A Phase Ib/II Study of Escalating Doses of Revlimid in Association with R-CHOP (R2-CHOP) in the Treatment of B-Cell Lymphoma

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Date of Protocol: Version Finale 6.2 – December 16, 2011
EUDRACT Number: 2007-007698-22

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## PROTOCOLE SUMMARY

<table>
<thead>
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<th>TRIAL ID</th>
<th>R2-CHOP</th>
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<tbody>
<tr>
<td>EUDRACT Number</td>
<td>2007-007698-22</td>
</tr>
</tbody>
</table>

### Protocol Title

**A PHASE I/II STUDY OF ESCALATING DOSES OF REVLIMID IN ASSOCIATION WITH R-CHOP (R2-CHOP) IN THE TREATMENT OF B-CELL LYMPHOMA**

### Protocol Version

Version 6.2 (December 16, 2011)

### Sponsor

Centre Henri Becquerel

### Principal Investigator

Hervé Tilly

### Protocol writing committee

Bertrand Coiffier, Corinne Haioun, Gilles Salles, Vincent Ribrag, Larissa Mege, Marion Fournier, Yvain Robreau

### Number of centers

25 centers in France.

### Project phase

Ib/II

### Objectives

**Primary objective:**

The primary objective of the Phase Ib part of the study is to determine the recommended dose (RD) of lenalidomide (Revlimid) when administered in association with R-CHOP.

The primary objective of the Phase II part of the study is to assess the efficacy of the association of Revlimid and R-CHOP in a population of patients with follicular lymphoma as measured by the response rate at the end of treatment.

**Secondary objectives:**

- To assess the safety of the association,
- To assess the efficacy of the association: response rate and complete response rate, progression free survival, response duration and overall survival.

### Study Design

This study is an open label, multicenter study with two phases:

**The Phase I b part of the study** is a dose escalation study of lenalidomide (Revlimid) administered orally during 14 days in combination with fixed doses of rituximab (R), cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) administered every 3 weeks (R-CHOP 21) in patients with B-cell lymphoma.

**The Phase II part of the study** is an efficacy study of the association of the recommended dose of lenalidomide associated with R-CHOP 21 in a selected population of patients with follicular lymphoma.

### Planned sample size

Approximately 110 evaluable subjects will be enrolled in the study: about 30 patients for the Phase Ib part and 80 patients in the Phase II part.

### Inclusion criteria

- **Phase Ib:** Patients with one of the following B-cell Lymphoma, CD 20 positive:
  - Mantle cell, Marginal zone, follicular
  - Histological transformation from low grade to high grade
  - Diffuse large B cell
**Phase II:** Patients with follicular lymphoma, WHO grade 1, 2 or 3a with at least one of the following signs requiring initiation of treatment:
- Bulky disease according to the GELF criteria: nodal or extra-nodal mass >7cm in its greater diameter
- B symptoms
- Elevated serum LDH or beta 2-microglobulin
- Involvement of at least 3 nodal sites (each >3cm)
- Symptomatic spleen enlargement
- Compressive syndrome
- Pleural or peritoneal effusion

- Aged from 18 to 70 years
- WHO performance status 0, 1 or 2
- Signed inform consent
- Life expectancy of ≥ 90 days (3 months).

- Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL not more than 3 days from the start of study drug and must either commit to continued abstinence from heterosexual intercourse (and confirmed on a monthly basis) or begin one effective method of birth control, at least four weeks before she starts taking lenalidomide, and maintain that method throughout the entire duration of study drug therapy (including dose interruptions), and for four weeks after the end of study treatment with lenalidomide, even if she has amenorrhea. FCBP must also agree to pregnancy testing at least every three weeks and must be counseled at a minimum of every three weeks about pregnancy precautions and risks of fetal exposure.

- Men must agree not to father a child and agree to use a condom throughout study drug therapy, during any dose interruption, and for one week after cessation of study drug therapy, if their partner is pregnant or of child bearing potential. Men must also agree not to donate semen during study drug therapy and for one week after end of study drug therapy. Men must be counseled at a minimum of every 4 weeks about pregnancy precautions and risks of fetal exposure.

- All subjects must abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy.
- Agree not to share study drug with another person and to return all unused study drug to the investigator.

† A female patient is considered to have childbearing potential unless she meets at least one of the following criteria 1) Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (amenorrhoea following cancer therapy does not rule out childbearing potential); or 2) Premature ovarian failure confirmed by a specialist gynaecologist or 3) Previous bilateral salpingo-oophorectomy, or hysterectomy, or 4) XY genotype, turner syndrome, uterine agenesis.

**Exclusion Criteria**

- Previous treatment with immunotherapy or chemotherapy, except for patients in phase IIB part:
  - Chlorambucil or Cyclophosphamide per os alone during less than 6 months, if stopped more than one year before inclusion
  - Rituximab alone during less than three months, if stopped more than one year before inclusion
- Previous radiotherapy except if localized to one lymph node area
Other type of lymphomas: Burkitt, T cell, lymphocytic, CD 20 negative
Central nervous system or meningeal involvement
Contraindication to any drug contained in the chemotherapy regimen
HIV disease, active hepatitis B or C
Any serious active disease or co-morbid medical condition (according to investigator’s decision)
Any of the following laboratory abnormalities.
  - Absolute neutrophil count (ANC) < 1,500 cells/mm3 (1.5 x 10^9/L).
  - Platelet count < 100,000/mm3 (100 x 10^9/L).
  - Serum SGOT/AST or SGPT/ALT 5.0 x upper limit of normal (ULN).
  - Serum total bilirubin > 2.0 mg/dL (34 µmol/L), except in case of hemolytic anemia.
Calculated creatinine clearance (Cockcroft-Gault formula) of < 50 mL/min
Prior history of malignancies other than lymphoma unless the subject has been free of the disease for > 5 years, except for cured basal cell carcinoma (surgery) or cured carcinoma in situ of the cervix (surgery).
Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
Pregnant or lactating females.
Prior ≥ Grade 3 allergic reaction/hypersensitivity to thalidomide.
Prior ≥ Grade 3 rash or any desquamating (blistering) rash while taking thalidomide.
Subjects with ≥ Grade 2 neuropathy.
Prior use of lenalidomide.
Use of any standard or experimental anti-cancer drug therapy within 28 days of the initiation (Day 1) of study drug therapy.

### Study medication

#### Treatment in Phase Ib part:
All patients will be treated with R2-CHOP at a three-week interval for 6 cycles.

<table>
<thead>
<tr>
<th>R2-CHOP</th>
<th>Dose (mg/m²)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCLOPHOSPHAMIDE</td>
<td>IV 750</td>
<td>1</td>
</tr>
<tr>
<td>DOXORUBICINE</td>
<td>IV 50</td>
<td>1</td>
</tr>
<tr>
<td>VINCRISTINE</td>
<td>IV 1,4 (max 2 mg)</td>
<td>1</td>
</tr>
<tr>
<td>PREDNISONE</td>
<td>PO 40</td>
<td>1 to 5</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>CI 375</td>
<td>1</td>
</tr>
<tr>
<td>LENALIDOMIDE</td>
<td>PO</td>
<td>See dose levels table</td>
</tr>
</tbody>
</table>

Patients with diffuse large B-cell lymphoma and an international prognostic index >1 will be given intrathecal methotrexate, 15 mg, at day 1 of the first four cycles.

#### Dose-levels of lenalidomide are defined as follows:

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Days of Treatment</th>
<th>Lenalidomide Dose</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>D1 to D14</td>
<td>2.5 mg</td>
<td>0-6</td>
</tr>
<tr>
<td>1</td>
<td>D1 to D14</td>
<td>5 mg</td>
<td>3-6</td>
</tr>
</tbody>
</table>
Dose escalation rules:
Dose escalation will begin at dose level 1. Dose escalation will be decided depending on the number of Dose Limiting Toxicities (DLTs) observed during the administration of the first 2 cycles of R2-CHOP.

<table>
<thead>
<tr>
<th>Number of patients with DLT at a given dose level</th>
<th>Rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 of first 3</td>
<td>Enter at least 3 patients at the next dose level.</td>
</tr>
<tr>
<td>1 out of 3</td>
<td>Enter up to 6 patients at this dose level. If 0 of the 3 additional patients experience DLT, then proceed to the next dose level. If 1 or more of 3 additional patients experience DLT, then dose escalation will be stopped. Three (3) additional patients will be entered at the previous dose level if 3 patients were treated at that dose.</td>
</tr>
<tr>
<td>≥ 2</td>
<td>Dose escalation will be stopped. Three (3) additional patients will be entered at the previous dose level if 3 patients were treated at that dose.</td>
</tr>
</tbody>
</table>

DLT definition
DLT is defined as any of the following events (toxicity):
- Grade ≥ 3 non hematological toxicity,
- Grade 3 hematological toxicity lasting more than 7 days,
- Grade 4 hematological toxicity lasting more than 3 days.

The recommended dose will be the dose level just below the MTD. The recommended dose level will be completed to include a total of 12 patients.

Treatment in Phase II part:
All patients will be treated with R2-CHOP at a three-week interval for 6 cycles, then with Rituximab for two cycles.

<table>
<thead>
<tr>
<th>R2-CHOP</th>
<th>Dose (mg/m²)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCLOPHOSPHAMIDE</td>
<td>IV 750</td>
<td>1</td>
</tr>
<tr>
<td>DOXORUBICINE</td>
<td>IV 50</td>
<td>1</td>
</tr>
<tr>
<td>VINCristINE</td>
<td>IV 1,4 (max 2 mg)</td>
<td>1</td>
</tr>
<tr>
<td>PREDNISONE</td>
<td>PO 40</td>
<td>1 to 5</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>CI 375</td>
<td>1</td>
</tr>
<tr>
<td>LENALIDOMIDE</td>
<td>PO 25 mg</td>
<td>1 to 14</td>
</tr>
</tbody>
</table>
Patients who achieve CR/Cru/PR at evaluation after 6 cycles of R2-CHOP and 2 rituximab will receive maintenance according to the PRIMA scheme with rituximab every two months during two years.

**At each phase**

Subjects should receive tumor lysis prophylaxis.

Pegfilgrastim will be given at D4 of each cycle at the dose of 6mg.

All subjects will be required to take a daily aspirin (100 mg) for deep vein thrombosis (DVT) prophylaxis during study period. Subjects who are unable to tolerate aspirin and subjects with prior history of DVT or at high risk should receive low molecular weight heparin therapy or warfarin (Coumadin) treatment.

A prophylaxis of pneumocystis carinii pneumonia, according to local usage, is highly recommended during study and until three months after last cycle administration.

A dosage of digoxinemia will be performed for all patients who will receive digoxin concomitantly with revlimid.

**Dose modifications rules**

**Phase Ib:**

In case of DLT, Revlimid will be definitively stopped.

There is no dose adjustment related to hematological toxicity. However, in the case where cytopenia (absolute neutrophil count < 1,500 cells/mm3 (1.5 x 10^9/L) or Platelet count < 100,000/mm3 (100 x 10^9/L) ) is observed at day 21, the next cycle will be postponed for 3 days. In the case of cytopenia persists on day 24, the next cycle will be postponed for 3-4 additional days. Persisting cytopenia at day 35 will be considered as an unacceptable toxicity.

In case of grade 1 neurological toxicity related to vincristine (sensory or motor neuropathy, constipation, visual or auditory changes), the dose will be reduced to 1 mg by cycle. If the neurological toxicity increased despite of dose reduced, vincristine will be definitively stopped.

**Phase II:**

There is no dose adjustment of CHOP components related to hematological toxicity. However, in the case where cytopenia (absolute neutrophil count < 1,500 cells/mm3 (1.5 x 10^9/L) or Platelet count < 100,000/mm3 (100 x 10^9/L) ) is observed at day 21, the next cycle will be postponed for 3 days. In the case of cytopenia persists on day 24, the next cycle will be postponed for 3-4 additional days.

In case of grade 1 neurological toxicity related to vincristine (sensory or motor neuropathy, constipation, visual or auditory changes), the dose will be reduced to 1 mg by cycle. If the neurological toxicity increased despite of dose reduced, vincristine will be definitively stopped.
The lenalidomide dosing should be reduced in case of related toxicities defined as follow:

- Grade 3 hematological toxicity (neutrophils and/or platelets) lasting more than 7 days
- Grade 4 hematological toxicity (neutrophils and/or platelets) lasting more than 3 days.
- Creatinine clearance between 30 and 50 mL/min
- Neurological toxicity > grade 2
- Any other toxicity ≥ grade 3 except for alopecia and for ALT and Bilirubin (see below specific guidelines)
- Cycle of R2-CHOP postponed for 7 days or more because of toxicity

Lenalidomide will be temporarily stopped for the current cycle and dose of lenalidomide will be reduced as follow:

If a patient has had dose reduction, then dose re-escalation of lenalidomide is not permitted at any time.

