunohistochemical evaluation only if BM was previously involved;
- Bone marrow aspirate and peripheral blood samples for PCR assessment of Bcl2/IgH rearrangement only if baseline PCR was positive (sample to be centralized) (Appendix C).

After this evaluation patients will be followed twice per year until the end of the study for the following:
- Survival
- Disease status
- Long term toxicity.

11.6 Investigations for evaluation of molecular response

*Note that sample shipment will be a pre-requisite for study inclusion and randomization at some specific time points.*

The PCR assessment of Bcl2/IgH rearrangement on bone marrow aspirate and peripheral blood samples must be done at baseline before start of induction therapy.

Only if Bcl2/IgH rearrangement is positive at baseline bone marrow aspirate and peripheral blood samples must be done:
- within 40 days from the last R administration of induction therapy;
- during maintenance every six months (months 6,12,18,24);
- in the experimental arm PET positive after (90)Y Ibritumomab Tiuxetan infusion (at full hematological recovery (2 months after (90)Y Ibritumomab Tiuxetan infusion);
- in the experimental arm PET negative one month after last Rituximab infusion (after four weekly infusions);
- during follow-up phase every six months (months +6,+12).

The molecular response will be evaluated for patients who will receive at least three cycles of immunochemotherapy.

Operative consideration concerning the identification of the reference lab as well as shipment procedures are detailed in Appendix C.

The form to enclose and the information concerning the courier are reported in Appendix C.
12. INDEPENDENT EXTERNAL PATHOLOGICAL REVIEW
An independent pathologist panel will review the lymph node/tumor biopsy, as well as any available bone marrow biopsy or other diagnostic material for retrospective confirmation of the diagnosis of cases classified by local pathologist as FL grade III or unspecified. The investigative site must submit the requested samples as part of the screening phase to allow for a histological review.

13. TREATMENT

13.1 Induction therapy
Patients will receive:
Rituximab: 375 mg/m² day 1 iv (Appendix E)
Cyclophosphamide: 750 mg/m² day 1 iv
Doxorubicin: 50 mg/m² day 1 iv
Vincristine: 1.4 mg/m² day 1 iv (max dose 2mg)
Prednisone: 100 mg day 1-5 os

Cycles are to be repeated every 21 days for a total of 6 courses.
After the sixth R-CHOP course patients will receive 2 additional doses of Rituximab (375 mg/m²) with a 21-days interval.

13.2 Maintenance

Standard arm
Patients in the standard arm will receive Rituximab maintenance as follow:
Rituximab 375 mg/m² every 2 months for 2 years (total 12 infusions).

Maintenance will have to be started no more than 12 weeks after last induction therapy infusion (8th Rituximab dose).

Experimental arm
PET negative and MDR negative (or without molecular marker)
Patients will not start maintenance therapy with Rituximab and will be followed-up with MRD monitoring. Patients changing from MRD negative to positive without radiological confirmed progression will receive a treatment with four weekly doses of Rituximab (375 mg/m²) and will then continue MRD monitoring according to study plan. If this treatment will turn MRD back to
negative, patients will continue with observation and regular follow-up. Rituximab could be repeated for MRD positive for a maximum of three courses (12 total doses).

*PET negative and MRD positive*

Patients will receive a pre-emptive [36] therapy with four weekly doses of Rituximab (375 mg/m²). If this treatment will turn MRD to negative, patients will continue with observation and regular follow-up. Rituximab could be repeated for MRD positive for a maximum of three courses (12 total doses).

*PET positive*

If required, before RIT administration peripheral blood stem cells will be collected. For the harvest, only growth factors-based mobilizing protocols will be accepted. Patients will receive radioimmunotherapy (RIT) (Appendix F):

- Rituximab: 250 mg/m² day 1 iv
- Rituximab: 250 mg/m² day 8 iv
- (90)Y Ibritumomab Tiuxetan: 0.4 mCi/Kg day 8 (range days 7 to 9) immediately after the second rituximab infusion.

RIT should start no later than 12 weeks after last induction chemoimmunotherapy infusion.

Following RIT patients will continue maintenance with Rituximab (375 mg/m² every 2 months) for a total of 11 infusions. The first R maintenance infusion will be administered two months after day 1 of RIT.

13.3 Warnings, dose delay and modification

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v 4.03 used as a guide for grading of severity.

13.3.1 Induction therapy

*Cycle delay and dose modification guidelines*

*Nonhematologic Toxicity*

**Cardiotoxicity.** A cumulative dose of 300 mg/m² of doxorubicin in this study should not be exceeded. Doxorubicin should be discontinued if evidence of left ventricular dysfunction or congestive heart failure develops.
Hepatic Toxicity. If bilirubin level is abnormal, the doxorubicin dose should be reduced to avoid myelotoxicity as outlined below (Table 1).

**Table 1**

| Serum bilirubin 1.5-3.0 mg/dL | • Decrease doxorubicin dose to 25 mg/m².  
| | • If improvement to <1.5 mg/dL, resume doxorubicin at 50 mg/m².  
| Serum bilirubin > 3.0 mg/dL or severe hepatic impairment | • Delay doxorubicin for a maximum of 3 weeks.  
| | • If improvement to 1.5-3.0 mg/dL, resume doxorubicin at 25 mg/m². If improvement to < 1.5 mg/dL, resume doxorubicin at 50 mg/m².  
| | • If no improvement, discontinue doxorubicin.  

Neurotoxicity. Dosing should be modified for neurotoxicity as outlined below (Table 2).

**Table 2**

| Grade 4 neurotoxicity | • Hold R-CHOP for a maximum of 3 weeks.  
| | • If improvement to Grade ≤ 2 within 3 weeks, continue full dose of R-CHOP, but without vincristin.  
| | • If improvement to Grade 3 only within 3 weeks, administer R without CHOP in the next cycle. If improvement to Grade ≤ 3 within 6 weeks, continue full dose of R-CHOP, but without vincristin.  
| Grade 1-3 neurotoxicity | • First episode: reduce vincristin for all subsequent cycles to 1 mg absolute; do not delay R-CHOP.  
| | • Second episode: eliminate vincristin for all subsequent cycles; do not delay R-CHOP.  

Tumor Lysis Syndrome. For patients with evidence of tumor lysis syndrome, treatment with R-CHOP should be discontinued and the patient should be treated as clinically indicated. Following the complete resolution of tumor lysis syndrome complications, treatment with R-CHOP may be resumed at the full dose at the next scheduled infusion in conjunction with prophylactic therapy.
**Hepatitis B Virus Reactivation.** Patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA must begin treatment with anti-viral medication (lamivudine) and will be immediately referred to a gastroenterologist or hepatologist for management.

If the HBV DNA assay becomes positive treatment with R-CHOP will be held and resume once the HBV DNA levels decrease to undetectable levels. If HBV DNA is positive for more than three weeks study treatment will be discontinued.

**Other Nonhematologic Toxicities.** For nausea or vomiting of all grades, optimize anti-emetic therapy.

For Grade ≥ 2 nonhematologic toxicities (excluding alopecia, nausea, and vomiting), treatment with R-CHOP will be delayed for a maximum of 3 weeks until resolution to Grade ≤ 1 (or baseline for all except hemorrhagic cystitis); for Grade 3 or 4 toxicities, dosing will be modified or discontinued as outlined in Table 3.

Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor.

It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reductions of rituximab (375 mg/m²).

Patients who have to discontinue rituximab treatment due to infusion-related symptoms or reaction may continue to receive chemotherapy alone and should continue to have disease assessments as per protocol.

For Grade 3 or 4 nonhematologic toxicities, doses of cyclophosphamide and doxorubicin should be decreased as outlined in Table 3.

**Table 3**

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Delay or Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 nonhematologic toxicity^a</td>
<td>• Delay doses of R-CHOP for a maximum of 3 weeks.</td>
</tr>
<tr>
<td></td>
<td>• First episode: if improvement to Grade ≤ 1 or baseline, decrease cyclophosphamide dose to 500 mg/m² and doxorubicin dose to 35 mg/m² for subsequent cycles.</td>
</tr>
<tr>
<td></td>
<td>• Second episode: if improvement to Grade ≤ 1 or baseline, decrease cyclophosphamide dose to 375 mg/m² and doxorubicin</td>
</tr>
</tbody>
</table>
| Grade 2 nonhematologic toxicity\(^a\) | • Delay doses of R-CHOP for a maximum of 3 weeks.  
• If improvement to Grade $\leq 1$ or baseline, administer previous dose of CHOP with full dose of rituximab. |
| Grade 1 nonhematologic toxicity\(^a\) | • No dose reduction or delay. |
| Grade 2-4 hemorrhagic cystitis | • Delay doses of R-CHOP for a maximum of 3 weeks.  
• If improvement to Grade $\leq 1$, decrease cyclophosphamide dose to 500 mg/m\(^2\) for next cycle. Mesna and hydration during the next administration of cyclophosphamide is recommended.  
• If symptoms do not recur, cyclophosphamide dose may be again increased to 750 mg/m\(^2\) for subsequent cycles. |

\(a\) Alopecia, nausea, and vomiting excluded. *In case of nausea or vomiting of all grades, optimize anti-emetic therapy; for cardiotoxicity, hepatic toxicity, neurotoxicity, tumor lysis syndrome, see guidelines above this table*

**Hematologic Toxicity** Note that lymphopenia is not considered to be a hematologic toxicity, because it is an expected outcome of therapy.