If ALT > 5 x ULN or Total bilirubin > 3 x ULN, Lenalidomide will be temporarily stopped for the current cycle. Then, at next cycle:
- if recovery from the event: dose of lenalidomide will be the same,
- if no, lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. If the values do not return to baseline within the two next cycles, lenalidomide dose should be discontinued

If creatinine clearance <30 mL/min, lenalidomide must be definitely stopped.

In case of DVT occurrence, antithrombotic treatment (heparin or coumadin [INR 2-3] must be started (and kept during the whole treatment duration with lenalidomide) and lenalidomide can be resumed without dose reduction.

**Assessment schedule**

Clinical examinations (including vital signs, ECOG performance status) and laboratory safety tests (including complete blood counts, serum chemistries) will be obtained prior to drug administration, and before each cycle of treatment, and up to 30 days after the last study treatment administration.

During the first two cycles of the phase Ia, clinical examination and complete blood cell counts will be obtained at day 7, day 10 and then every two days (± 1 day) until the absolute neutrophil count reach $1.5 \times 10^9/L$ and platelet count reach $100 \times 10^9/L$.

AEs/SAEs type, severity (according NCI-CTCAE v. 3.0), cycle, duration, seriousness, and relationship to study treatment will be assessed. Laboratory
abnormalities will be assessed according to the NCI-CTCAE v. 3.0.
Tumor assessment (clinical examination, laboratory tests, abdominal and chest CT scan, PET scan, bone marrow examination) will be performed at baseline, after cycle 4 and three weeks after the last treatment dose. To ensure comparability, baseline and on-study methods for response assessment will be performed using identical techniques.

<table>
<thead>
<tr>
<th>Statistical considerations</th>
<th>SAMPLE SIZE CALCULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the phase Ia part of the study, sample size is not based on statistical power calculation. The number of dose levels and the emerging dose limiting toxicities will determine the sample size. It is anticipated that approximately 30 patients will be required to establish the maximum tolerated dose (MTD) and the recommended dose of lenalidomide (Revlimid). For the phase II part of the study, the sample size calculation is based on Simon's randomized phase II design testing the null hypothesis that the complete response rate is less than or equal to 65% versus the alternative hypothesis that the response rate is greater than or equal to 80%. A total of 73 evaluable will provide nominal power of 80% at the nominal one-sided 2.5% significance level. Assuming an estimated drop out of 10%, a total of 80 patients will be enrolled.</td>
<td></td>
</tr>
</tbody>
</table>

**ANALYSIS PLAN**

For the phase Ia part of the study, the primary endpoint is the determination of the Recommended Dose of lenalidomide (Revlimid) in combination with R-CHOP regimen. Therefore, primary analysis will be based on safety parameters and particularly on incidence of DLTs. Frequency of patients with DLT during the first 2 cycles of R2-CHOP will be reported by dose level.

For the phase II part of the study, the primary endpoint is the Complete Response Rate (CR+CRu) according to IWCR 1999 at the end of treatment.

Efficacy data (response rates, PFS, OS, duration of response) will be assessed with Kaplan-Meier method for censored data. Analysis of safety will be performed by summarizing adverse events, laboratory data, vital signs and ECOG performance status. When applicable, summary of safety data will also be performed by cycle.

**PLANNED TIME TO ANALYSIS**

Safety data and, when available, preliminary efficacy data will be used to define dose escalation increments. The cut-off for main criteria analysis is defined when safety data for the first 2 cycles of R2-CHOP are available for all patients. Then, the cut-off for efficacy data and safety data for cycles 3 to 6 of this part of the study will be established at 3 months after the end of treatment for the last patient. A last cut-off will occur 2 years after the last treatment last patient.

For the phase II part of the study, a two-stage analysis will be conducted. The first stage analysis will be performed after 39 evaluable patients have been included. The trial will be terminated if 26 or fewer patients respond to treatment and treatment will be considered as ineffective. The probability of early termination is 0.645. All data available at the scheduled time of interim analysis will be used for these patients. Otherwise, the trial will proceed to second stage and include 34 additional patients. Thus, a total of 73 evaluable patients will be studied. At the end of the second stage, if the total number of responder patients is less than or equal to 55, treatment will be considered as inefficient. Cut-off for final analysis will occur one year after last treatment last patient.

<table>
<thead>
<tr>
<th>Planned start/End dates for the study</th>
<th>The duration of the study is estimated to be 8 years.</th>
</tr>
</thead>
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| Estimated recruitment period: June 2008 – May 2012 | }
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<th>ABBREVIATION</th>
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<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>alanine transaminase (serum glutamic pyruvic transaminase)</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>aspartate transaminase (serum glutamic oxaloacetic transaminase)</td>
</tr>
<tr>
<td>β-hCG</td>
<td>beta-human chorionic gonadotropin</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CD20</td>
<td>antigen expressed on the surface of normal and malignant B lymphocytes</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CHOP</td>
<td>cyclophosphamide, doxorubicin, vincristine, and prednisone</td>
</tr>
<tr>
<td>CI</td>
<td>Continuous infusion</td>
</tr>
<tr>
<td>CPMP</td>
<td>Committee for Proprietary Medical Products</td>
</tr>
<tr>
<td>CPP</td>
<td>Comité de Protection des Personnes</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>CRu</td>
<td>complete response unconfirmed</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Toxicity Criteria for Adverse Events</td>
</tr>
<tr>
<td>DLBCL</td>
<td>diffuse large cell B-cell lymphoma cell line</td>
</tr>
<tr>
<td>DLT</td>
<td>dose limiting toxicity</td>
</tr>
<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
</tr>
<tr>
<td>ERC</td>
<td>Ethical review committees</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>Emax</td>
<td>maximum effect</td>
</tr>
<tr>
<td>ESMO</td>
<td>European Society for Medical Oncology</td>
</tr>
<tr>
<td>FCBP</td>
<td>Females of childbearing potential</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FL</td>
<td>Follicular cell lymphoma</td>
</tr>
<tr>
<td>GELA</td>
<td>Groupe d’Etude des Lymphomes de l’Adulte</td>
</tr>
<tr>
<td>GELARC</td>
<td>Groupe d’Etude des Lymphomes de l’Adulte – Recherche Clinique</td>
</tr>
<tr>
<td>GELF</td>
<td>Groupe d’Etude des Lymphomes Folliculaires</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td>GLSG</td>
<td>German Low Grade Lymphoma Study Group</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>granulocyte macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>H-DLT</td>
<td>hematologic dose limiting toxicity</td>
</tr>
<tr>
<td>HDT</td>
<td>high dose chemotherapy</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>LDH</td>
<td>lactic dehydrogenase</td>
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<td>MCL</td>
<td>Mantle Cell Lymphoma</td>
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<td>MTD</td>
<td>maximum tolerated dose</td>
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<td>NCI</td>
<td>National Cancer Institute</td>
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<td>National Cancer Institute of Canada - Clinical Trials Group</td>
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<tr>
<td>NHL</td>
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<td>Primary Rituximab and Maintenance study</td>
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<tr>
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<tr>
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<td>serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>stable disease</td>
</tr>
<tr>
<td>SUSAR</td>
<td>suspected unexpected serious adverse events</td>
</tr>
<tr>
<td>TTP</td>
<td>time to progression</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VGPR</td>
<td>very good partial response</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
1. RESPONSIBILITIES

1.1. TITLE OF THE TRIAL

A PHASE Ib/II STUDY OF ESCALATING DOSES OF REVLIMID IN ASSOCIATION WITH R-CHOP (R2-CHOP) IN THE TREATMENT OF B-CELL LYMPHOMA.

1.2. SPONSOR AND PROGRAM COORDINATION CENTER

1.2.1. Sponsor

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Investigator Coordinator:

Pr Hervé TILLY

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The present protocol is supported by Celgene.
1.2.2. Program coordination center

GELARC : Groupe d’Etude des Lymphomes de l’Adulte - Recherche Clinique

Groupe d’Etude des Lymphomes de l’Adulte - Recherche Clinique

Centre Hospitalier Lyon Sud - Secteur Sainte Eugénie (Bâtiment 6D) - Chemin du Grand Revoyet - 69310 Pierre Bénite - France

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laurence.girard@gelarc.org marion.fournier@gelarc.org

1.2.3. Protocol writing committee

Corinne Haioun, Gilles Salles, Bertrand Coiffier, Vincent Ribrag, Hervé Tilly, Marion Fournier, Larissa Mege, Yvain Robreau.

1.3. INVESTIGATORS

Six GELA centers may include patients in the phase Ib of the study and twenty five in the phase II. Before any inclusion, each center must have been declared to the Ethical Committee / IRB and government according to each country procedures and have had the initiation visit. To be declared as a participating center, the principal investigator must have sent to the GELARC his curriculum vitae with the local number affiliation to the Conseil de l’Ordre des Médecins.

1.4. LABORATORY SITES

Laboratories used for hematological and biochemical tests and assays during the study are individual center laboratories. All the laboratories must provide their normal values and an updated accreditation for quality control.
2. BACKGROUND AND STUDY RATIONALE

2.1 B-CELL LYMPHOMAS AND FOLLICULAR LYMPHOMA

The incidence of non-Hodgkin's lymphoma (NHL) has been increasing worldwide during the last 40 years and accounts for 4% of all cancer diagnoses. An estimated 53,000 new cases are diagnosed annually in the United States (US) with a similar number estimated for the European Union (1). NHL arising from B-cells accounts for approximately 80% of cases. Although localized NHL does occur, most patients present with disseminated disease. This is true in approximately 90% of follicular lymphomas and 70% of diffuse lymphomas. Treatment for later stage indolent disease has varied considerably from watch and wait, through treatment with a single agent, a combination of agents, interferon, and antibody therapy. Although these treatments can result in increased survival in terms of years, more than 50% of patients with aggressive lymphomas and most patients with low-grade lymphomas are not cured (2).

Follicular lymphoma (FL) is a slowly growing cancer of the lymphatic system. In the WHO classification the histology is further classified into grade 1, 2 or 3 follicular lymphoma, depending on the percentage of large cells seen on high power field microscopy (3). Biologically FL is characterized in most of the cases by the presence of a t(14;18) translocation causing an over expression of the bcl-2 protein, which inhibits apoptosis of lymphoid cancer cells (4,5). The clinical course of indolent NHL is characterized by a cycle of relapse and remission. As the disease is incurable with the currently available treatment options, the majority of patients die after multiple remissions and subsequent relapses with the median survival in these patients being 6-10 years (6). Initial treatment with (immuno-) chemotherapy such as alkylating agents, prednisone, anthracycline, vinca alkaloids, purine analogues, associated with interferon or anti CD20 monoclonal antibodies such as rituximab is associated with a relatively high rate of clinical response, followed invariably by relapse (6,7,8). The duration of the response decreases with subsequent regimens. In 30 to 70% of the cases, follicular lymphoma eventually transforms to a high-grade lymphoma (6). Given the limitations of the currently available regimens, there is a high need to improve the clinical outcome of FL with new treatment options.

2.2. RITUXIMAB IN COMBINATION WITH CHOP (R-CHOP)

Several trials have demonstrated the efficacy of rituximab single agent therapy in indolent CD20+ B-cell NHL leading to the approval of the drug in the United States and Europe (7,8). Then, a number of phase II or randomized phase III studies have demonstrated the efficacy and safety of rituximab when added to various chemotherapy regimens for the first line treatment of FL without adding significant toxicity (9).

A Phase II trial of rituximab combined with CHOP chemotherapy was conducted in patients with low-grade/indolent CD20+ lymphoma (10). Forty patients with either untreated or relapsed low-grade/indolent NHL were enrolled in the study; 31 were previously untreated. In an intent-to-treat analysis, the objective response rate was 95% (38 of 40 patients); 22 patients (55%) experienced a CR and 16 patients (40%) had a partial response (PR). The toxicity of the treatment appeared to be comparable to that observed with CHOP alone.

The German Low Grade Lymphoma Study Group (GLSG) conducted a large, randomised Phase III study comparing rituximab plus CHOP (R-CHOP) to CHOP in previously untreated patients with follicular NHL (11). Responding patients underwent a second randomisation to different maintenance schedules with interferon-alpha or high dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT). Interim data demonstrated a high ORR with R-CHOP (97%, CR 21%) and CHOP (93%, CR 17%) with the differences not reaching statistical significances. Importantly, the median TTF was 31 months in the CHOP arm, but was not reached in the R-CHOP arm (p<0.007) demonstrating the superiority of the combined immunochemotherapy regimen.

Based on these data, R-CHOP has become a standard induction treatment for previously untreated patients with follicular lymphoma.