For Grade $\geq 3$ hematologic toxicities (defined as neutropenia, anemia, or thrombocytopenia), treatment with R-CHOP will be delayed for a maximum of 3 weeks until resolution to Grade $\leq 2$. In case of recurring Grade 3 hematological toxicity, dosing of cyclophosphamide, doxorubicin, rituximab will be modified or discontinued as outlined in Table 4. For Grade 4 toxicities, dosing will be modified or discontinued as outlined in Table 4.

Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reduction of rituximab (375 mg/m\(^2\)).

If myelosuppression is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the cyclophosphamide and doxorubicin doses, for the first cycle only.
### Table 4

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Delay or Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 hematologic toxicity</td>
<td>• Delay doses of R-CHOP for a maximum of 3 weeks.</td>
</tr>
<tr>
<td></td>
<td>• Administer myeloid growth factors for neutropenia.</td>
</tr>
<tr>
<td></td>
<td>• Administer RBCs or platelets as required.</td>
</tr>
<tr>
<td></td>
<td>• First episode: if improvement to Grade $\leq 2$, decrease cyclophosphamide dose to 500 mg/m² and doxorubicin dose to 35 mg/m² for subsequent cycles.</td>
</tr>
<tr>
<td></td>
<td>• Second episode: if improvement to Grade $\leq 2$, decrease cyclophosphamide dose to 375 mg/m² and doxorubicin dose to 25 mg/m² for subsequent cycles.</td>
</tr>
<tr>
<td></td>
<td>• Third episode: discontinue CHOP. If improvement to Grade $\leq 2$, continue full dose of rituximab.</td>
</tr>
<tr>
<td></td>
<td>• Fourth episode: discontinue all study treatment.</td>
</tr>
<tr>
<td>Grade 3 hematologic toxicity</td>
<td>• Delay doses of R-CHOP for a maximum of 3 weeks.</td>
</tr>
<tr>
<td></td>
<td>• Administer myeloid growth factors for neutropenia.</td>
</tr>
<tr>
<td></td>
<td>• Administer RBCs or platelets as required.</td>
</tr>
<tr>
<td></td>
<td>• First episode: if improvement to Grade $\leq 2$, administer previous dose of CHOP with full dose of rituximab.</td>
</tr>
<tr>
<td></td>
<td>• Second episode: if improvement to Grade $\leq 2$, decrease cyclophosphamide dose to 500 mg/m² and doxorubicin dose to 35 mg/m² for subsequent cycles.</td>
</tr>
<tr>
<td></td>
<td>• Third episode: if improvement to Grade $\leq 2$, decrease cyclophosphamide dose to 375 mg/m² and doxorubicin dose to 25 mg/m² for subsequent cycles.</td>
</tr>
<tr>
<td></td>
<td>• Fourth episode: discontinue CHOP. If improvement to Grade $\leq 2$, continue full dose of rituximab.</td>
</tr>
<tr>
<td></td>
<td>• Fifth episode: discontinue all study treatment.</td>
</tr>
<tr>
<td>Grade 1 or 2 hematologic toxicity</td>
<td>• No dose reduction or delay.</td>
</tr>
</tbody>
</table>

*If myelosuppression is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the cyclophosphamide and doxorubicin doses, for the first cycle only.*
13.3.2 Maintenance therapy

Rituximab

Nonhematologic Toxicities. For Grade $\geq 2$ nonhematologic toxicities, treatment with rituximab will be delayed for a maximum of 3 weeks until resolution to Grade $\leq 1$ or baseline (see Table 5). Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles are delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reductions or skipping of rituximab (375 mg/m$^2$).

Hepatitis B Virus Reactivation. Patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA must begin treatment with anti-viral medication (lamivudine) and will be immediately referred to a gastroenterologist or hepatologist for management.

If the HBV DNA assay becomes positive treatment with R-CHOP will be held and resume once the HBV DNA levels decrease to undetectable levels.

Hematologic Toxicity. Note that lymphopenia is not considered to be a hematologic toxicity, because it is an expected outcome of therapy.

For Grade $\geq 3$ hematologic toxicities (defined as neutropenia, anemia, or thrombocytopenia), treatment with rituximab will be delayed for a maximum of 3 weeks until resolution to Grade $\leq 2$ (see Table 5). Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor.

It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reductions of rituximab (375 mg/m$^2$).

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Delay or Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2, 3, or 4 nonhematologic toxicity</td>
<td>• Delay doses of rituximab for a maximum of 3 weeks.</td>
</tr>
<tr>
<td></td>
<td>• If improvement to Grade $\leq 1$ or baseline, administer full dose of rituximab.</td>
</tr>
</tbody>
</table>

Table 5
<table>
<thead>
<tr>
<th>Grade 1 nonhematologic toxicity</th>
<th>• No dose reduction or delay.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 hematologic toxicity</td>
<td>• Delay doses of rituximab for a maximum of 3 weeks.</td>
</tr>
<tr>
<td></td>
<td>• Administer myeloid growth factors for neutropenia.</td>
</tr>
<tr>
<td></td>
<td>• Administer RBCs or platelets as required.</td>
</tr>
<tr>
<td></td>
<td>• If improvement to Grade $\leq 2$, administer full dose of rituximab.</td>
</tr>
<tr>
<td>Grade 1 or 2 hematologic toxicity</td>
<td>• No dose reduction or delay.</td>
</tr>
</tbody>
</table>

(90)Y Ibritumomab Tiuxetan

**Hematologic Toxicity.** 90Y Ibritumomab Tiuxetan must be administered as follow:

<table>
<thead>
<tr>
<th>Platelets</th>
<th>Dose 90Y Ibritumomab Tiuxetan</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&gt; 150,000$/mmc</td>
<td>0.4 mCi/kg</td>
</tr>
<tr>
<td>100,000-150,000/mmc</td>
<td>0.3 mCi/kg</td>
</tr>
<tr>
<td>$&lt; 100,000$/mmc or if there is a BM infiltration greater than 25% at the end of induction therapy</td>
<td>not administrated</td>
</tr>
</tbody>
</table>

### 13.4 Concomitant Treatment

The following medication and supportive therapies may be used if needed during the study:
- Antibiotics, antiviral and antifungal treatments
- Antiemetic agents
- Immunoglobulin iv
- ESA

The use of rasburicase for the treatment of tumor lysis syndrome and the prevention of hyperuricemia is allowed according to institutional guidelines.

Mesna may be administered as prophylaxis per institutional guidelines to treat hemorrhagic cystitis. Prophylaxis with Lamivudine is mandatory for HBcAb+ patients. Occult carriers must receive treatment with Lamivudine 100 mg for the duration of treatment program and at least 12 months after treatment cessation; HBV-DNA levels and HBsAg will be monitored every month.

The use of G-CSF for prophylaxis is recommended according to ASCO guidelines; either filgrastim, lenograstim or peg-filgrastim can be used.

Before RIT only growth factors-based mobilizing protocols will be accepted.
Concomitant treatment to Rituximab:

- Paracetamole and diphenhydraminehydrochloride: prior to Rituximab infusion pretreatment must be given with paracetamole (1000 mg) and diphenhydraminehydrochloride (50 to 100) or similar drugs according to local practice.
- Corticosteroids are recommended prior to the first infusion of Rituximab (hydrocortisone 200 mg or methylprednisolone 20 mg).

13.5 Excluded Treatment
The following medications and supportive therapies are prohibited at any times:

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

14. Removal of Subjects from Treatment and/or Study
14.1 Discontinuation from Study Treatment
A patient should discontinue induction therapy (R-CHOP) if any of the following occurs:

- Grade 4 infusion-related symptom or anaphylaxis; the patient should be withdrawn from study treatment immediately.
- Recurrence of Grade 3 infusion-related symptom at re-challenge despite adequate preventive measures (i.e., acetaminophen/paracetamol plus antihistamine plus corticosteroid), regardless of timing (e.g., within the same session or at a subsequent session).
- Fourth recurrence of Grade 4 hematologic toxicity (each episode of which delayed the start of the next treatment cycle) despite adequate dose reductions
- Fifth recurrence of Grade 3 hematological toxicity (each episode of which delayed the start of the next treatment cycle) despite adequate dose reductions
- Grade ≥ 2 nonhematologic toxicity that does not resolve to Grade ≤ 1 or baseline despite delaying treatment for at least 3 weeks
- Fourth episode of Grade ≥ 2 nonhematologic toxicity (each episode of which delayed the start of the next treatment cycle) despite adequate dose reductions in R-CHOP
- Grade 1–4 heart failure or Grade 3–4 left ventricular systolic dysfunction
- Progression of disease during treatment
- Stable disease or partial response less than 50% at the intermediate evaluation
- Hepatitis B reactivation despite the appropriate anti-viral therapy
• The investigator believes that for safety reasons (e.g. adverse event) it is in the best interest of the subject to stop treatment
• The subject becomes pregnant
• The subject starts taking any concomitant lymphoma therapy

A patient should discontinue maintenance therapy if any of the following occurs:
• Progression of disease during treatment
• The investigator believes that for safety reasons (e.g. adverse event) it is in the best interest of the subject to stop treatment
• The subject becomes pregnant
• Occurrence of an unacceptable adverse event
• The subject starts taking any concomitant lymphoma therapy
• Hepatitis B reactivation despite the appropriate anti-viral therapy

Patients who discontinue treatment (induction therapy or maintenance) prior to the completion of the full number of cycles for any reason should be evaluated as described in section 11.5 “early withdrawn evaluation” and followed twice per year until the end of the study.

14.2 Withdrawal of subjects from the study
A subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.
A subject must be withdrawn from study treatment if retires the consent or doesn’t respect the inclusion criteria. In these cases patient must be considered off protocol and cannot be calculated for study endpoints.
The primary reason for a patient’s withdrawal from the study is to be recorded in the source document.

15 EFFICACY MEASUREMENT
15.1 Tumor response criteria
Criteria of tumor response will be defined according to the Revised Response Criteria for Non-Hodgkin’s Lymphomas(Cheson 2007).
Treatment response will be determined as follows:
Response Definitions for Clinical Trials
CR

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤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 involvement is 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.

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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.

**PR**

The designation of PR requires all of the following:

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 least 2 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.

No increase should be observed in the size of other nodes, liver, or spleen.

Splenic and hepatic nodules must regress by $\geq 50\%$ in their SPD or, for single nodules, in the greatest transverse diameter.

With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

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 (eg, 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.

No new sites of disease should be observed.

Typically FDG-avid lymphoma: for patients with no pre-treatment 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.

Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more
than two residual lesions are unlikely to be PET negative and should be considered partial responders.

* Patients with bone marrow infiltrate at diagnosis who fulfil criteria for CR at CT or PET but who are not reevaluated with bone marrow biopsy at the end of treatment will be considered in PR.

**Stable Disease**

Stable disease (SD) is defined as the following:

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 fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

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.

Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment 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. Lymph nodes $\geq 1.0 \times \geq 1.0$ cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 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 (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 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).

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 (eg, 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.

Evaluable not measurable disease will be assessed for complete response (complete disappearance) of all known disease. Spleen and liver, if considered to be enlarged before therapy on the basis of a CT scan must have regressed in size and must not be palpable on physical examination. Disappearance of bone marrow involvement as evaluated by bone marrow aspirate and trephine biopsy or progressive disease/relapse (appearance of any new lesion not previously identified or any size increase in existing lesions).

15.2 Molecular response criteria
The molecular response is defined by achievement of negative PCR for Bcl2/IgH rearrangement on all the planned timepoints and all of them will be tested in terms of predictive value regardless of the clinical response status. It is expected to have patients entering molecular remission while being in either in clinical CR or PR. The intersection of PCR status and PET status has not been investigated so far and will be the object of specific investigation in the context of the present trial.

15.3 PET response criteria
End-therapy PET scans will be uploaded to the dedicated website along with the baseline scans. PET scan images will be automatically distributed to the reviewers. PET scan central review will be made with the Deauville criteria (see Appendix D). Reviewers will score the scans within 72 hours from the date of PET scan upload in the website. The final PET judgement (Positive or negative) will be automatically distributed to the FIL clinical centers via e-mail.

Patients with a Positive PET Scan Patients with a Deauville score 4-5
Patients with a Negative PET scan Patients with a Deauville score 1-3
16 SAFETY MEASUREMENT

16.1 Safety criteria
All patients who have received at least one dose of study treatment will be evaluable for toxicity from the time of their first drug administration. When toxicity occurs, it should be graded according to the NCI Common Toxicity Criteria, version 4.03. 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.

16.2 Risks associated with Rituximab
Please see the prescribing information for Rituximab for full information.

a. Infusion-Related Reactions
Patients treated with R in combination with chemotherapy are at risk for IRRs. Fatal infusion reactions within 24 hours of R infusion can occur; approximately 80% of fatal reactions occurred with the first infusion. Severe reactions to Rituximab typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

b. Tumor Lysis Syndrome
Patients may be at risk for tumor lysis syndrome. With R treatment, acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, sometimes fatal, can occur within 12–24 hours after the first infusion of R in patients with NHL. A high number of circulating malignant cells (≥25,000/mm3) or high tumor burden confers a greater risk of tumor lysis syndrome. For patients with evidence of tumor lysis syndrome, R should be discontinued and the patient treated as clinically indicated.

c. Hepatitis B Virus Reactivation
HBV reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with R. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of R and approximately 1 month after the last dose. Patients with chronic hepatitis B viral infection (i.e., hepatitis B surface antigen [HBsAg] positive) are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and hepatitis B core antibody [HBcAb] positive) are at a lower risk for reactivation. In a study of 51 hepatitis B carriers with DLBCL who received R, 12% of patients developed evidence of
Patients who demonstrate evidence of reactivation while receiving an appropriate anti-viral therapy will discontinue study treatment.

d. Progressive Multifocal Leukoencephalopathy
Rare cases of PML have been reported in patients treated with R alone or in combination with other immunosuppressive medications [38-40]. In a review of 57 patients who developed PML after R administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem-cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with R is extremely rare but should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received R in combination with chemotherapy or as part of a hematopoietic stem-cell transplant. Most cases of PML were diagnosed within 12 months of the patient's last infusion of R.

e. Cardiac Toxicity
Angina and cardiac arrhythmias have occurred with R treatment and can be life threatening. Patients in the CHOP arm who have been treated with doxorubicin, an anthracyline-based chemotherapy, are at risk for cardiotoxicity and will be required to have assessments of left ventricular ejection fraction.

f. Infection
Serious infections, including fatal, bacterial, fungal, and new or reactivated viral infections (e.g., cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C), can occur during and up to 1 year following the completion of rituximab-based therapy.

g. Severe Mucocutaneous Reactions
Severe reactions, including fatal, mucocutaneous reactions, can occur in patients receiving R. These reactions include paraneoplastic pemphigus, Stevens–Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following R exposure.

h. Bowel Obstruction and Perforation
Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving Rituximab in combination with chemotherapy. In postmarketing reports of Rituximab, the mean time to documented gastrointestinal perforation was 6 days (range, 1–77) in patients with NHL.
16.3 Risks associated with CHOP
Please refer to prescribing information for doxorubicin, cyclophosphamide, vincristine, and prednisone for risks related to CHOP chemotherapy. Patients in the CHOP arm treated with doxorubicin, an anthracycline-based chemotherapy are at risk for cardiotoxicity. Although the risk increases with cumulative dose, irreversible cardiotoxicity may occur at any dose level. Patients with preexisting heart disease, hypertension, concurrent administration of other antineoplastic agents, prior or concurrent chest irradiation, and advanced age are at increased risk. Baseline and periodic monitoring of ECGs and left ventricular ejection fraction (LVEF), as determined by echocardiogram or multiple-gated acquisition (MUGA) scan, will be required. The evaluation of LVEF is required at baseline and after 300 mg/m2 of doxorubicin (Schwartz et al. 1987). Patients who receive doxorubicin and develop evidence of impaired cardiac function (LVEF of ≤ 50% in the presence of an absolute decrease in LVEF of ≥ 10%) will be given the option of switching to a non-cardiotoxic regimen (i.e., CVP) or discontinuing from trial participation.

16.4 Risks associated with Y(90) Ibritumomab Tiuxetan
Please see the prescribing information for Y(90) Ibritumomab Tiuxetan for full information. The most serious adverse reactions caused by the Y(90) Ibritumomab Tiuxetan therapeutic regimen include infections (predominantly bacterial in origin), allergic reactions (bronchospasm and angioedema), and hemorrhage while thrombocytopenic (resulting in deaths). In addition, patients who have received the Y(90) Ibritumomab Tiuxetan therapeutic regimen have developed myeloid malignancies and dysplasias. The most common toxicities reported were neutropenia, leucocytopenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, asthenia, pyrexia, rigors, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity.

17 SAFETY AND EFFICACY ASSESSMENT

17.1 Safety analysis
Patients will be considered for safety analysis if they complete at least 1 dose of study treatment. Tolerability of treatment will be evaluated by assessment of laboratory parameters and adverse events.
Incidence of all adverse events commencing during treatment and up to 30 days after the last drug infusion will be registered.