2.3 LENALIDOMIDE IN LYMPHOMA

Lenalidomide is approved in the US for treatment of multiple myeloma and it has demonstrated activity in a variety of hematological malignancies including B-cell lymphoma. Although the mechanism of action of lenalidomide remains under investigation several observed activities of IMIDs argue in favour of a potential interest in the treatment of B-cell lymphomas (12): they inhibit the proliferation of lymphoma cells in vitro, enhance cellular immunity and natural killer effector function by costimulating CD4+ and CD8+ cells, exert antiangiogenic effects in the tumor microenvironement and reduce endothelial cells migration. Furthermore, T-cell co-stimulation could increase antibody dependent cytotoxicity (ADCC) and potentialise cytotoxic action of rituximab.

A phase II study has confirmed the efficacy of lenalidomide in patients with refractory/relapsed B-cell aggressive lymphoma (12). Forty-nine patients with diffuse large-B cell lymphoma, grade 3 follicular lymphoma, mantle cell lymphoma or transformed lymphoma were treated with lenalidomide 25 mg orally once daily on days 1–21 of every 28 day cycle during 52 weeks. Seventeen patients (35%) exhibited an objective response (2 CR, 4 CRu and 11 PR), response were seen in each of the subtypes. Of the 5 patients with follicular lymphoma, 1 had a CRu and 2 a PR. The most common grade 3 and 4 adverse events were neutropenia (33%) and thrombocytopenia (20%), requiring a dose reduction in 16 patients. The ongoing median response duration was 6.2 months. Factors associated with good response to lenalidomide were a low tumor burden and a long interval since last rituximab treatment.

Preliminary results of a phase II study in patients with refractory/relapsed indolent lymphoma has been presented recently (13). Patients received 25 mg lenalidomide orally once daily on Days 1–21 every 28 days and continued therapy for 52 weeks as tolerated or until disease progression. Forty-three patients were enrolled in the study. Histology was small lymphocytic lymphoma [SLL] (n=18), follicular center lymphoma grades 1,2 [FCL] (n=22) and marginal B-cell lymphoma [NML] (n=3). Eleven patients (26%) exhibited an objective response (2 CR, 1 CRu and 8 PR). Responses were produced in SLL (4/18) and FCL (7/22). Most responses develop at more than 4 months. The median duration of response is >10 months. Fifteen patients (35%) exhibited Grade 3-4 neutropenia, and 7 grade 3-4 thrombocytopenia (16%).

An international study in refractory/relapsed aggressive non-hodgkin lymphoma is ongoing were the enrolment of 200 patients is planned. Early results (14) are consistent with those of the previous study.

2.4 LENALIDOMIDE IN ASSOCIATION WITH CHEMOTHERAPY

Lenalidomide is approved in the US and in Europe in combination with dexamethasone for the treatment of patients with multiple myeloma who had received at least one prior therapy (15). Several trials of lenalidomide in association with chemotherapy in the setting of multiple myeloma are now ongoing.

The NCIC CTG is conducting phase II testing to establish the tolerability and estimate the efficacy of combining lenalidomide (L) and melphalan (M) over multiple cycles for previously untreated patients with multiple myeloma who are ineligible for stem cell transplantation (16). The MY.11 trial was initially designed as a randomized phase II test of M 9 mg/m² given on days 1–4 (M9) plus either L 10 mg (L10) or 20 mg given on days 1–21 of a 28 day cycle. Primary prophylaxis with G-CSF was not included, but use of G-CSF for established neutropenia was permitted. A dose attenuation schedule was developed for neutropenia and/or thrombocytopenia that was severe and occurred during the administration of L or was persistent and caused a delay in the next treatment cycle. A hematologic dose limiting toxicity (H-DLT) was defined as the need for 2 dose attenuations of L or 1 dose attenuation of M. Prior to the randomized phase of the trial, a safety run-in phase testing M9+L10 in 6 patients was planned; closure of this arm was to occur if, during the first 3 treatment cycles, there were ≥3 H-DLTs or any non-hematologic serious adverse event (SAE) judged to be treatment related. Four of the planned 6 patients were entered; during their first 3 treatment cycles, each experienced a H-DLT and one died from sepsis. The study was therefore amended with the intent to conduct a randomized phase II test of M 4 mg/m² days 1–4 plus L 15 mg days 1–21 (M4L15) and M 6 mg/m² days 1–4 plus L 10 mg days 1–21 (M6L10). Prior to the randomized phase of testing, each regimen was tested in non-randomized safety run-ins that included 6 patients per arm. The same parameters as above for study arm closure were applied. If the M6L10 arm was closed, the trial would proceed to test M 5 mg/m² days 1–4 and L 10 mg days 1–21 (M5L10). Six patients were enrolled to M4L15; during their first 3 treatment cycles, 4 patients experienced H-DLTs related to severe or persistent grade 3–4 neutropenia and one other patient experienced an SAE related to hallucinations and multiple constitutional complaints. This arm was therefore closed to accrual. Six patients were enrolled to M6L10: during their first 3 treatment cycles, 3 patients experienced H-DLTs related to severe or persistent grade 3–4 neutropenia. One of these patients was hospitalized with pulmonary edema and another with febrile neutropenia. This arm was therefore closed and the MY.11 trial amended to proceed as a single-arm phase II testing M5L10. It was concluded that although M + L holds promise as an effective combination for previously untreated myeloma patients, the regimen was associated with
considerable myelosuppression. The efficacy of the combination when given at tolerable doses remains to be established.

The initial results from a phase II trial combining lenalidomide and low dose dexamethasone with cyclophosphamide (CRd) as initial therapy of newly diagnosed MM have been reported recently (17). The trial was initiated in July 2006 and completed the target accrual of 33 patients by July 2007. The treatment protocol consisted of lenalidomide given orally at a dose of 25 mg daily on days 1–21 of a 28-day cycle. Dexamethasone (dex) was given orally at a dose of 40 mg on days 1, 8, 15, and 22 of each cycle. Cyclophosphamide at a dose of 300 mg/m² was given on days 1, 8, and 15 of each cycle. Patients also received an aspirin once daily as thromboprophylaxis. The median age was 63 years (range, 44–79). At the time of analysis, 19 of the 33 patients are evaluable for confirmed responses. Of these, 2 achieved VGPR and 13 had a partial response giving an overall response rate of 79%. The response rate was affected by 5 of 19 patients who went off study within three cycles due to toxicities [interstitial nephritis (1 pt), multiple grade 3 toxicities including infection (1 pt) atrial fibrillation and infection (1 pt)] or alternative treatment [no response and possible renal toxicity (1 pt) and progression at 4 cycles (1 pt)]. Overall, hematological toxicity was the most common with grade 4 toxicity seen in 6 patients (20%). Non-hematological grade 3 or higher toxicities included fatigue (4 pts), thrombosis (3 pts) and renal failure (2 pts). One patient with thrombosis came off study for other toxicities, and the other two continued on study with anticoagulation. Thirteen patients (43%) had dose reductions of both cyclophosphamide and lenalidomide, most commonly due to hematological toxicity. So far, 12 patients have gone off study, 6 went to stem cell transplant, 3 due to adverse events, 1 due to disease progression and 2 patients went to alternate treatment. It was concluded that CRd has excellent activity in newly diagnosed myeloma with an estimated overall response rate of 79% but the initial use of a 300 mg/m² dose of cyclophosphamide resulted in 5 of the first 19 pts experiencing early toxicity and withdrawal. As a result, an expansion of the current trial is evaluating lower doses of cyclophosphamide (300 mg fixed dose).

A multicentre dose-finding phase I/II trial involving the RAD regimen (Revlimid, Adriamycin, Dexamethasone) has been conducted in patients with multiple myeloma (18). Myeloma patients were required to have adequate hematopoietic and organ function. RAD was administered for 6 28-day cycles along with either aspirin 100 mg/day or low-molecular-weight heparin for prophylaxis of venous thromboembolism. Phase I was a dose-escalating study with increasing doses of either lenalidomide (10–25 mg/day) or adriamycin (4–9 mg/m²/day). Using pegfilgrastim support (6 mg, day 6), the maximum tolerated dose was not reached, even at the 5th dose level (lenalidomide 25 mg d1–21; adriamycin 9 mg/m² as a 24h infusion d1–4; and dexamethasone 40 mg d1–4 and 17–20 of each 28-day cycle). This dose was next used in the ongoing phase II.

An experience of the association of lenalidomide with chemotherapy in solid tumors has been reported (19). This phase I trial of docetaxel and lenalidomide was undertaken to evaluate the maximal tolerated dose (MTD) for this combination. Patients with advanced solid tumors with adequate organ function were eligible. Lenalidomide was given orally days 1–14, and docetaxel was administered intravenously on day 1 of each 21-day cycle. DLT was defined as grade 3 or higher non-hematologic toxicity, grade 4 neutropenia with fever, and grade 4 anemia or thrombocytopenia. Nineteen patients, with tumor types including prostate (7), sarcoma (3), head and neck (2), pancreatic, colon, melanoma, adenocarcinoma of unknown primary, gastric, bladder, and GIST have been enrolled. A total of 64 cycles have been administered (range 1 to 12). In the first nine evaluable patients, eight (89%) had grade 3 or 4 neutropenia. Docetaxel 75 mg/m² given every 3 weeks with lenalidomide 5 mg on days 1–14 exceeded the MTD due to one grade 3 nausea/vomiting and one grade 4 neutropenia with fever. After the addition of pegfilgrastim on day 2, there has not been any neutropenia in the subsequent seven evaluable patients. Other grade 3 and 4 toxicities included leukopenia (31%), lymphopenia (19%), as well as nausea, vomiting, fatigue, anemia, infection, hyponatremia, and hypokalemia (6% each). Enrollment is still ongoing and the current dose level is docetaxel 75 mg/m², lenalidomide 10 mg days 1–14, and pegfilgrastim on day 2.

### 2.5 Lenalidomide in Association with Rituximab

It has been shown that lenalidomide enhanced natural cell mediated ADCC of rituximab on non-hodgkin lymphoma cell lines in vitro (20). The combination of lenalidomide with rituximab has been evaluated in a phase I/II study in patients with refractory/relapsed mantle cell lymphoma (21). Rituximab was administered by intravenous infusion weekly x 4 during one cycle and lenalidomide on days 1-21 of a 28-day cycle. The most common nonhematological adverse events reported included fatigue, pruritus, rash and non neutropenic infection. Grade 3-4 neutropenia occurred in 22 of 71 cycles of lenalidomide. Two DLT occurred in cycle 1 at 25mg of lenalidomide: one was characterised by hypercalcemia, hyperuricemia and renal insufficiency which resolved in 3 days and the second one was a grade 4 nonneutropenic fever with hypotension and sepsis resulting in patient death. The maximum tolerated dose of lenalidomide in association with rituximab was then estimated to be 20 mg daily.
2.6 RATIONALE FOR PERFORMING THE STUDY OF THE COMBINATION OF R-CHOP AND LENALIDOMIDE

There is a need for improvement of R-CHOP long term results in follicular lymphoma. Maintenance treatment with rituximab is currently investigated in the large phase III PRIMA study but results will not be available before two years. The combination of lenalidomide to standard immunochemotherapy will explore novel mechanisms of action. Data emerging from early clinical trials demonstrated that lenalidomide has a significant activity against B-cell lymphoma. It is therefore warranted to investigate the combination of lenalidomide with current treatment.

This trial is thus designed:
1) Phase Ib: To determine the recommended dose of lenalidomide in association with R-CHOP. As hematological toxicity is the main adverse event of both treatments, a growth factor support will be given to all patients.
2) Phase II: To assess the efficacy of the association of R-CHOP and the recommended dose of lenalidomide in a population of patients with follicular lymphoma as measured by the response rate at the end of treatment.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of the Phase Ib part of the study is to determine the recommended dose (RD) of lenalidomide (Revlimid) when administered in association with R-CHOP.

The primary objective of the Phase II part of the study is to assess the efficacy of the association of Revlimid and R-CHOP in a population of patients with follicular lymphoma as measured by the response rate at the end of treatment.

3.2. SECONDARY OBJECTIVES

The secondary objectives of this study are:
- To assess the safety of the association,
- To assess the efficacy of the association: overall response rate and complete response rate, progression free survival, response duration and overall survival.

4. STUDY DESIGN

This study is an open label, multicenter study with two phases:

The Phase Ib part of the study is a dose escalation study of lenalidomide (Revlimid) administered orally during 14 days in combination with fixed doses of rituximab (R), cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) administered every 3 weeks (R-CHOP 21) in patients with B-cell lymphoma.

The Phase II part of the study is an efficacy study of the association of the recommended dose of lenalidomide associated with R-CHOP in a selected population of patients with follicular lymphoma.

It is anticipated that approximately 30 patients will be enrolled for the Phase Ib part and 80 patients for the Phase II part.

Patients will be recruited approximately over 2,5 years and each patient will be followed during five years.