Adverse events will be classified with regard to severity, duration, and frequency of the event. Full details of adverse events will be listed by patient, including time of onset, duration, toxicity grade, corrective therapy, outcome and relationship to study drug.

The safety parameters will be evaluated by an independent Data Safety and Monitoring Committee that every time will consider the serious event and what to do (See section 18).

### 17.2 Efficacy analysis

Patients will be considered on an intent to treat basis for efficacy analysis if they:

- complete at least 1 cycle and undergo response assessment or receive less than 2 cycles and are withdrawn before from study for SD/PD.

**Primary variable**

*Progression Free Survival (PFS)* PFS will be measured from the date of randomization to the date of documented first occurrence of disease progression or relapse or to the date of death from any cause. Responding patients and patients who are lost to follow up will be censored at their last assessment date.

**Secondary variable**

- *Complete Response Rate (CRR)* is defined as the number of CR after the completion of the study treatment. Patients without a response assessment (due to any reasons) will be considered as non-responders.

- *Overall Response Rate (ORR)* after the completion of the treatment, defined as the sum of Complete Response and Partial Response. Patients without a response assessment (due to any reasons) will be considered as non-responders.

- *Duration of Response (DR)* is from the time when criteria for response (ie, CR or PR) are met, to the first documentation of relapse or progression.

- *Event Free Survival (EFS)* is measured from the time from study entry to any treatment failure including disease progression, or discontinuation of treatment for any reason (eg, disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death).
- *Overall survival (OS)* is defined as the time from the first day of study treatment until the date of death irrespective of cause. Patients who have not died at the time of end of the whole study, and patients who are lost to follow up, will be censored at the date of the last contact.

### 17.3 Molecular response analysis

- Rate of molecular remission will be defined as the proportion of patients PCR negative for Bcl2/IgH at different time-points including those achieving continuous MR in two or more consecutive time-points. Patients without a response assessment (due to any reasons) will be excluded from the analysis.
- Rate of conversion will be defined as the proportion of patients from baseline PCR-positivity to PCR-negativity. Patients without a response assessment (due to any reasons) will be excluded from the analysis.
- Rate of molecular relapse will be defined as the proportion of patients from PCR-negativity to PCR-positivity. Patients without a response assessment (due to any reasons) will be excluded from the analysis.

### 17.4 Data Safety and Monitoring Committee (DSMC)

A data safety monitoring committee (DSMC), including at least four independent members (2 experts in NHL, 1 expert in medical ethics and one independent statistician) has been established. The DSMC will meet periodically to review the safety and efficacy data from the trial prepared by the independent statistician who will also perform the interim analysis. All data presented at the meeting will be confidential. Following each meeting the DSMC will prepare a report and may recommend changes in trial conduct.

### 18 SAFETY DEFINITION, MONITORING AND REPORTING

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

**Definitions**

**Adverse Event Definitions and Classifications**

**Adverse Event**

An adverse event (AE) is any untoward medical occurrence in a clinical investigation 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
serious adverse event (SAE) as defined by ICH is any untoward medical occurrence that at any dose:
- 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 inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (a substantial disruption of the patient’s ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- constitutes an important medical event

Note: 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.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report form must be completed.
For each SAE, the investigator will provide information on severity, start and stop dates, relationship to (investigational product) study drug, action taken regarding (investigational product) study drug and outcome.

**Suspected Unexpected Serious Adverse Reaction (SUSAR)**

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product information. For an investigational drug, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure of experimental drug. For drugs with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC.

**Classification of severity**

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The severity of adverse events (AEs) will be graded on a scale of 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE). A copy of the NCI-CTCAE Version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page ([http://evs.ncti.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06.pdf](http://evs.ncti.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06.pdf)). In those cases where the NCI CTCAE does not apply, intensity should be defined according to the following criteria:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Mild</strong></td>
</tr>
<tr>
<td>2</td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td>3</td>
<td><strong>Severe</strong></td>
</tr>
<tr>
<td>4</td>
<td><strong>Life-threatening</strong></td>
</tr>
<tr>
<td>5</td>
<td><strong>Death</strong></td>
</tr>
</tbody>
</table>
Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

- **Not related.** An adverse event that is not related to the use of the investigational product.
- **Unlikely/Doubtful.** An AE 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 AE that might be due to the use of the investigational product. 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 AE that might be due to the use of the investigational product. 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 AE that is listed as a possible adverse event 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).
- **Not assessable:** there is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

**Treatment-related mortality**

If an adverse event considered associated with the study medication results in a patient’s death, then the event will be listed as a “treatment-related mortality”.

**Procedures for recording adverse events**

*Diagnosis/Causative Event versus Signs and Symptoms*

All AEs and SAEs should be reported. If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single syndrome at the time of reporting, each individual sign and/or symptom should be recorded as an AE or SAE on the CRF. If a constellation of signs and/or symptoms can be medically characterized as a single syndrome (e.g., nausea and vomiting), the most medically significant sign and/or symptom should be reported as the adverse event and the
additional signs and/or symptoms captured in the additional case details section of the CRF. If a diagnosis is subsequently established, the reported event term should be updated to reflect the medical diagnosis.

In general, AEs occurring secondary to other events (e.g., cascade of events or clinical sequelae) should be identified by their primary cause (causative event) and the additional sequelae captured in the additional case details section of the CRF.

However, AEs occurring secondary to an initiating event that are separated in time or medically significant should be recorded as independent events on the CRF.

*Persistent or Recurrent Adverse Events*

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should be recorded only once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event CRF.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent AEs should be recorded on Adverse Event CRF.

*Abnormal Laboratory Values*

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF. Criteria for clinical significance are the following:

- Laboratory abnormality is accompanied by clinical symptoms.
- Laboratory abnormality requires study drug dose modification or interruption or permanent discontinuation of study treatment.
- Laboratory abnormality requires more frequent follow-up assessments, further diagnostic investigation, etc.
- Laboratory abnormality requires a change in concomitant medication, therapy, or treatment.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.
**Deaths**
For this protocol, PFS is the primary efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of NHL will be recorded only on CRF. All other on-study deaths, regardless of attribution, will be recorded on an CRF and expeditiously reported to the Sponsor.

**Preexisting Medical Conditions**
A preexisting medical condition is one that is present at the start of the study.
A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study.
When recording such events on an Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

**Progression of Non-Hodgkin's Lymphoma**
Progression of NHL should not be recorded as an AE or SAE if it is clearly consistent with the suspected progression of the underlying cancer as defined by the criteria as determined by protocol. These data will be captured as efficacy assessment data only.
Hospitalization due solely to the progression of underlying NHL should NOT be reported as a SAE.

**Hospitalization, Prolonged Hospitalization, or Surgery**
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol.
There are some hospitalization scenarios that do not require reporting as a SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:
- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study
**Pregnancy**

If a female patient becomes pregnant while receiving investigational therapy or within 1 year after the last dose of study treatment or if the partner of a male patient becomes pregnant while receiving investigational therapy or within 3 months after the last dose of investigational product and paternity can be assured, a report should be sent to the Sponsor.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (because the Sponsor considers these medically significant), recorded on CRF, and expeditiously reported to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

**Procedures for reporting adverse events**

All AEs, SAEs that occur between the first study-related procedures and for 30 days following the last dose of investigational product will be reported.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded in the CRF. They must be recorded using medical terminology ([http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06.pdf)).

Investigators must record also in the CRF their opinion concerning the relationship of the adverse event to the study therapy. All measures required for adverse event management must be recorded in the source document.

Investigators must submit reports of all SAEs, regardless of attribution to the Sponsor within 24 hours of learning of the events.

For initial SAE investigators should record all case details that can be gathered within 24 hours on a SAE form (Appendix G). This form must be completed and supplied by e-mail or fax to Trial Office within 24 hours/1 business day or at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up SAE form as soon as it becomes available and/or upon request.

The Investigator(s) must keep copies of all SAE information on file. All SAEs that have not resolved upon discontinuation of the patient’s participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).
19 STATISTICAL CONSIDERATIONS

Phase III study, two arms randomized trial.

Primary end-point: Progression Free Survival (PFS): time to the documented detection of progression or to the patient’s death as results of any causes. Cases with incomplete follow-up or without disease evaluations will be censored at the date last documented to be free of failure.

The primary comparison will be an intention to treat analysis (ITT) including all randomized patients.

We considered a PFS of 70% at 3 years for the reference arm, with 4 years of uniform accrual and 3 years of follow-up, from the last accrued patients, with randomization 1:1.

The primary analysis of PFS will be performed using a two-sided log-rank test using an overall type I error of 2.5%. Allowing for the interim analysis, a total accrual of 546 patients and a total information of 210 failures is planned under $H_1$, to give 82% power to detect a 33% reduction in the PFS failure hazard rate.

If PFS follow an exponential distribution, this difference correspond to an improvement in PFS at 3 years from 70% to 79% (+9%) with a hazard ratio of 0.67.

Taking in account 10% of drop-out the final sample size will be 602 patients, randomized 1:1 ratio (301 by arms).

We considered two interim analysis of PFS, after 40% and 60% of planned full information has occurred. The study continuing until the second criteria for early stopping are met or full information is reached. To preserve the overall type I error rate, critical values at the interim analysis will be determined using a truncated version of the Lan-DeMets error spending function corresponding to the O’Brien-Fleming boundary.

If criteria of early stopping are not met, then the final analysis will be performed when approximately 210 failures have been observed under $H_1$. If for any reason that does not occur
within 3 years after completion of accrual, then the final analysis will be performed after 3 years of the last patient registration.

20. GOOD CLINICAL PRACTICE QUALITY CONTROL AND QUALITY ASSURANCE

20.1 Monitoring, Audits and Inspections
During the study the monitoring will be prevalently made by e-mail and telephone. The field monitor will visit the site, when needed, mainly in presence of data incongruity, to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice and the progress of enrolment. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. FIL Safety Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

20.2 Investigator (s) Responsibilities
Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice. The investigator must give the monitor access to relevant records to confirm the above.

The Investigator(s) is responsible for keeping a record of all patients who sign an Informed Consent Form and are screened for entry into the study. For those patients who fail screening the reason(s) for exclusion must be recorded in the patient’s source documents.

No procedure/assessment/measurement/test other than those outlined here, or in the schedule of study assessments, is to be performed without the prior written approval of Principal Investigator, or unless deemed by the investigator(s) as necessary for the patient’s medical care. Investigator(s)
and/or authorized designee(s) must enter study data onto electronic CRFs supplied by FIL. The data on the CRF will be recorded in an anonymous manner to protect the patient’s identity by using a unique identifier that will prevent personal identifiable information.

The Investigator(s), or a designated member of the Investigators’ staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the patient’s records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The CRFs must be completed as soon as possible after the patient’s visit, but no later than prior to each monitoring visit and be made available to the FIL representative(s) so that the accuracy and completeness may be checked.

21. ETHICAL AND REGULATORY CONSIDERATIONS

21.1 Institutional Review Board/Independent Ethics Committee Review and Approval

This study will be conducted according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients (see: http://www.wma.net/e/policy/b3.html for more information). The review of this protocol by the IRB/IEC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Patients and Part 56 Institutional Review Boards.

Before implementing this study, the protocol, the proposed informed consent form and other information to patients, must be reviewed by a properly constituted IRB/IEC. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to FIL before the study initiation. The names and occupations of the chairman and the members of the IRB/IEC must be supplied to FIL.

The FIL as sponsor of the study, together with site Investigator(s), will be responsible for preparing documents, where ever applicable, for submission to the relevant IRB/IEC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

A copy of the IRB/IEC approval for the protocol and the Informed Consent is to be provided to FIL and site Investigator(s). The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

The Investigator(s) is responsible for notifying the FIL Safety Monitoring Office and the IRB/IEC of any serious deviations from the protocol, or anything else that may involve added risk to patients. Any advertisements used to recruit patients for the study must be reviewed and approved by FIL and the IRB/IEC prior to use.
Before the start of the study, the FIL will provide the IRB/IEC with current and complete copies of the following documents:

1. final protocol and, if applicable, amendments
2. informed consent form (and any other written materials to be provided to the subjects)
3. Investigator’s Brochure (or equivalent information) and amendments
4. information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
5. investigator’s curriculum vitae or equivalent information (unless not required, as documented by IRB/IEC)
6. any other documents that the IRB/IEC requests to fulfil its obligation.

During the study the FIL according with site investigators will send the following documents to the IRB/IEC for their review and approval, where appropriate:

1. protocol amendments
2. revision(s) to informed consent form and any other written materials to be provided to subjects
3. revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
4. Investigator’s Brochure amendments or new edition(s)
5. summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IRB/IEC)
6. reports of adverse events that are serious, unexpected and associated with the investigational drug
7. new information that may affect adversely the safety of the subjects or the conduct of the study
8. deviations from or changes to the protocol to eliminate immediate hazards to the subjects
9. report of deaths of subjects under the investigator's care
10. notification if a new investigator is responsible for the study at the site
11. any other requirements of the IRB/IEC

21.2 Protocol Amendments
Any amendment to this protocol that seems appropriate, as the study progresses will be submitted to the IRB/IEC for written approval before the implementation of the amended version. The written
signed approval from the IRB/IEC should refer specifically to the investigator(s) and to the protocol number and title and mention any amendment numbers that are applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

21.3 Informed Consent
The Investigator(s) must obtain informed consent of a patient or his/her designee prior to any study related procedures as per Good Clinical Practices (GCP). Documentation that informed consent occurred prior to the patient’s entry into the study and of the informed consent process should be recorded in the patient’s source documents. 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. MRD detection is part of the study and patients are required to undergo this analysis.
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.
The original consent form signed and dated by the patient and by the person consenting the patient prior to the patient’s entry into the study must be maintained in the Investigator’s study files and a copy given to the patient. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent must be revised. Patients participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent. The revised consent form signed and dated by the patient and by the person consenting the patient must be maintained in the Investigator’s study files and a copy given to the patient.
22. DATA HANDLING AND RECORDKEEPING

22.1 Data/Documents
The investigator(s) must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; patient’s diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; patient files) and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, filed and retained.

22.2 Data Management
Data will be entered into the clinical database as per FIL SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary, in the form of a Data Clarification Form (DCF). Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

22.3 Retention of Records
The investigator(s) must maintain records of all study documents and supporting information relating to the conduct of the study. This documentation includes, but is not limited to, protocols, case report forms, advertising for patient participation, adverse event reports, patient source data, correspondence with health authorities and IRBs/IECs, informed consent forms, investigator(s) curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice specified below. The study monitor must be consulted if the investigator(s) wishes to assign the study files to someone else, remove them to another location or is unable to retain them for a specified period. The investigator(s) must retain study records for the time period according to local laws or requirements, whichever is longer. The monitor will inform the investigator(s) of the dates for retention. All study documents should be made available if required by relevant health authorities. The investigator(s) records must be retained until at least 2 years after the last approval.
of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by other applicable regulatory requirements.

23. 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

1. processed fairly and lawfully
2. collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
3. adequate, relevant, and not excessive in relation to said purposes
4. 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.

Patients will be registered in the study via website the end of their staging, before beginning the treatment. The name of the patient will not be asked for not recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify and must be included on all case report form.
References

17. Gribben JG, Neuber D, Barber M et al. Detection of residual lymphoma cells by polymerase chain reaction in peripheral blood is significantly less predictive for relapse than detection in bone marrow. Blood 1994; 83: 3800-3807.
36. Ferrero S, Monitillo L, Mantovan B et al. Pre-emptive rituximab-based treatment of molecular relapses in follicular and mantle cell lymphoma. Haematologica 2012; 97(s1); Abs#0804.


### APPENDIX A

#### ECOG PERFORMANCE STATUS*

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

## APPENDIX B: Ann Arbor Staging Classification of Lymphomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td>Involvement of a single lymphatic region (I), or localized involvement of a single extra-lymphatic organ or site (IE)</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>Involvement of two or more lymphatic regions on the same side of the diaphragm (II), or localized involvement of a single extra-lymphatic organ or site and of one or more lymphatic regions on the same side of diaphragm (IIE). An optional recommendation is that the number of lymphatic regions involved should be indicated by a subscript (e.g. II3)</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>Involvement of lymphatic regions on both sides of the diaphragm (III), which may also be accompanied either by localized involvement of an extra-lymphatic organ or site (IIIE), or by involvement of spleen (IIIS), or by both (IIIE+S)</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Diffuse or disseminated involvement of one or more extra-lymphatic organs with or without associated lymphatic involvement. The organ involved should be identified by a symbol: H for liver, L for lung, M for bone marrow, P for pleura, O for bone, D for skin</td>
</tr>
</tbody>
</table>

The absence or presence of unexplained fever, night sweats, and/or unexplained weight loss of more than 10% of the usual body weight in the 6 months prior the diagnosis is denoted by the suffix letters A or B, respectively.
APPENDIX C

MODALITY OF COLLECTION AND SHIPMENT OF BONE MARROW ASPIRATE AND PERIPHERAL BLOOD SAMPLES FOR THE STUDY OF MOLECULAR RESPONSE

REFERENCE LABORATORIES

MRD analysis will be conducted in the context of the FIL-MRD network which includes four MRD laboratories. Every Center will refer to a different lab based on geographic position. In particular assignment will be done on a provincial basis as follows:

TORINO (BLUE LAB):

Address:
LABORATORIO BIOLOGIA MOLECOLARE DOTT. MARCO LADETTO
c/o laboratorio EMATOLOGIA UNIVERSITARIA 1 - Prof. Mario Boccadoro
Ospedale San Giovanni Battista - Molinette,
Via Genova 3, (Piano Terra)
10126 Torino
PROTOCOLLO FIL FOLL12

Help-desk for the MRD study please contacts the following: Dott.ssa Barbara Mantoan, Dott.ssa Luigia Monitillo or Dott.ssa Daniela Drandi, Molecular Biology Laboratory, Division of Hematology, University of Torino; TEL: +39-011-6336884; FAX: +39-011-6963737; e-mail contacts: barbara.mantoan@unito.it, luigia.monitillo@unito.it, daniela.drandi@unito.it

PISA (PINK LAB):
The pink lab will receive samples from: La Spezia, Piacenza, Parma, Reggio Emilia, Modena, Massa-Carrara, Pistoia, Lucca, Prato, Pisa, Livorno, Firenze, Arezzo, Siena, Grosseto, Viterbo, Perugia, Terni, Palermo, Trapani, Messina, Catania, Enna, Caltanissetta, Agrigento, Ragusa, Siracusa.