The total duration of the study is expected to be 8 years.
5. STUDY POPULATION

5.1. TARGET POPULATION

**Phase Ib:** Patients with one of the following B-cell Lymphoma, CD 20 positive:
- Mantle cell, Marginal zone, follicular
- Histological transformation from low grade to high grade
- Diffuse large B cell

**Phase II:** Patients with follicular lymphoma, CD 20 positive, WHO grade 1, 2 or 3a with at least one of the following signs requiring initiation of treatment:
- Bulky disease according to the GELF criteria: nodal or extra-nodal mass >7cm in its greater diameter
- B symptoms
- Elevated serum LDH or beta2-microglobulin
- Involvement of at least 3 nodal sites (each >3cm)
- Symptomatic spleen enlargement
- Compressive syndrome
- Pleural or peritoneal effusion

5.2. INCLUSION CRITERIA

Each subject must meet all of the following inclusion criteria during screening to be enrolled in the study:
- Aged from 18 to 70 years
- WHO performance status 0, 1 or 2
- Signed informed consent
- Life expectancy of \( \geq 90 \) days (3 months).
- Females of childbearing potential (FCBP)\(^\ddagger\) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL not more than 3 days from the start of study drug and must either commit to continued abstinence from heterosexual intercourse (and confirmed on a monthly basis) or begin one effective method of birth control, at least four weeks before she starts taking lenalidomide, and maintain that method throughout the entire duration of study drug therapy (including dose interruptions), and for four weeks after the end of study treatment with lenalidomide, even if she has amenorrhea. FCBP must also agree to pregnancy testing at least every three weeks and must be counseled at a minimum of every three weeks about pregnancy precautions and risks of fetal exposure.
- Men must agree not to father a child and agree to use a condom throughout study drug therapy, during any dose interruption, and for one week after cessation of study drug therapy, if their partner is pregnant or of child bearing potential. Men must also agree not to donate semen during study drug therapy and for one week after end of study drug therapy. Men must be counseled at a minimum of every 4 weeks about pregnancy precautions and risks of fetal exposure.
- All subjects must abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy.
- Agree not to share study drug with another person and to return all unused study drug to the investigator.

\(^\ddagger\) A female patient is considered to have childbearing potential unless she meets at least one of the following criteria 1) Age \( \geq 50 \) years and naturally amenorrhoeic for \( \geq 1 \) year (amenorrhoea following cancer therapy does not rule out childbearing potential); or 2) Premature ovarian failure confirmed by a specialist gynaecologist or 3) Previous bilateral salpingo-oophorectomy, or hysterectomy, or 4) XY genotype, turner syndrome, uterine agenesis.
5.3. EXCLUSION CRITERIA

Subjects meeting any of the following exclusion criteria are not allowed to be enrolled in the study:

- Previous treatment with chemotherapy except, for patients in phase Ib part:
  - Chlorambucil or Cyclophosphamide per os alone less than 6 months
  - Rituximab alone during less than three months, if stopped more than one year before inclusion
- Previous radiotherapy except if localized
- Other type of lymphomas: Burkitt, T cell, lymphocytic, CD 20 negative
- Central nervous system or meningeal involvement
- Contraindication to any drug contained in the chemotherapy regimen
- HIV disease, active hepatitis B or C
- Any serious active disease or co-morbid medical condition (according to investigator’s decision)
- Any of the following laboratory abnormalities.
  - Absolute neutrophil count (ANC) < 1,500 cells/mm³ (1.5 x 10⁹/L).
  - Platelet count < 100,000/mm³ (100 x 10⁹/L).
  - Serum SGOT/AST or SGPT/ALT > 5.0 x upper limit of normal (ULN).
  - Serum total bilirubin > 2.0 mg/dL (34 µmol/L), except in case of hemolytic anemia.
- Calculated creatinine clearance (Cockcroft-Gault formula) of < 50 mL/min
- Prior history of malignancies other than lymphoma unless the subject has been free of the disease for > 5 years, except for cured basal cell carcinoma (surgery) or cured carcinoma in situ of the cervix (surgery).
- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
- Pregnant or lactating females.
- Prior ≥ Grade 3 allergic reaction/hypersensitivity to thalidomide.
- Prior ≥ Grade 3 rash or any desquamating (blistering) rash while taking thalidomide.
- Subjects with ≥ Grade 2 neuropathy.
- Prior use of lenalidomide.
- Use of any standard or experimental anti-cancer drug therapy within 28 days of the initiation (Day 1) of study drug therapy.

6. STUDY TREATMENT

6.1. REVLIMID™: DESCRIPTION, STORAGE AND HANDLING

See Investigator Brochure.

6.2. TREATMENT SCHEDULE AND DESIGN

Study drug will be administered only to eligible subjects under the supervision of the investigator or identified sub-investigator(s). Subjects will normally be treated on an outpatient basis. The subject should be considered clinically stable by the investigator before discharge from the treatment facility.

6.2.1. Treatment in Phase Ib part:

All patients will be treated with R2-CHOP at a three-week interval for 6 cycles.

<table>
<thead>
<tr>
<th>R2-CHOP</th>
<th>Dose (mg/m²)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCLOPHOSPHAMIDE</td>
<td>IV 750</td>
<td>1</td>
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</tbody>
</table>
DOXORUBICINE IV 50 1
VINCRISTINE IV 1.4 (max 2 mg) 1
PREDNISONE PO 40 1 to 5
RITUXIMAB CI 375 1
LENALIDOMIDE PO See dose levels table 1 to 14

Patients with diffuse large B-cell lymphoma and an international prognostic index >1 will be given intrathecal methotrexate, 15 mg, at day 1 of the first four cycles.

Dose-levels of lenalidomide are defined as follows:

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Days of treatment</th>
<th>Lenalidomide Dose</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>D1 to D14</td>
<td>2.5 mg</td>
<td>0-6</td>
</tr>
<tr>
<td>1</td>
<td>D1 to D14</td>
<td>5 mg</td>
<td>3-6</td>
</tr>
<tr>
<td>2</td>
<td>D1 to D14</td>
<td>10 mg</td>
<td>3-6</td>
</tr>
<tr>
<td>3</td>
<td>D1 to D14</td>
<td>15 mg</td>
<td>3-6</td>
</tr>
<tr>
<td>4</td>
<td>D1 to D14</td>
<td>20 mg</td>
<td>3-6</td>
</tr>
<tr>
<td>5</td>
<td>D1 to D14</td>
<td>25 mg</td>
<td>3-6</td>
</tr>
</tbody>
</table>

Expansion group: D1 to D14
Recommended dose: Up to 12 patients

Dose escalation rules:
Dose escalation will begin at dose level 1. Dose escalation will be decided depending on the number of Dose Limiting Toxicities (DLTs) observed during the administration of the first 2 cycles of R2-CHOP.

<table>
<thead>
<tr>
<th>Number of patients with DLT at a given dose level</th>
<th>Rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 of first 3</td>
<td>Enter at least 3 patients at the next dose level.</td>
</tr>
<tr>
<td>1 out of 3</td>
<td>Enter up to 6 patients at this dose level. If 0 of the 3 additional patients experience DLT, then proceed to the next dose level. If 1 or more of 3 additional patients experience DLT, then dose escalation will be stopped. Three (3) additional patients will be entered at the previous dose level if 3 patients were treated at that dose.</td>
</tr>
<tr>
<td>≥ 2</td>
<td>Dose escalation will be stopped. Three (3) additional patients will be entered at the previous dose level if 3 patients were treated at that dose.</td>
</tr>
</tbody>
</table>

At level 5, if no DLT is observed on the first three patients or if only one DLT is observed on the first six patients, the group is expanded up to twelve patients and level 5 is the recommended dose.

DLT definition
DLT is defined as any of the following events (toxicity):
- Grade $\geq 3$ non hematological toxicity,
- Grade 3 hematological toxicity lasting more than 7 days,
- Grade 4 hematological toxicity lasting more than 3 days.

The recommended dose will be the dose level just below the MTD.
The recommended dose level will be completed to include a total of 12 patients.

### 6.2.2. Treatment in Phase II part:
All patients will be treated with R2-CHOP at a three-week interval for 6 cycles, then with Rituximab for two cycles.

<table>
<thead>
<tr>
<th>R2-CHOP</th>
<th>Dose (mg/m²)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCLOPHOSPHAMIDE</td>
<td>IV 750</td>
<td>1</td>
</tr>
<tr>
<td>DOXORUBICINE</td>
<td>IV 50</td>
<td>1</td>
</tr>
<tr>
<td>VINCRIStINE</td>
<td>IV 1,4 (max 2 mg)</td>
<td>1</td>
</tr>
<tr>
<td>PREDNISONE</td>
<td>PO 40</td>
<td>1 to 5</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>CI 375</td>
<td>1</td>
</tr>
<tr>
<td>LENALIDomIDE</td>
<td>PO 25 mg</td>
<td>1 to 14</td>
</tr>
</tbody>
</table>

Patients who achieve CR/Cru/PR at evaluation after 6 cycles of R2-CHOP and 2 rituximab will receive maintenance according to the PRIMA scheme with rituximab every two months during two years.

### 6.3. Prophylactic measures

#### 6.3.1. Prophylactic measures
Subjects should receive tumor lysis prophylaxis:
- Allopurinol 300mg/d for 3 days prior to initiating lenalidomide treatment and for a minimum of the first 3 cycles,
- Oral hydration (approximately 2.5L) for the first 7 days of each cycle (hydration should be adjusted according to age and clinical status).

Pegfilgrastim will be given at D4 of each cycle at the dose of 6mg.

All subjects will be required to take a daily aspirin (100 mg) for deep vein thrombosis (DVT) prophylaxis during study period. Subjects who are unable to tolerate aspirin and subjects with prior history of DVT or at high risk should receive low molecular weight heparin therapy or warfarin (Coumadin) treatment.

A prophylaxis of pneumocystis carinii pneumonia, according to local usage, is highly recommended during study and until three months after last cycle administration.

A dosage of digoxinemia will be performed for all patients who will receive digoxin concomitantly with Revlimid.

#### 6.3.2. Pregnancy prevention
Safety advice for women of childbearing potential:
- The need to avoid foetal exposure
- Need for effective contraception (even if woman has amenorrhoea) (See below #)
  - At least 4 weeks before commencing treatment
  - During lenalidomide treatment, including any dose interruption
- At least 4 weeks after finishing lenalidomide treatment
  - Pregnancy test regime
    - In the 3 days before commencing treatment
    - During lenalidomide treatment at least every 3 weeks except in case of confirmed tubal sterilization.
    - After finishing lenalidomide treatment and 4 weeks after the end of lenalidomide treatment
  - Need to stop Revlimid immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy

(#) The following are effective methods of contraception
  - Implant
  - Levonorgestrel-releasing intrauterine system (IUS)
  - Medroxyprogesterone acetate depot
  - Tubal sterilisation
  - Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
  - Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

Safety advice for men:
- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or of childbearing potential (even if man has had a vasectomy)
  - During Revlimid treatment
  - For four weeks following final dose
- That the patient should not donate semen
  - During Revlimid treatment
  - For one week finishing treatment
- That if his partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid he should inform his treating doctor immediately.

Requirements in the event of pregnancy:
- Instructions to stop Revlimid immediately upon suspicion of pregnancy
- Need to refer to an obstetrician/gynaecologist experienced in reproductive toxicity and its diagnosis for evaluation and counselling.

6.4. TREATMENT ASSIGNMENT

Patient eligibility must be verified by the investigator and each eligible patient must be registered by faxing the study screening CRF page to the GELARC prior to the start of study treatment. A written confirmation of each eligible patient’s identification number and, for phase I_B part, treatment dose level, will then be forwarded to the investigator. A copy will be kept in the patient’s records.

During the phase I_B part of the study, periodical phone conferences will be organized between site investigators, coordinating investigator and study coordinator in order to check for possible DLT and to decide dose level allocation.
6.5. DOSE MODIFICATION

**Phase Ia:**
In case of DLT, Revlimid will be definitively stopped.

There is no dose adjustment related to hematological toxicity. However, in the case where cytopenia (absolute neutrophil count < 1,500 cells/mm³ (1.5 x 10⁹/L) or Platelet count < 100,000/mm³ (100 x 10⁹/L)) is observed at day 21, the next cycle will be postponed for 3 days. In the case of cytopenia persists on day 24, the next cycle will be postponed for 3-4 additional days. Persisting cytopenia at day 35 will be considered as an unacceptable toxicity.

In case of grade 1 neurological toxicity related to vincristine (sensory or motor neuropathy, constipation, visual or auditory changes), the dose will be reduced to 1 mg by cycle. If the neurological toxicity increased despite of dose reduced, vincristine will be definitively stopped.

**Phase II:**
There is no dose adjustment of CHOP components related to hematological toxicity. However, in the case where cytopenia (absolute neutrophil count < 1,500 cells/mm³ (1.5 x 10⁹/L) or Platelet count < 100,000/mm³ (100 x 10⁹/L)) is observed at day 21, the next cycle will be postponed for 3 days. In the case of cytopenia persists on day 24, the next cycle will be postponed for 3-4 additional days.

In case of grade 1 neurological toxicity related to vincristine (sensory or motor neuropathy, constipation, visual or auditory changes), the dose will be reduced to 1 mg by cycle. If the neurological toxicity increased despite of dose reduced, vincristine will be definitively stopped.

The lenalidomide dosing should be reduced in case of related toxicities defined as follow:
- Grade 3 hematological toxicity (neutrophils and/or platelets) lasting more than 7 days,
- Grade 4 hematological toxicity (neutrophils and/or platelets) lasting more than 3 days,
- Creatinine clearance between 30 and 50 mL/min,
- Neurological toxicity > grade 2,
- Any other toxicity ≥ grade 3 except for alopecia and for ALT and Bilirubin (see below specific guidelines),
- Cycle of R2-CHOP postponed for 7 days or more because of toxicity.

Lenalidomide will be temporarily stopped for the current cycle and dose of lenalidomide will be reduced as follow:

- 25mg
- 20mg
- 15mg
- Permanently stopped

If a patient has had dose reduction, then dose re-escalation of lenalidomide is not permitted at any time.

If ALT > 5 x ULN or Total bilirubin > 3 x ULN, Lenalidomide will be temporarily stopped for the current cycle. Then, at next cycle:
- if recovery from the event: dose of lenalidomide will be the same,
- if no, lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. If the values do not return to baseline within the two next cycles, lenalidomide dose should be discontinued.

If creatinine clearance <30 mL/min, lenalidomide must be definitely stopped).

In case of DVT occurrence, antithrombotic treatment (heparin or coumadin [INR 2-3] must be started (and kept during the whole treatment duration with lenalidomide) and lenalidomide can be resumed without dose reduction.

6.6. CONCOMITANT MEDICATION

All patient treatments 8 days prior to study treatment, at any time during the study, and up to 30 days after the end of the study treatment will be considered as concomitant treatments. Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient’s welfare and are unlikely to interfere with the investigational products, they may be given at the discretion of the investigator and recorded in the case report form.

The following concomitant treatments are permitted during this study treatment:

- All supportive measures (including blood transfusions) consistent with optimal patient care will be given throughout the study and should be documented in the CRF.
- Medications for chronic pain management, including narcotic analgesics, are permitted as clinically indicated.

The following concomitant treatments are not permitted during this study treatment:

- Systemic anticancer agents other than study drugs.
- Other investigational therapies or devices.
- Concomitant radiotherapy.

If a patient’s clinical status requires administration of a prohibited concomitant medication or treatment, then administration of study drugs should be stopped, and the patient will be withdrawn from the study. The change in clinical status mandating the use of the medication in question must be reported as the reason for study drug discontinuation.

6.7. DRUGS DISPENSATION AND ACCOUNTABILITY

6.7.1. Revlimid

Celgene Corporation will supply lenalidomide capsules in 2.5 mg, 5 mg and 10 mg strengths. The bottles containing capsules will be labelled according to the Good Manufacturing Practice guidelines and the local requirements. Bottles will be labelled as follows:

- Sponsor’s name, address,
- Protocol/Study number, Eudract number,
- Lenalidomide: dosage, number of capsules,
- Batch number, expiry date,
- Subject identification,
- Date of dispensed,
- Investigator name and phone number,
- Storage conditions, directions for use and regulatory mentions.
All drug packages are to be inspected upon receipt at the study site prior to being drawn up. If any particulate matter is detected, the bottle is not to be used. Damaged bottles are to be reported to the sponsor and stored until instructions have been given.

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product (Revlimid) will be responsible for ensuring that the Investigational Product used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements. All Investigational Product must be stored in accordance with labelling and shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained. Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pertaining documentation, labelling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure. Under no circumstances will the Investigator supply Investigational Product to a third party, allow the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

All partially used or unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned Investigational Product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team. The Investigator will not destroy the unused Investigational Product unless the Sponsor provides written authorization. A potential defect in the quality of Investigational Product may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational product. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments dispensed and used for each patient. The study monitor will periodically check the supplies of investigational products held by the investigator or pharmacist to verify accountability of all investigational products used. All unused investigational products and all medication containers will be returned to the Sponsor unless other arrangements have been approved by the Sponsor. The Sponsor will verify that a final report of drug accountability to the unit dose level is prepared and maintained in the investigator study file. Administration of the study treatment will be supervised by the investigator or subinvestigator.

6.7.2. R-CHOP and R

Each individual site will be responsible for obtaining commercially available rituximab, doxorubicin, cyclophosphamide, vincristine and prednisone. The local pharmacist will record the lot numbers, brand name and expiration dates of the dispensed products to allow drug accountability.

7. STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS AND PROCEDURES

7.1. STUDY FLOW CHART

See Appendix 17.1.

7.2. SCREENING EXAMINATION AND SELECTION PROCEDURES

See Appendix 17.2.

The subject will be required to give written informed consent to participate in this study before any non routine screening tests or evaluations are conducted.

The inclusion and exclusion criteria (see section 5.2 and 5.3) will be assessed during the screening period. Subjects must continue to meet all eligibility criteria on Day 1 of Cycle 1.
The following assessments must be conducted during the screening period (up to 14 days before first dose of study drug):

- Subject demographics including at least birth date and sex.
- Complete relevant medical history including complete lymphoma history.
- Concomitant medication assessment.
- ECOG Performance Status (see Appendix 17.6).
- Weight, height, body surface area (BSA – see Appendix 17.5)
- Pulse, blood pressure, body temperature,
- Physical examination.
- Biochemical tests: calcium, sodium, potassium, glucose, albumin, creatinine, LDH, ALT, AST, total bilirubin, alkaline phosphatase.
- Serum β-human chorionic gonadotropin (β-hCG) pregnancy test (sensitivity ≥ 25 mUI) for female subjects (not required for post-menopausal or surgically sterilized women).
- Bone marrow aspirate and biopsy (up to 56 days before first dose of study drug).
- Chest, abdomen and pelvis CT scan with oral and IV contrast and PET-scan (up to 28 days before first dose of study drug). The scans may be performed with oral contrast only, if a subject is allergic to IV contrast agents.
- Any other evaluations or procedures required to assess baseline disease for other sites of disease will be performed (cerebral CT scan if clinically indicated) (up to 28 days before first dose of study drug).
- Complete blood cell counts.
- Stage and extent of the current disease according to the American Joint Committee on Cancer Non Hodgkin’s Lymphoma (AJCC – see Appendix 17.4) (35).

7.3. STUDY EVALUATION DURING TREATMENT PHASE

The following assessments must be conducted during the treatment period (See Appendix 17.2):

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight and body surface area (BSA - see Appendix 17.5)</td>
<td>Day 1 of each cycle</td>
</tr>
<tr>
<td>Pulse, blood pressure, body temperature</td>
<td>Day 1 of each cycle</td>
</tr>
<tr>
<td></td>
<td>During cycle 1 and 2 of phase Ia: day 7 and 10, continued every two days (± 1 day) until the absolute neutrophil count reach 1.5 x 10^9/L and platelet count reach 100 x 10^9/L.</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Day 1 of each cycle</td>
</tr>
<tr>
<td></td>
<td>During cycle 1 and 2 of phase Ia: day 7 and 10, continued every two days (± 1 day) until the absolute neutrophil count reach 1.5 x 10^9/L and platelet count reach 100 x 10^9/L.</td>
</tr>
<tr>
<td>ECOG PS (see Appendix 17.6)</td>
<td>Day 1 of each cycle</td>
</tr>
<tr>
<td></td>
<td>During cycle 1 and 2 of phase Ia: day 7 and 10, continued every two days (± 1 day) until the absolute neutrophil count reach 1.5 x 10^9/L and platelet count reach 100 x 10^9/L.</td>
</tr>
<tr>
<td>Biochemical tests: calcium, sodium, potassium, glucose, albumin, creatinine, LDH, ALT, AST, total bilirubin alkaline phosphatase</td>
<td>Day 1 of each cycle</td>
</tr>
<tr>
<td>Complete blood cell counts</td>
<td>Days 1, 7, 10 and 14 of each cycle.</td>
</tr>
</tbody>
</table>
During cycle 1 and 2 of phase Ib: continued every two days (± 1 day) until the absolute neutrophil count reach 1.5 x 10⁹/L and platelet count reach 100 x 10⁹/L.

<table>
<thead>
<tr>
<th>Task</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>The adverse events must be reported and followed during the entire treatment period (until end of treatment evaluation)</td>
<td>AE reported and followed during the entire treatment phase</td>
</tr>
<tr>
<td>Bone marrow aspirate and biopsy to confirm an initial documentation of CR or CRu in subjects with a positive bone marrow result at screening</td>
<td>From day 14 through 21 of cycle 4</td>
</tr>
<tr>
<td>Chest, abdomen and pelvis CT with oral and IV contrast and PET-scan. Disease response assessment results must be available and reviewed by the investigator before the first dose of study drug in the next planned cycle</td>
<td>From day 14 through 21 of cycle 4</td>
</tr>
<tr>
<td>Evaluation of the disease response (Cheson et al., 1999)</td>
<td>From day 14 through 21 of cycle 4</td>
</tr>
<tr>
<td>Serum β-human chorionic gonadotropin (β-hCG) pregnancy test (sensitivity ≥ 25 mUI) for female subjects (not required for post-menopausal or surgically sterilized women)</td>
<td>Day 1 of each cycle or at least every 28 days in case of postponed cycle.</td>
</tr>
<tr>
<td>Any other evaluations or procedures performed at baseline for evaluation of the disease response</td>
<td>From day 14 through 21 of cycle 4</td>
</tr>
</tbody>
</table>

Patients with at least Stable disease at the interim evaluation visit (after 12 weeks of treatment) will pursue the treatment period.

### 7.4. END OF TREATMENT STUDY EVALUATIONS

The following assessments must be conducted 30 days after the last treatment administration of cycle 8 (See Appendix 17.2):

- Weight and body surface area (BSA - see Appendix 17.5).
- Pulse, blood pressure, body temperature.
- Physical examination.
- ECOG PS.
- Biochemical tests: calcium, sodium, potassium, glucose, albumin, creatinine, LDH, ALT, AST, total bilirubin, alkaline phosphatase.
- Complete blood cell counts.
- Bone marrow aspirate and biopsy to confirm an initial documentation of CR or CRu in subjects with a positive bone marrow result at screening (assessment not required for patients with already cleared bone marrow at previous evaluation).
- Chest, abdomen and pelvis CT scan with oral and IV contrast and PET-scan.
- Evaluation of the disease response according to IWCR 1999 (Cheson et al., 1999).
- Any other evaluations or procedures performed at baseline for evaluation of the disease response.
- Serum β-human chorionic gonadotropin (β-hCG) pregnancy test (sensitivity ≥ 25 mUI) for female subjects (not required for post-menopausal or surgically sterilized women).
- Adverse events.

In case of premature withdrawal during the study treatment period, the evaluation should be performed 30 days after the last drug administration or before any new treatment start date.
Toxicities (see section 9) must be reported during the study period up to 90 days after the last drug administration.

### 7.5. Study Evaluation during Post-treatment Phase

The following assessments must be conducted at each follow-up visit every 2 months during two years until all required data for final analysis are collected (See Appendix 17.2):

- Weight.
- Pulse, blood pressure, body temperature.
- Physical examination.
- ECOG PS (see Appendix 17.6).
- Biochemical tests: calcium, sodium, potassium, glucose, albumin, creatinine, LDH, ALT, AST, total bilirubin, alkaline phosphatase.
- Complete Blood cell counts.
- Bone marrow aspirate and biopsy if clinically indicated.
- Chest, abdomen and pelvis CT with oral and IV contrast (every 6 months)
- Evaluation of the disease response (Cheson et al., 1999).
- Any other evaluations or procedures performed at baseline for evaluation of the disease response (every 6 months).
- Adverse events.

The following assessments must be conducted at each follow-up visit every 6 months during the next three years until all required data for final analysis are collected (See Appendix 17.2):

- Weight.
- Pulse, blood pressure, body temperature.
- Physical examination.
- ECOG PS (see Appendix 17.6).
- Biochemical tests: calcium, sodium, potassium, glucose, albumin, creatinine, LDH, ALT, AST, total bilirubin, alkaline phosphatase.
- Complete Blood cell counts.
- Bone marrow aspirate and biopsy if clinically indicated.
- Chest, abdomen and pelvis CT with oral and IV contrast (every 12 months)
- Evaluation of the disease response (Cheson et al., 1999).
- Any other evaluations or procedures performed at baseline for evaluation of the disease response (every 12 months).
- Adverse events.