Address:
LABORATORIO BIOLOGIA MOLECOLARE DOTT.SSA SARA GALIMBERTI
Help-desk for the MRD study please contacts the following: Dott.ssa Sara Galimberti or Dott.ssa Elena Ciabatti  Molecular Biology Laboratory, Division of Hematology, University of Pisa; TEL: +39-050-992815; e-mail contacts: s.galimberti@med.unipi.it, e.ciabatti@med.unipi.it.

BOLOGNA (YELLOW LAB):
The yellow lab will receive samples from: Trieste, Gorizia, Udine, Pordenone, Belluno, Treviso, Venezia, Vicenza, Padova, Rovigo, Verona, Ferrara, Ravenna, Bologna, Forlì-Cesena, Rimini, Pesaro-Urbino, Ancona, Macerata, Fermo, Ascoli Piceno, Pescara, Chieti.
Address:
LABORATORIO BIOLOGIA MOLECOLARE DOTT. PIERPAOLO PICCALUGA
Pad 8 L.A.Seragnoli
Ospedale Sant’Orsola Malpighi
Via Massarenti , 9
40138 Bologna
PROTOCOLLO FIL FOLL12

Help-desk for the MRD study please contacts the following: Dott. Pierpaolo Piccaluga or Dott.ssa Anna Gazzola, Molecular Biology Laboratory, University of Bologna; TEL: +39-051-6363047; e-mail contacts: pierpaolo.piccaluga@unibo.it, anna.gazzola@libero.it.

ROMA (GREEN LAB):
The green lab will receive samples from: L’Aquila, Rieti, Roma, Frosinone, Latina, Campobasso, Isernia, Caserta, Benevento, Napoli, Avellino, Salerno, Foggia, Barletta-Andria-Trani, Bari, Brindisi, Lecce, Taranto, Potenza, Matera, Maratea, Cosenza, Crotone, Catanzaro, Vibo Valentia, Reggio Calabria.
Address:
LABORATORIO DI IMMUNOLOGIA DOTT.SSA ILARIA DEL GIUDICE
C/O Ematologia
Via Benevento 6

Version 1.0- 02 July 2012
Help-desk for the MRD study please contacts the following: Dott.ssa Ilaria del Giudice or Dott.ssa Irene della Starza, Immunology Laboratory, University of Roma; TEL: +39-06-441639822; e-mail contacts: delgiudicebce@uniroma1.it, irene.x@virgilio.it.

GEOGRAPHICAL ALLOCATION OF FIL MRD NETWORK LABORATORIES

- Torino
- Pisa
- Bologna
- Roma
Table 1: TIME POINTS FOR MRD EVALUATION. PERIPHERAL BLOOD AND BONE MARROW ARE REQUIRED

1. Baseline (within 6 weeks before Day1Study)
   
   *Only if baseline PCR was positive:*

2. within 40 days from the last R administration of induction therapy;
3. during maintenance every six months (months 6,12,18,24);
4. during maintenance in the experimental arm PET positive after (90)Y Ibritumomab Tiuxetan infusion (at full hematological recovery (2 months after (90)Y Ibritumomab Tiuxetan infusion));
5. during maintenance in the experimental arm PET negative one month after last Rituximab infusion (after four weekly infusions);
6. during follow-up phase every six months (months +6,+12).

In case of early withdrawn (discontinuation from study treatment) only if baseline PCR was positive, MRD evaluation should be done at one month after last treatment administration.

A number of well defined molecular time points are planned in this study. For any time point, both BM and PB will be required. Both at baseline and follow-up time points at least seven ml of BM and 14 ml of PB are required.

In absence of BM invasion at baseline, it is recommended (though not required) to send a sample from lymph node or other diagnostic tissue biopsy for the detection of a molecular marker. Also a pre-stored tumor invaded DNA sample (either BM or PB or other) taken during previous treatment phases (i.e. at diagnosis) might be used to identify a molecular marker.

Note that sample shipment will be a pre-requisite for study inclusion and randomization. This means that the software will not allow to complete the required procedures if the laboratory has not received the biological sample.

**OPERATIVE CONSIDERATIONS FOR SAMPLE SHIPMENT**

BM mand PB samples will be collected according to a schedule which has been previously described.

**Please follow carefully the following** instructions:
1. **Obtain PB and BM** from the patient: for any time point both BM and PB will be required. Both at baseline and follow-up time points at least 7 ml of **heparinized bone marrow aspirate in a lithium heparin or citrate sodium tubes** and 14 ml of **PB in citrate sodium tubes** should be collected.

2. **In absence of BM invasion at baseline**, it is recommended to send a frozen or paraffin embedded (the latter choice is sub-optimal) sample having a tumor invasion of at least 5%. Also a **tumor invaded DNA sample** (either BM or other) **taken during previous treatment phases** (i.e. at diagnosis) **might be used to identify a molecular marker**. These samples might derive either from lymph node or extra nodal tissue.

3. **Apply adhesive labels** specifying the kind of sample (e.g. PB, BM), the patient code and the treatment phase (e.g. “Baseline”, “Restaging after chemoimmunotherapy”, etc…). DO NOT write the name of the patient. Secure the biohazard box.

4. Apply the address on the external side of the box.

5. Contact FIL Secretariat by e-mail segreteria@filinf.it or fax (+39-0131-263455)

6. **Shipment is mandatory for enrollment**, so please check after three days that the laboratory has received the sample.

Samples should be **sent at room temperature from Monday to Thursday and should not reach destination after 4 p.m.**

It is advisable to send no samples the day before an Italian vacation day, if occurring on Friday or Monday, because this will result in a >72 hour delay in sample processing.

*For non Italian centres: be careful about Italian vacation days. The list of Italian vacation days is: 1 January, 6 January, Easter Monday (variable), 25 April, 1 May, 2 June, 15 August, 1 November, 8 December, 25 December, 26 December.*

Please note that sample shipment on Friday will often cause a 48 hour delay of processing, resulting in a sub-optimal pre-analytical procedure. We thus recommend sending samples on Friday only in cases which are extremely urgent.

**FOR THE PRESENT PROTOCOL WE DO NOT RECOMMEND THE SHIPMENT OF ALREADY EXTRACTED DNA OR FROZEN CELLS.**

Samples should be sent through the TNT EXPRESS, according to the geographical allocation describe above.
MRD study

Patient code: ____________

Date of sampling: ______/____/____
                 dd / mm / yy

Timing

Baseline □
After induction therapy □
Maintenance phase □  month________
Follow up phase □  month________

Centre: ____________________________
Sender information:

Name_______________
Telephone number__________________
Fax number_______________________
e.mail__________________________
APPENDIX D

FDG-PET scanning and central review

Patient scanning will be made according to the European guidelines for patients scanning [41]. Patient scanning will be made with PET/CT equipments. Three PET scan will be made during the study: PET-0 (at baseline), PET-4 (approximately 14 days after the fourth R-CHOP 21 course) and PET-end (at the end of treatment). Fasting glucose levels should not exceed 120 mg/dl. PET-4 and PET-end should be made not earlier than 14 days after chemotherapy administration and not earlier than 5 days after steroid withdrawal.

End-PET scans, along with PET-0 and PET-4 scans will be uploaded to the dedicated website (https://magic5.to.infn.it/) that will be set-up for the study. Imaging upload in the web and distribution to reviewers will be made thanks to WIDEN ® (Web-based Imaging Diagnosis by Expert Network). Five expert nuclear medicine reviewers will score the scans according to the Deauville score by comparing the sites of uptake that were deemed to be involved by lymphoma on the baseline scan to the uptake in the normal mediastinal blood pool and the liver as follows:

a. Score 1, No uptake
b. Score 2, Uptake $\leq$ mediastinum
c. Score 3, Uptake $>$ mediastinum and $\leq$ liver
d. Score 4, Uptake moderately increased above liver at any site
e. Score 5, Markedly increased uptake above the liver and/or new site of disease

For the purposes of this trial PET scans with score 1–3 are considered negative; score 4–5 are considered positive. Reviewers will score the scans blinded to the clinical outcome.

The concordance rules for a final scan result definition will be set a priori. A scan will be defined as positive or negative where at least 3 reviewers agree that a particular scan was positive or negative, respectively. Reviewers will score the scan within 72 hours from the upload in the website independently and blinded to lymphoma treatment outcome. Binary and overall concordance among reviewers will be calculated automatically by WIDEN using k Cohen’s coefficient for binary concordance (negative vs. positive) and alpha Krippendorf’s coefficient for overall concordance (negative vs. positive).
APPENDIX E

ADMINISTRATION OF RITUXIMAB

Caution: Do not administer rituximab as an intravenous push or bolus.

- Oral premedication (1000 mg of paracetamole and 50-100 mg diphenhydramine hydrochloride) needs to be administered 30-60 minutes prior to starting each infusion.
- 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.

FIRST INFUSION

- 1st dose 100 mg in 100 ml saline solution
- 2nd dose the remaining amount in 1000 ml saline solution

Begin infusion at the initial rate of 50 mg/hr

If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate

SUBSEQUENT INFUSIONS

If no adverse events occurred during first rituximab infusion, subsequent infusion will be performed as follow

- 1st dose 100 mg in 100 ml saline solution
- 2nd dose the remaining amount in 250ml saline solution

<table>
<thead>
<tr>
<th>Hours</th>
<th>ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>100</td>
</tr>
<tr>
<td>1 – 3</td>
<td>125</td>
</tr>
</tbody>
</table>
APPENDIX F

RADIOIMMUNOTHERAPY

Initiate the (90)Y Ibritumomab Tiuxetan therapeutic regimen if the patient has less than 25% BM infiltration at the restaging and following recovery of platelet counts to $\geq 150,000$/mmc at least 6 weeks, but no more than 12 weeks, following the last dose of first-line chemotherapy. If the patient doesn’t meet these two criteria will proceed directly to maintenance. If at week 11 platelets are between 100,000 and 150,000/mmc proceed with (90)Y Ibritumomab Tiuxetan 0.3 mCi/kg the following week.

- **Rituximab** 250mg/m$^2$ i.v. Day 1 and Day 8

  Administer rituximab 250 mg/m$^2$ intravenously at an initial rate of 100 mg/hr. Increase rate by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr, as tolerated. If infusion reactions occurred during rituximab infusion on Day 1 of treatment, administer rituximab at an initial rate of 50 mg/hr and escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

- **(90)Y Ibritumomab Tiuxetan** i.v. Day 8

  Administer over 10 minutes as an intravenous injection within 4 hours after completion of the rituximab infusion.

  - NOTE 0.4 mCi/kg if platelets $\geq 150,000$/mmc, 0.3 mCi/kg if platelets are between 100,000 and 150,000/mmc).

Follow Institutional rules for radioprotection after RIT Infusion.

REFERENT OF RIT:
**Stefano Fanti, M.D** Nuclear Medicine Division and of PET Unit at the S. Orsola Malpighi Hospital, University of Bologna, Italy. e-mail: s.fanti@unibo.it
### APPENDIX G

**Serious Adverse Event Report Form**

#### Study Information

1. **Country:**

   [[Blank Line]]

   **Centre:**

   [[Blank Line]]

   **Indication:**

   [[Blank Line]]

   **Study ID:**

   [[Blank Line]]

2. **Initial:**

   [ ] 
   Recurrent events or complications of a previously reported event should be reported as follow-up

   **Follow-up:**

   [ ]

#### Subject Information

3. **Subject ID:**

   [[Blank Line]]

   **Subject Initials:**

   [[Blank Line]]

   **Date of Birth:**

   dd mon yyyy

   **Age:**

   [[Blank Line]]

   **Sex:**

   [ ] Male

   [ ] Female

   **Ethnicity:**

   [ ] Caucasian

   [ ] Hispanic

   [ ] Other

   [ ] Black

   [ ] Asian

   [ ] Unknown

   **Weight:**

   [ ] kg

   [ ] lbs

   Please tick which unit is appropriate

   **Height:**

   [ ] cm

   [ ] in

   Please tick which unit is appropriate

4. **Medical history relevant to the SAE including concurrent and pre-existing conditions (please provide dates):**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Onset date</th>
<th>Ongoing at time of SAE?</th>
<th>If no, End date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
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<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
## Serious Adverse Event Report Form

### Study Treatment Information

<table>
<thead>
<tr>
<th>Study treatment</th>
<th>Treatment dates</th>
<th>Dosage</th>
<th>Action taken</th>
<th>Mark if event improved (x)</th>
<th>Mark if event restarted (x)</th>
<th>Mark if event reoccurred (x)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(or state if blinded / run in phase / screening)</td>
<td>date dose first received</td>
<td>date this dose last taken prior to SAE</td>
<td>amount, unit, route, frequency (e.g. 20mg oral bid) for blinded titration studies please specify the study treatment level</td>
<td><strong>please specify dates below (and provide dose changes as a separate entry)</strong></td>
<td><strong>Mark if study treatment restarted</strong></td>
<td><strong>Mark if event reoccurred (x)</strong></td>
</tr>
<tr>
<td>dd mon yyyy</td>
<td>dd mon yyyy</td>
<td>1-6 dd mon yyyy</td>
<td>1. Study treatment continued unchanged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Study treatment withdrawn**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Study treatment dose reduced**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. Study treatment dose increased**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5. Study treatment interrupted**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6. Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Relevant concomitant medication excluding those used to treat the SAE

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Reason for use</th>
<th>Treatment dates</th>
<th>Dosage</th>
<th>Action taken</th>
<th>Mark if event improved (x)</th>
<th>Mark if event restarted (x)</th>
<th>Mark if event reoccurred (x)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>date dose first received</td>
<td>date this dose last taken prior to SAE</td>
<td>amount, unit, route, frequency (e.g. 20mg oral bid) for blinded titration studies please specify the study treatment level</td>
<td><strong>please specify dates below (and provide dose changes as a separate entry)</strong></td>
<td><strong>Mark if study treatment restarted</strong></td>
<td><strong>Mark if event reoccurred (x)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dd mon yyyy</td>
<td>dd mon yyyy</td>
<td>1-6 dd mon yyyy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Information on Serious Adverse Event(s)

#### 7. Serious Adverse Event

**Specify diagnosis, if possible, otherwise note key signs and symptom(s)**

*Please note that if any of the symptoms of the diagnosis are indicative of a greater severity or are a change in the expected nature of the diagnosis please also report these*

<table>
<thead>
<tr>
<th>Mark if diagnosis (x)</th>
<th>Onset date</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td>1. Not recovered / Not resolved / Unchanged</td>
</tr>
<tr>
<td></td>
<td>1-7 dd mon yyyy</td>
<td>2. Condition deteriorating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Recovered / resolved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Improving / recovering / resolving</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Recovered with sequelae (please specify sequelae in section 10 or 15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Fatal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Unknown (please specify dates in box)</td>
</tr>
</tbody>
</table>

**Is there a reasonable possibility that the study treatment caused the event?**

(if on multiple study treatments, please specify which is suspected, if any)

**Is there a reasonable possibility that any other medications contributed to the event?**

If so, please specify Y/N

**Other possible contributory factors:**

1. Lack of efficacy to study treatment
2. Progression of study indication*
3. Progression of concomitant disease (specify disease in box).
4. Aggravation of study indication (specify cause of aggravation in box).
5. Study conduct (please specify in box).
6. Other (please specify in box).
7. None.

**Other possible contributory factors:**

<table>
<thead>
<tr>
<th>Mark if diagnosis (x)</th>
<th>Onset date</th>
<th>Outcome</th>
<th>Y/N</th>
<th>Treatment Name</th>
<th>Y/N</th>
<th>Treatment Name</th>
<th>1-7</th>
<th>Specify</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dd mon yyyy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<tr>
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<td>dd mon yyyy</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Seriousness criteria**

1. Death, 2. Life threatening, 3. Involved or prolonged inpatient hospitalization, 4. Results in persistent or significant disability/incapacity, 5. Congenital anomaly/birth defect.