### 8. Study Procedures

#### 8.1. Informed Consent

Written informed consent in compliance with local regulatory authority will be obtained from each subject prior to entering the trial or prior to performing any unusual or non-routine procedure that involves any risk to the subject in the purpose of evaluating the subject of the study.
The patient and the investigator will date and sign the informed consent form, and the GELARC will be notified of the investigator’s request to register the patient for the study.

The investigator shall provide a copy of the signed consent to the study patient, a copy shall be maintained in the investigator’s study file. For French subjects only, a copy of the signed consent form will be recovered by the sponsor in a sealed envelop.

8.2. INCLUSION PROCEDURE

A patient will be registered after verification of eligibility directly on the data capture system 24 hours a day, 7 days a week by the investigators through the internet network with the following address http://csonline.gela.org. To access the interactive registration program, the investigator needs to record the study name, a username and a password. Alternatively registration can be done by fax to the Gelarc from 9 am to 5 pm (GMT+1) from Monday through Friday, and the study site will receive back the inclusion number for the included patient.

This must be done before the start of the protocol treatment.

Internet: http://csonline.gela.org
Fax: + 33 4 72 66 93 71

The GELARC coordination center will be the contact by phone for any request: + 33 4 72 66 93 33.

The investigator should fax to the coordination center the following documents whatever the registration way used: inclusion and exclusion criteria checked, and a copy of the Pathology report.

8.3. PATHOLOGICAL REVIEW

The process of tissue review will be organized by the GELA-Pathology Institute according to procedures commonly used in the clinical trials of the GELA:

Centralized collection of the tumor material in the GELA Pathology Institute (GELA-P), located at Hôpital Henri Mondor, Créteil (Sce d’Anatomie et Cytologie Pathologiques). The request of the tumor tissue will be done by the GELA-P project manager after inclusion of the patient and receipt of a copy of the pathology report (by Fax) indicating the reference number of the report.

Tissue microarray (TMA) construction: For tissue microarray construction, a slide stained with hematoxylin and eosin will be prepared from each formalin-fixed paraffin donor block, and three tissue cylinders representative of tumor regions with a diameter of 0.6 mm will be punched and transferred into a recipient paraffin block using a manual tissue arrayer (Beecher Instruments). Reactive lymphoid tissues will be also included in the TMA blocks, as controls. Therefore, two twins TMA blocks will be prepared, according to procedures used in the GELA-P.

Review process: For the review process, routinely stained (hematoxylin-eosin, Giemsa) sections will be obtained and an appropriate panel of antibodies according to morphological aspects will be applied; a review of the case will be organized by a Pathology Panel comprising at least 2 expert hematopathologists.

Study of biomarkers: some biomarkers could be studied on pathological tissue according to ancillary studies.

When the review process is achieved, with establishment of the Tissue Array, the remaining material is sent back to the initial pathologist, by appropriate secured mail. The Pathology Panel will establish a report sent to the initial pathologist and the investigator of the inclusion center.

8.4. PET-SCAN REVIEW

The PET-scans will be centrally assessed to confirm disease responses at the interim evaluation and at the end of treatment evaluation.
8.5. INDEPENDENT DATA SAFETY MONITORING COMMITTEE

A data safety monitoring committee (DSMC), including at least three independent members will be established. The DSMC will meet periodically to review the safety data from the trial prepared by the statistical coordinator. The DSMC will specifically meet to study the results of the main cut-off analysis of phase I B in order to confirm the recommended dose of lenalidomide to be used in the phase II part and to allow the initiation of this part. All data presented at the meeting will be considered confidential.

During the phase II part of the study, all second malignancies cases occurred in the study will be submitted to the Remarc study DSMC (eudract number 2008-008202-52). Every 6 months, the DSMC will decide on further study in view of these data.

Following each meeting the DSMC will prepare a report and may recommend changes in the conduct of the trial. The sponsor will notify Celgene of any decision on the conduct of the study and specify the decisions on the recommended dose for the phase II.

9. SAFETY PARAMETERS

9.1. DEFINITIONS

9.1.1. Adverse Events

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

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

9.1.2. Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death or
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) or
- Requires in-patient hospitalization or prolongation of existing hospitalization or
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect or
- Is medically significant according to investigator’s decision.

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

Hospitalizations for previously planned procedure or convenience will not be considered as reportable SAE if reported in the patient’s medical record.

9.1.3. Intensity

The intensity of the event will be graded according to the CTCAE grading system v3.0 (see Investigator’s file or online at http://ctep.cancer.gov/reporting/ctc.html) in the toxicity categories that have recommended grading.

Adverse events not listed on this grading system will be graded according to the four-point system below:

- Mild (grade 1) — Discomfort noticed but no disruption of normal daily activity
9.2. ADVERSE EVENTS REPORTING

All adverse events (AE) occurring from the date of informed consent signature to end of treatment evaluation will be recorded in the AE pages of the CRF as defined below:

- Planned hospital admissions or surgical procedures for an illness or disease which existed before the subject was enrolled in the study or before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).
- Adverse events (serious or not) will not be recorded after new treatment administration, including maintenance.
- Only Grade 3 or 4 toxicities or grade 2 for infections (CTCAE Common Terminology Criteria for Adverse Events – version 3.0) must be reported as “Adverse Event” in the appropriate CRF pages.
- Any episode of any grade of toxicities, related to a Serious Adverse Event as described in section 9.3, must be reported as “Adverse Event” in the appropriate CRF pages.
- Disease progression and events related to lymphoma manifestation are not reported as “Adverse Event”.
- “Alopecia” toxicity (any grade) will never be reported as “Adverse event”.

The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapies given, outcome of all adverse events and his opinion as to whether the adverse event can be related to the studied drug REVLIMID and to R-CHOP.

9.3. SERIOUS ADVERSE EVENTS REPORTING

All defined Serious Adverse Events (SAEs), whether or not ascribed to the study, will be recorded in the Serious Adverse Event pages from the date of informed consent signature to the end of treatment evaluation.

A serious adverse event occurring during the study or which comes to the attention of the investigator within 3 months after stopping the Revlimid, whether considered treatment-related or not, must be reported. A serious adverse event that occurs after this time, including during the follow-up period, if considered related to the study medication (Revlimid), should be reported.

- Disease progression and events related to lymphoma manifestation are not reported as “Serious Adverse Event”.
- Adverse event (serious or not) will not be recorded after new treatment administration.
- Planned hospital admissions or surgical procedures for an illness or disease which existed before the subject was enrolled in the study or before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).

**Secondary malignancies:*

Second malignancies must be reported as serious adverse event regardless of when they occur and regardless of their relationship to study treatments/procedures.
For serious adverse events, the following must be assessed: relationship to test substance (Revlimid), action taken, and outcome to date. The causality is initially assessed by the investigator. For serious adverse events, causality can be one of two possibilities:

- Unrelated: An adverse event which is not related to the use of the drug.
- Related: An adverse event which might be due to the use of the drug.

All serious adverse events (SAE) must be reported to the GELARC by fax within 24 hours of the initial observation of the event. It is a legal requirement to report serious adverse events.

All serious adverse events must also be reported on the Adverse Event page of the CRF. All details should be documented on the specified Serious Adverse Event form.

Initial reports must be followed up by a complete report within a further 10 calendar days and sent to GELARC.

**PLEASE SEND THE REPORTS TO GELARC: FAX NUMBER +33(0) 3 59 11 01 86.**

**ALL Forms must be dated and signed by the responsible investigator or one of his/her authorized staff Members.**

Feel free to join any anonymous copy of pertinent results, exams or reports related to the serious event.

The GELARC pharmacovigilance desk will decide of the expected or unexpected nature of this event. An unexpected adverse event is one of which the nature or severity is not consistent with the applicable product information (Investigator Brochure). Suspected unexpected serious adverse events (SUSARs) will be reported to the Health Authorities and Ethics Committees within 7 days for fatal or life-threatening events and within 15 days for other serious adverse events.

The GELARC pharmacovigilance desk will write and notify the annual Safety Reports to the Health Authorities and Ethics Committees.

The GELARC pharmacovigilance desk will send to Celgene a duplicate of each serious adverse event as they occur and will also provide Celgene with a copy of the Annual Safety Report.

### 9.4. FOLLOW UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All adverse events must be documented and followed up until the event is either resolved or adequately explained, even after the subject has completed his/her study treatment, excepted unrelated or moderate events that must be followed for 30 days after the last study drug administration.

Severe, life-threatening or related events must be followed until the resolution, the patient’s death, the start of a new cancer therapy or the relationship is re-assessed.

All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Any additional information known after the event has been initially reported should be sent to the GELARC as information becomes available.

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

### 9.5. MANAGEMENT OF PREGNANCIES OCCURRING ON STUDY

**Female of Childbearing potential:**

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while subjects are on study drug or within 4 weeks after a subject’s last dose of study drug must be reported to the investigator and the Ethics Committee immediately. The continuation of the treatment will be decided by the investigator in consultation with the Ethics Committee.

Pregnancies and suspected pregnancies of a male subject must be reported to the investigator and the Ethics Committee immediately. The continuation of the treatment will be decided by the investigator in consultation with the Ethics Committee.

**All Forms must be dated and signed by the responsible investigator or one of his/her authorized staff Members.**

Feel free to join any anonymous copy of pertinent results, exams or reports related to the serious event.

The GELARC pharmacovigilance desk will decide of the expected or unexpected nature of this event. An unexpected adverse event is one of which the nature or severity is not consistent with the applicable product information (Investigator Brochure). Suspected unexpected serious adverse events (SUSARs) will be reported to the Health Authorities and Ethics Committees within 7 days for fatal or life-threatening events and within 15 days for other serious adverse events.

The GELARC pharmacovigilance desk will write and notify the annual Safety Reports to the Health Authorities and Ethics Committees.

The GELARC pharmacovigilance desk will send to Celgene a duplicate of each serious adverse event as they occur and will also provide Celgene with a copy of the Annual Safety Report.
drug (lenalidomide) are considered events to be reported immediately to Sponsor or duly assigned designee. If the subject is on study drug, the study drug is to be discontinued immediately and the subject is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test, must be reported to the sponsor or duly assigned designee immediately of the Investigator’s knowledge of the pregnancy by phone and facsimile using the SAE Form.

**GELARC Fax Number: +33(0) 3 59 11 01 86.**

The female should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify the sponsor or duly assigned designee of the outcome of the pregnancy (including notification of false-positive tests) immediately. The Investigator will provide this information as a follow-up to the initial report by fax.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted foetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should follow the procedures for reporting SAEs.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects related to the in-utero exposure to the study drug should also be reported immediately. An SAE report should be addressed by fax to the sponsor or duly assigned designee.

If the female is found not to be pregnant, any determination regarding the subject’s continued participation in the study will be determined by the Investigator.

The sponsor or duly assigned designee must report to Celgene the pregnancy, its follow-up and outcomes, immediately of its knowledge by phone and facsimile using the SAE Form (if any technical issues with Celgene France, please report immediately to Celgene Drug Safety in the US by email at drugsafety@celgene.com or by phone at +1 800 640 7854).

**Male Subjects:**

Female partners of males taking investigational lenalidomide should be advised to call their healthcare provider immediately if they get pregnant. The male subject should notify the investigator of his partner’s pregnancy and her healthcare provider information. The investigator will then provide the information to the sponsor or duly assigned designee for follow-up as necessary.

10. CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

10.1. WITHDRAWAL OF SUBJECTS

Circumstances that lead to premature withdrawal of a subject from the trial must be clearly reported by the investigator on the appropriate CRF page.

Criteria for subject withdrawal include (but are not limited to):

- death,
- disease progression
- initiation of alternate anti-neoplastic therapy,
- toxicity,
- intercurrent illness,
- non compliance (including loss of subject to follow-up),
- voluntary withdrawal,
- voluntary cessation of treatment,
- failure to meet the eligibility criteria.
Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study or to stop the treatment, he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed (30 days after last drug administration for the “End of study” visit – see Section 6.4).

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

Subjects who are withdrawn from the study will not be replaced. Furthermore, those subjects may not re-enter the study at any time.

10.2. PREMATURE CLOSURE OF THE STUDY

Study participation by individual sites or the entire study may be prematurely terminated, if in the opinion of the sponsor, there is sufficient reasonable cause. Any investigator who wants to discontinue his/her participation to the study must immediately inform the sponsor in writing of this decision.

Written notification documenting the reason for study termination will be provided to the investigator by the terminating party.

Examples of circumstances that may warrant termination include:

- Failure to enter subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug.

Should the study be closed prematurely, all study materials (completed, partially completed, and blank CRFs, SAE forms…) must be returned to the sponsor.

10.3. INITIATION OF PHASE II PART OF THE STUDY

Phase II part of the study will only be initiated after confirmation of the recommended dose of lenalidomide and approval by the DMSC.

Celgene approval will also be required prior to initiation of the Phase II part of the study.

11. STUDY CRITERIA OF EVALUATION

11.1. SAFETY MEASUREMENTS

11.1.1. Criteria for Dose Limiting Toxicities (DLT)

In the phase Ia part of the study, DLT will be defined as any of the following events occurring during the first two cycles of treatment, using the Common Terminology Criteria for Adverse Events:

- Grade $\geq$ 3 non hematological toxicity,
- Grade 3 hematological toxicity lasting more than 7 days,
- Grade 4 hematological toxicity lasting more than 3 days.
11.1.2. Criteria for safety measurements

The detailed and schedules for the procedures listed below are presented in Appendices 17.2., respectively:

- Adverse events
- Physical examination
- Vital signs
- Weight
- Clinical laboratory evaluations

11.2. Efficacy measurements

11.2.1. Criteria for response categories

Response rates are defined, according to Cheson et al. (1), as:

1. **Complete Response (CR):** complete disappearance of all detectable clinical and radiologic evidence of disease, normalization of biological abnormalities, assignable to lymphoma, seen at diagnosis and no new lesion. If the bone marrow was involved before treatment, the infiltrate must be cleared on repeat biopsy.

**A CR requires all of the following:**

a) Complete disappearance of all detectable clinical and radiographic evidence of disease, disappearance of all disease-related symptoms, and normalization of biochemical abnormalities definitely assignable to lymphoma (eg, LDH)

b) All lymph node masses must have regressed to normal size. Lymph node masses that were >1.5 cm in longest transverse dimension must have regressed to ≤1.5 cm. Lymph node mass that was 1.1-1.5 cm in longest transverse dimension and thought to be involved with lymphoma must have regressed to ≤1 cm, or by more than 75% of the product of the longest perpendicular dimensions compared to pretreatment baseline.

c) If the spleen was considered to be enlarged due to involvement with lymphoma prior to therapy, it must have regressed in size, and must not be palpable on physical examination.

d) If the bone marrow was involved by lymphoma before treatment, an adequate aspirate and biopsy of the same site must be cleared of lymphoma.

2. **Undocumented Complete Response (CRu):** disappearance of nearly all lesions and all clinical symptoms but persistence of some clinical or radiologic abnormalities which have regressed of more than 75% (in the sum of the products of the greatest diameters) with normalization of all biologic abnormalities and normalization of the PS. In case of demonstration of persisting lymphoma cell in any puncture or biopsy analysis, these patients will be named as PR.

**A CRu requires the following:**

Criteria a) and c) for CR are satisfied.

However:

a) Any residual lymph node mass >1.5 cm in longest transverse dimension must have regressed by more than 75% of the product of the longest perpendicular dimensions compared to the pre-treatment baseline.

b) The bone marrow aspirate may be indeterminate (contain increased number or size of lymphoid aggregates without cytologic or architectural atypia).

3. **Partial Response (PR):** regression of more than 50% (in the sum of the products of the greatest diameters) of all measurable lesions and disappearance of non-measurable lesions and no new lesion.

**A PR requires ALL of the following:**
a) 50% or greater decrease in the sum of the products of the longest perpendicular dimensions (SPD) of the previously identified dominant lymph node masses (up to 6)
b) No increase in the size of other lymph nodes, the liver, or the spleen
c) 50% or greater decrease in SPD of splenic and hepatic nodules
d) No new sites of lymphoma

4. **STABLE DISEASE (SD):** no response to the treatment; regression of less than 50% (in the sum of the products of the greatest diameters) of any measurable lesion; regression of more than 50% but with the persistence of clinical symptoms; or no change for the non-measurable lesions; and without any growth for the existing lesions, unless lower than 50%, or any new lesion.

**A SD requires the following:** Disease response is less than that required for PR, but the criteria for relapsed or progressive disease are not met.

5. **PROGRESSIVE DISEASE (PD) FOR PR AND NON RESPONDING PATIENTS:** appearance of any new lesion or any growth (or re-growth from nadir) of more than 50% (in the sum of the products of the greatest diameters) of a measurable lesion. Relapsed disease for patients in CR or CRu: appearance of any new lesion or increase by more than 50% (in the sum of the products of the greatest diameters) of any residual site.

**Progressive Disease or Relapsed Disease (ie, relapse from CR or CRu) is indicated by ANY of the following:**

a) Appearance of any new sites of lymphoma
b) 50% or greater increase in the product of the longest perpendicular dimensions of any previously identified lymph node mass
c) 50% or greater increase in the longest dimension of any previously identified lymph node mass greater than 1 cm in longest transverse dimension
d) 50% or greater increase in the size of any other previously involved site of lymphoma

In all cases the smallest prior measurement should be used as the baseline for comparison when evaluating for progressive or relapsed disease.

11.2.2. **Definitions of measurable and assessable disease**

Eligible subjects must have at least 1 measurable lymph node mass that is >1.5 cm in 2 perpendicular dimensions and, that has not been previously irradiated or has grown since previous irradiation.

- Measurable sites of disease are defined as lymph node masses, splenic nodules, and hepatic nodules that are thought to contain lymphoma, and are greater than 1 cm in the longest transverse dimension. Other sites of disease are considered assessable, but not measurable.

- Dominant lymph node masses include up to 6 nodal masses that are clearly measurable in 2 perpendicular dimensions and >1.5 cm in each dimension. Measurement may be by radiographic imaging or physical examination. The dominant nodal masses should be chosen such that they are representative of the subject’s disease. If there are lymph node masses in the mediastinum or pelvis larger than 1.5 cm in 2 perpendicular dimensions, they should always be chosen as dominant masses. In addition, the dominant masses should be from as disparate regions of the body as possible.

- Assessable disease includes objective evidence of disease that is identified by radiographic imaging, physical examination, or other procedure as necessary but is not measurable as defined above. Examples of assessable disease include sites of disease other than lymph node masses, splenic nodules, and hepatic nodules; such as lung nodules, effusions, pleural, peritoneal or bowel wall thickening, and disease limited to bone marrow.
12. STATISTICAL CONSIDERATIONS

12.1. STUDY DESIGN

This study is designed as a phase I/II trial. The first part, to be applied to the phase I_B part of this study, is a classical dose escalation design to explore the safety and assess the recommended dose of lenalidomide (Revlimid) in combination with R-CHOP21 regimen in patients with B-cell lymphoma. The second part, depending on the selected dose after the completion of phase I_B part of the study, will further explore safety in addition to efficacy of the association of the recommended dose of lenalidomide associated with R-CHOP21 in a selected population of patients with follicular lymphoma.

12.2. PRIMARY ENDPOINT

The primary endpoint for the phase I_B part of the study is the determination of the Recommended Dose of lenalidomide (Revlimid) in combination with R-CHOP regimen. Therefore, primary analysis will be based on safety parameters and particularly on incidence of DLTs as defined in section 7.3. Frequency of patients with DLT during the first 2 cycles of R2-CHOP will be reported by dose level.

Toxicities related to study regimen and occurring during the assessment period will be reviewed to confirm if they were dose limiting according to protocol and initial patient condition (pre-existing signs and symptoms, medical history). A listing will provide the description of DLTs observed by dose level.

The primary endpoint for the phase II part of the study is the Complete Response Rate (CR+CRu) at the end of treatment. Assessment of response will be based on the International Workshop to Standardize Response criteria for NHL 1999 (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson, 1999, section 11.2.1). Response at the end of treatment will be assessed at the end of complete treatment if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) will be considered as non-responder. A descriptive analysis will also be performed considering as non-responders all patients who relapsed or died during treatment phase even if they were prematurely withdrawn as responder.

12.3. SECONDARY ENDPOINTS

12.3.1. Efficacy endpoints

Secondary efficacy endpoints (for phase I_B and II parts of the study unless otherwise specified) will include:

**COMPLETE RESPONSE RATE AT THE END OF TREATMENT (ONLY FOR PHASE I_B PART)**

Disease response evaluation at the end of treatment will be used to determine the Complete Response Rate. Response at the end of treatment will be assessed at the end of complete treatment if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) will be considered as non-responder. A descriptive analysis will also be performed considering as non-responders all patients who relapsed or died during treatment phase even if they were prematurely withdrawn as responder.

**OVERALL RESPONSE RATE AT THE END OF TREATMENT**

The same disease response assessment used for complete response rate will be considered to determine the Overall Response Rate. Patient is defined as a responder if he/she has a complete response (CR/CRu) or partial response (PR) at the end of treatment. A descriptive analysis will also be performed considering as non-responders all patients who relapsed or died during treatment phase even if they were prematurely withdrawn as responder.

**COMPLETE AND OVERALL RESPONSE RATES AFTER INDUCTION**

Disease response evaluation after 3 cycles will be used to determine Complete and Overall Response rates after induction. Response after 3 cycles will be assessed only if patient completes induction phase. Patient without response assessment (due to whatever reason) will be considered as non-responder. A descriptive analysis will also be performed taking into account response at withdrawal, if patient has prematurely withdrawn before response assessment.
PROGRESSION-FREE SURVIVAL (PFS)

Progression-Free Survival will be measured from the date of inclusion to the date of first documented disease progression, relapse or death from any cause, according to Cheson 2007 criteria. Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

OVERALL SURVIVAL (OS)

Overall survival will be measured from the date of inclusion to the date of death from any cause. Patients who are alive at the time of analysis will be censored at the date of the last contact.

DURATION OF RESPONSE

Duration of response will be measured from the date of first documentation of a response (CR/CRu or PR after induction or at the end of treatment) to the date of first documented evidence of progression/relapse or death from any cause, according to Cheson 2007 criteria. Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

12.3.2. Safety endpoints

All subjects who received at least one dose of any investigational drugs will be described. All subjects who received any amount of Revlimid™ will be considered evaluable and analysed for safety.

Analysis of safety will be performed by summarizing adverse events, laboratory data, vital signs and ECOG performance status. When applicable, summary of safety data will also be performed by cycle.

All adverse events will be tabulated and graded according to the NCI-CTCAE (Version 3.0) for each patient. Toxicities will be summarized for each designation by worst grade per patient and by grade by cycle. Verbatim descriptions of AEs reported during the study period will be mapped to MedDRA-PREFERRED Term and System Organ Class. All treatment-emergent AEs (i.e., occurring from cycle 1) will be summarized in frequency tables by dose level for the phase IB part of the study and overall for the phase II part of the study. All treatment-emergent SAEs will be listed and summarized in frequency tables by dose level for the phase IB part of the study and overall for the phase II part of the study.

Clinical laboratory tests and their change from baseline will be summarized in terms of mean, median, minimum and maximum values and standard deviation by dose level and visit for the phase IB part of the study and overall and by visit for the phase II part of the study.

Vital signs and their change from baseline will be summarized in terms of mean, median, minimum and maximum values and standard deviation by dose level and visit for the phase IB part of the study and overall and by visit for the phase II part of the study.

12.3.3. Exploratory analyses

A case-controlled study will be performed by matching the R2-CHOP phase II population with patients treated with R-CHOP from previous GELARC PRIMA trial. This pair-matched analysis will compare efficacy and safety of both cohorts.

PET-scans assessments from central review will be used to explore the prognostic impact and results will be compared with those from with GELARC PET-FL study.

All other analyses (like subgroup analyses, prognostic factors) will be considered as exploratory analyses.

12.4. STATISTICAL AND ANALYTICAL METHODS

12.4.1. Statistical methods

Continuous variables will be summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles will also be presented when considered relevant. Categorical data will be described in counts and percentages (of non-missing data).
Censored data will be presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% CIs. The median time to event will be calculated (if reached) with 95% confidence intervals.

The number and percent of subjects falling into each category of response (CR, CRu, PR, SD, PD, Not evaluated, Missing) will be provided. Deaths will also be included as a category, if patients died during the corresponding period. Response rates will be expressed with 95% confidence limits according to Pearson-Clopper method. The effects of prognostic factors on response rates will be assessed in an exploratory analysis using logistic regression. The results will be presented in terms of odds ratios including 95% confidence limits and associated p-values.

For exploratory purpose, impact of individual important baseline prognostic factors on PFS/OS will be assessed by a two-sided log-rank test and estimates will be expressed as risk ratios based on the Cox regression analysis with 95% confidence intervals. A multivariate Cox regression analysis will then be performed with these factors.

### 12.4.2. Hypothesis testing

For the phase I part of the study, no formal hypothesis testing is planned.

For the phase II part of the study, statistical analysis will focus on the need to estimate response rates in order to determine if treatment has sufficient efficacy to warrant further clinical study. The analysis will be based on complete response rate.