6. Medically significant event (For definition please refer to SAE Quick Reference Guide)

* Please note that progression of study indication should usually be assessed as not suspected because the event occurred in spite of study treatment administration

#### 8. Please provide rationale for causality assessment to study treatment

---

Version 1.0- 02 July 2012
9. Description of the event(s) including all hospitalization start and stop dates

10. If subject died, was an autopsy performed?  
   - Yes*  
   - No  
   - Unknown  
   *If yes, date of autopsy: dd mon yyyy

Please provide the primary cause of death and any relevant findings as determined by the autopsy, if performed, in section 7

**Treatment of the reported event(s)**

<table>
<thead>
<tr>
<th>Details of drug &amp; non-drug treatment</th>
<th>Start</th>
<th>Stop</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dd</td>
<td>mon</td>
<td>yyyy</td>
</tr>
<tr>
<td></td>
<td>dd</td>
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</tr>
<tr>
<td></td>
<td>dd</td>
<td>mon</td>
<td>yyyy</td>
</tr>
</tbody>
</table>

**Laboratory, test or scan data relevant to the reported SAE**

<table>
<thead>
<tr>
<th>Date</th>
<th>Test</th>
<th>Results (with units)</th>
<th>Normal values</th>
<th>CTCAE grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>dd</td>
<td>mon</td>
<td>yyyy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dd</td>
<td>mon</td>
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<tr>
<td>dd</td>
<td>mon</td>
<td>yyyy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*if CTCAE grade 4 or above, or considered to be serious for any other reason, please also list in section 7

13. Comments on laboratory and test data findings

Version 1.0- 02 July 2012
### Serious Adverse Event Report Form

<table>
<thead>
<tr>
<th>Study ID:</th>
<th>Subject ID:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Centre ID:</th>
<th>initials:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14. Please provide additional information from any previous section here. 
*Please do not attach discharge summaries, copies of medical records or examination results unless specifically requested.*

**Please check this box if the causality between study treatment and all the events reported on this form are NOT SUSPECTED**

### Reporter Information

15. Name and address of investigator/reporter (please print)

<table>
<thead>
<tr>
<th>Investigator name</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporter name (if different)</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Title</th>
<th>First name</th>
<th>Last name</th>
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<table>
<thead>
<tr>
<th>Tel</th>
<th>Fax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Signature of investigator

Date of signature [dd mon yyyy]

Thank you very much for your co-operation in this matter.

Please fax the completed form to FIL Data Center +390594223707:
# APPENDIX H

## Schedule of Investigations During Treatment

### Screening and Induction therapy

<table>
<thead>
<tr>
<th>Day</th>
<th>Screening</th>
<th>Induction Therapy Cycle 1-6</th>
<th>Intermediate evaluation after four courses of R-CHOP</th>
<th>Rituximab (2 infusions)</th>
<th>End of induction treatment (one month after last treatment administration)</th>
<th>Early withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>within 6 weeks prior to Study Day 1</td>
<td>within 2 weeks prior to Study Day 1</td>
<td>1</td>
<td>7-14</td>
<td>1</td>
<td>At one month after last treatment administration</td>
</tr>
<tr>
<td>Complete medical history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital sign measurements</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height, weight and body surface</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Disease related sign and symptoms</td>
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<td>X</td>
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<td>Serious event evaluation and recording</td>
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<td>X</td>
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</tr>
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</tr>
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<td>Prednisone dosing</td>
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</tbody>
</table>

1. PE: physical examination
2. Vital sign: Temperature, pulse, systolic and diastolic blood pressure and respiratory rate
3. Hematology: hemoglobin, ANC and WBC count, platelets
4. HBV-DNA, HCV-RNA for patients with positive serology for HBV or HCV respectively
5. The diagnosis of FL should have been performed on lymphnode or tissue biopsy with immunohistochemistry study. A new tissue biopsy is not required for patients with FL progressing from a watch & wait approach unless there is a suspect of transformation into high grade NHL.
6. if clinically indicated
7. in case of suspicious leukemic dissemination
8. CT scan: neck, chest, abdomen and pelvis including inguinal and axillary lymph nodes
9. if applicable
10. Biochemistry: Serum glucose, AST, ALT, total bilirubin, creatinine, Na, K, uric acid, total protein with serum protein electrophoresis, albumin
11. Biochemistry: Serum glucose, AST, ALT, total bilirubin, creatinine, uric acid
12. Prednisone on Day 1 through day 5 of each cycle.
13. To be performed only if BM was previously involved
14. To be performed only if PCR assessment of Bcl2/IgH rearrangement was previously positive

Version 1.0- 02 July 2012
### Maintenance phase: standard arm, responding patients

<table>
<thead>
<tr>
<th>2 years maintenance</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>PE&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>ECOG</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease related sign and symptoms</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serious event evaluation and recording</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Hematology&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Biochemistry&lt;sup&gt;4&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>ESR</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>LDH</td>
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<td>Beta2 microglobulin</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Serum IgG, IgM, IgA</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>BM aspirate and peripheral blood samples to centralize&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>CT scan&lt;sup&gt;6&lt;/sup&gt;</td>
<td>X&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1. PE: physical examination
2. Every 2 months from evaluation of final response to induction therapy
3. Hematology: hemoglobin, ANC and WBC count, platelets
4. Biochemistry: Serum glucose, AST, ALT, total bilirubin, creatinine, Na, K, uric acid, total protein with serum protein electrophoresis, albumin
5. To be performed only if PCR assessment of Bcl2/IgH rearrangement was previously positive
6. CT scan: neck, chest, abdomen and pelvis including inguinal and axillary lymph nodes
7. Every 6 months from evaluation of final response to induction therapy

### Maintenance phase: experimental arm PET negative

<table>
<thead>
<tr>
<th>2 years maintenance</th>
<th>Before each R infusion</th>
<th>One month after last Rituximab infusion (after four weekly infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
</tr>
<tr>
<td>ECOG</td>
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<td>X</td>
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<td>Disease related sign and symptoms</td>
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<td>Serious event evaluation and recording</td>
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<td>Hematology&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Biochemistry&lt;sup&gt;4&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>ESR</td>
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<tr>
<td>LDH</td>
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<tr>
<td>Beta2 microglobulin</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Serum IgG, IgM, IgA</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>BM aspirate and peripheral blood samples to centralize&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>CT scan&lt;sup&gt;6&lt;/sup&gt;</td>
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</tbody>
</table>

1. PE: physical examination
2 Every 2 months from evaluation of final response to induction therapy
3 Hematology: hemoglobin, ANC and WBC count, platelets
4 Biochemistry: Serum glucose, AST, ALT, total bilirubin, creatinine, Na, K, uric acid, total protein with serum protein electrophoresis, albumin
5 To be performed only if PCR assessment of Bcl2/IgH rearrangement was previously positive
6 CT scan: neck, chest, abdomen and pelvis including inguinal and axillary lymph nodes
7 Every 6 months from evaluation of final response to induction therapy

**Maintenance phase: experimental arm PET positive**

<table>
<thead>
<tr>
<th>Before each R infusion</th>
<th>After (90)Y Ibritumomab Tiuxetan infusion</th>
<th>Two years maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE¹</td>
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<td>X'</td>
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<td>X'</td>
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<td>Disease related sign and symptoms</td>
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<td>X³</td>
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<td>Serious event evaluation and recording</td>
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<tr>
<td>Hematology⁴</td>
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<td>X'</td>
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<td>Biochemistry⁵</td>
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<td>Beta2 microglobulin</td>
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<td>Serum IgG, IgM, IgA</td>
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<tr>
<td>BM aspirate and peripheral blood samples to centralize⁵</td>
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<td>CT scan⁶</td>
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<td>FDG-PET scan⁷</td>
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</table>

1 PE: physical examination
2 Every 2 months from evaluation of final response to induction therapy
3 Hematology: hemoglobin, ANC and WBC count, platelets
4 Biochemistry: Serum glucose, AST, ALT, total bilirubin, creatinine, Na, K, uric acid, total protein with serum protein electrophoresis, albumin
5 To be performed only if PCR assessment of Bcl2/IgH rearrangement was previously positive
6 CT scan: neck, chest, abdomen and pelvis including inguinal and axillary lymph nodes
7 Every day until full hematological recovery (ANC>1.5x10⁹L and PTLS>75x10⁹L)
8 To be performed at full hematological recovery (2 months after (90) Ibritumomab Tiuxetan)
9 Every 6 months from evaluation of final response to induction therapy
10 To be performed one time after (90) Ibritumomab Tiuxetan

**Follow-up phase (1 year)**

<table>
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<th>Every six months</th>
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<tbody>
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<td>BM biopsy and immunohistochemical</td>
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<td>BM aspirate and peripheral blood samples to centralize</td>
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1. PE: physical examination
2. Hematology: hemoglobin, ANC and WBC count, platelets
3. Biochemistry: Serum glucose, AST, ALT, total bilirubin, creatinine, Na, K, uric acid, total protein with serum protein electrophoresis, albumin
4. CT scan: neck, chest, abdomen and pelvis including inguinal and axillary lymph nodes
5. To be performed only if BM was previously involved and examination is clinically indicated. BMB is mandatory at the end of follow-up
6. To be performed only if PCR assessment of Bcl2/IgH rearrangement was previously positive