Based on a two-stage design, the hypotheses are:

\[ H_0: p < p_0 \quad \text{versus} \quad H_1: p > p_1 \]

where \( p_0 \) and \( p_1 \) are complete response rates such that the test regimen does or does not merit further testing at given levels of statistical significance (\( \alpha \)) and power (1-\( \beta \)). Rejection of \( H_1 \) is possible at stage 1, but acceptance can only occur at stage 2. Rejection of \( H_0 \) (or \( H_1 \)) means that further (or no further) study should be carried out.

For secondary parameters, statistical tests will be two-sided and performed using a 5% level of significance. Given the exploratory nature of the analyses, no adjustment for multiple comparisons will be made.

### 12.4.3. Types of analyses

- **Full Analysis Set** (following an intent-to-treat principle)
  
  All enrolled patients regardless of whether they have received study treatment or not will be included in this analysis. This will be the efficacy population for the phase II part of the study.

- **All treated patients**
  
  The all treated population will be based on all enrolled patients who received at least one dose of any investigational drugs. This will be the population for safety analysis. Emphasis will be put on patients who received at least one dose of lenalidomide (separate analysis).

- **Patients evaluable for DLT assessment**
  
  For the phase I part of the study, the evaluable for DLT population is the subset of patients from all treated population with a DLT assessment during the first 2 cycles of R2-CHOP.

### 12.5. Sample size calculation

For the phase I part of the study, the number of dose levels and the emerging dose limiting toxicities will determine the sample size. It is anticipated that up to 30 patients will be required to establish the maximum tolerated dose (MTD) and the recommended dose of lenalidomide (Revlimid).

For the phase II part of the study, in our previous studies in this population of high tumor burden follicular lymphoma patients, we estimated that the complete response rate (CR + CRu) was about 65% according to IWC
criteria. Thus, a two-stage phase II design (Simon, R. “Optimal Two-Stage Designs for Phase II Clinical Trials,” Controlled Clinical Trials, 1989, Volume 10, pages 1-10) will be used to test the null hypothesis that the complete response rate is less than or equal to 65% versus the alternative hypothesis that the response rate is greater than or equal to 80%.

The first stage will include 39 evaluable patients and a total of 73 evaluable patients if trial proceeds to second stage. This design provides nominal power of 80% at the nominal one-sided 2.5% significance level (to be consistent with two-sided confidence interval).

Assuming an estimated drop out of 10%, a total of 80 patients will be enrolled.

12.6. INTERIM ANALYSIS

The study design involves two different parts:

The phase I part of the study will primarily focus on the exploration of the safety and if possible, will assess the recommended dose of lenalidomide. Safety data and, when available, preliminary efficacy data will be used to define dose escalation increments. The cut-off for main criteria analysis is defined when safety data for the first 2 cycles of R2-CHOP are available for all patients. Then, the cut-off for efficacy data and safety data for cycles 3 to 6 of this part of the study will be established at 3 months after the end of treatment for the last patient. A last cut-off will occur 2 years after the last treatment last patient.

For the phase II part of the study, a two-stage analysis will be conducted. The first stage analysis will be performed after 39 evaluable patients have been included. The trial will be terminated if 26 or fewer patients respond to treatment and treatment will be considered as ineffective. The probability of early termination is 0.645. All data available at the scheduled time of interim analysis will be used for these patients. Otherwise, the trial will proceed to second stage and include 34 additional patients. Thus, a total of 73 evaluable patients will be studied. At the end of the second stage, if the total number of responder patients is less than or equal to 55, treatment will be considered as inefficient. Cut-off for final analysis will occur one year after last treatment last patient.

13. STUDY MONITORING

13.1. RESPONSABILITIES OF THE INVESTIGATORS

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

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

Subject compliance to the study treatment is the investigator’s responsibility and will be checked during site monitoring visits by a representative of the GELARC.

13.2. RESPONSABILITIES OF THE SPONSOR

The sponsor of this study has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the project leader and of his clinical research support team (GELARC) is to help the investigator maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, by a representative of the monitoring team (GELARC) to review study progress, investigator and subject adherence to protocol requirements and any emergent problems.
Monitoring and auditing procedures developed by GELARC will be followed, in order to comply with GCP guidelines. On-site checking of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

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

### 13.3. SOURCE DOCUMENT REQUIREMENTS

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

### 13.4. USE AND COMPLETION OF THE CASE REPORT FORMS (CRF)

A Case report form will be completed for each study subject. It is the investigator’s responsibility to ensure the accuracy, completeness, legibility and timeliness of the data reported in the subject’s CRF. Source documentation supporting the CRF data should indicate the subject’s participation in the study and should document the dates and details of study procedures, adverse events and subject status.

The investigator, or designated representative, should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

Case report forms should be filled out with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking out the erroneous information with a single line. Each correction, addition or deletion must be initiated and dated by the investigator or investigator’s designated representative. The investigator must sign and date the Investigator’s Statement at the end of the CRF to endorse the recorded data.

### 13.5. STUDY DRUG MONITORING

Accountability for the study drug at the clinical site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug’s delivery date to the site, inventory at the site, use by each subject, or disposal of the drug will be maintained by the clinical site. These records will adequately document that the subjects were provided the doses as specified in the protocol. The sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

All unused study drug will be retained at the site until they are inventoried by the monitor. All used, unused or expired study drug and all material containing Revlimid™ will be treated and disposed of as hazardous waste in accordance with governing regulations.
14. ETHICAL AND REGULATORY STANDARDS

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

14.2. LAWS AND REGULATIONS
This protocol is also in accordance with laws and regulations of the country(ies) in which the trial is performed, as well as any applicable guidelines.

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

The informed consent document used by the investigator for obtaining subject's informed consent must be reviewed and approved by GELARC prior to Ethical Committee / IRB submission.

14.4. ETHICS REVIEW COMMITTEE (ERC)
The investigator must submit this protocol to an Ethics Review Committee (ERC) or a similar body (IRB, CPP, etc.), and he is required to forward a copy of the written approval / advice signed by the chairman to the sponsor.

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

Drug supplies will not be released and the trial will not start until a copy of this written approval / advice has been received by the GELARC.

15. ADMINISTRATIVE PROCEDURES

15.1. CURRICULUM VITAE
An updated copy of the curriculum vitae of each investigator and co-investigator will be provided to the GELARC prior to the beginning of the study.

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

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

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

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.
15.3. **RECORD RETENTION IN INVESTIGATING CENTRE(S)**

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.

However national regulations should be taken into account, the longest time having to be considered.

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

Any center will notify the sponsor before destroying any data or records.

15.4. **OWNERSHIP OF DATA AND USE OF THE STUDY RESULTS**

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, only for its own scope and research program excluding any use for profit or use for industrial development of Revlimid and declares that data and results will not in any manner be employed for third parties commercial business. To comply with EU directives and local regulation, the sponsor may also submit study results and data to the health authorities of participating countries.

15.5. **PUBLICATION**

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

All study data and publications are the property of the Sponsor.

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

15.6. **INSURANCE COMPENSATION**

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

A certificate of insurance will be provided to the investigator.

15.7. **INSPECTIONS BY REGULATORY AGENCIES**

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines it may be necessary to conduct a site audit or an inspection.

By signing this protocol, the investigator agrees to allow the Sponsor and its representative, and drug regulatory agencies to have direct access to his study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in CRF, review of documentation required to be maintained, and checks on drug accountability.

GELARC will in all cases help the investigator prepare for an inspection by any regulatory agency.
15.8. **CLINICAL STUDY REPORT**

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

15.9. **PROTOCOL AMENDMENTS**

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

No changes or amendments to this protocol may be made by the investigator or by the sponsor after the protocol has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the investigator and the GELA.

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

Approval / advice of amendments by Ethical Committee / IRB is required prior to their implementation, unless there are overriding safety reasons.

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

In some instances, an amendment may require a change to a consent form. The investigator must receive approval / advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

Prior to initiating the changes, protocol amendment must be submitted to regulatory agencies, where applicable, except under emerging conditions.

16. **REFERENCES**


18. Knop S, Gerecke C, Liebisch P et al. The Efficacy and Toxicity of the RAD Regimen (Revlimid(R), Adriamycin(R), Dexamethasone) in Relapsed and Refractory Multiple Myeloma - A Phase I/II Trial of "Deutsche Studiengruppe Multiples Myelom". ASH Annual Meeting Abstracts 2007 110: 2716


17. APPENDICES

17.1. STUDY FLOW CHART

17.1.1. Phase IB

---

R2-CHOP TREATMENT

18 weeks

FOLLOW-UP

5 years

C1  C2  C3  C4  C5  C6
3 w  3 w  3 w  3 w  30 days  3 months  3 months

INCLUSION  RESPONSE  RESPONSE

Study Evaluation

FU1  FU2

...
17.1.2. Phase II

6x R2-CHOP
18 weeks

2 x R
6 weeks

MAINTENANCE / FOLLOW-UP
5 years

C1
3w

C2
3w

C3
3w

C4
3w

C5
3w

C6
3w

C7
30 days

C8

Study Evaluation

FU1
2 months

FU2
2 months

...
### 17.2. Schedule of Evaluations

<table>
<thead>
<tr>
<th>Events</th>
<th>Screening</th>
<th>Cycle 1 to Cycle 6 (Ib) or 8 (II)</th>
<th>End of treatment evaluation</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>within 14 days before first dose</td>
<td>D1, D7, D10, D14</td>
<td>30 days after the last drug administration</td>
<td>every 2 months during 2 years</td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/Non inclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics <em>(a)</em></td>
<td>X</td>
<td>X <em>(f)</em></td>
<td>X <em>(f)</em></td>
<td>X <em>(f)</em></td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td>X <em>(g,h)</em></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Complete relevant medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td>X</td>
<td>X <em>(g,h)</em></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vital signs <em>(b)</em></td>
<td>X</td>
<td>X <em>(g,h)</em></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Chest, abdomen, pelvis CT with oral and IV contrast</td>
<td>X *(c)</td>
<td>X *(c)</td>
<td></td>
<td>X *(c)</td>
</tr>
<tr>
<td>Other relevant evaluations of sites of disease (PET, ...)</td>
<td>X *(c)</td>
<td>X *(c)</td>
<td></td>
<td>X *(c)</td>
</tr>
<tr>
<td>Bone marrow aspirate and biopsy</td>
<td>X *(d)</td>
<td>X *(d)</td>
<td></td>
<td>X *(d)</td>
</tr>
<tr>
<td>Complete Blood cell counts</td>
<td>X</td>
<td>X *(d)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Clinical biochemistry <em>(e)</em></td>
<td>X</td>
<td>X *(h)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Serum β-HCG pregnancy test (sensitivity ≥ 25 mU/L) when applicable</td>
<td>X *(m)</td>
<td>X *(m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events (AE)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation of the disease response</td>
<td>X</td>
<td>X *(h)</td>
<td></td>
<td>X *(h)</td>
</tr>
</tbody>
</table>

(a) Weight, height, body surface area, medical history, demographics  
(b) Pulse, Blood pressure and Body temperature  
(c) May be performed up to 28 days before first dose of study drug.  
(d) May be performed up to 56 days before first dose of study drug.  
(e) Calcium, sodium, potassium, glucose, albumin, creatinine, LDH, ALT, AST, total bilirubin, alkaline phosphatase.  
(f) Weight and body surface area during treatment period and at last treatment evaluation (30 days after last drug administration). Weight only during follow-up period.  
(g) During cycle 1 and 2 of phase Ib of the study only.  
(h) During cycle 1 and 2 of phase Ib: continued every two days (± 1 day) until the absolute neutrophil count reach 1.5 x 10^9/L and platelet count reach 100 x 10^9/L.  
(i) Bone marrow aspirate and biopsy to be performed to assess CR or CRu in subjects with a positive bone marrow result at screening (not required for patients with already cleared bone marrow at previous evaluation)  
(j) Every 6 months  
(k) Bone marrow aspirate and biopsy to be performed if clinically indicated.  
(l) Every 12 months unless clinically indicated.  
(m) In the 3 days before day 1 of cycle 1, day 1 of cycle 2 to 8.
17.3. **FOLLICULAR LYMPHOMA GRADING SYSTEM (WHO CLASSIFICATION)**

**Follicular Cell Lymphomas: Grading and Variants**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>0-5 centroblasts/hpf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>6-15 centroblasts/hpf</td>
</tr>
<tr>
<td>Grade 3</td>
<td>15 centroblasts/hpf</td>
</tr>
<tr>
<td>3a</td>
<td>15 centroblasts, but centrocytes are still present</td>
</tr>
<tr>
<td>3b</td>
<td>Centroblasts form solid sheets with no residual centrocytes</td>
</tr>
</tbody>
</table>

**Variants**

- Cutaneous follicle center lymphoma
- Diffuse follicle center lymphoma

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>0-5 CB/hpf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>6-15 CB/hpf</td>
</tr>
</tbody>
</table>


17.4. **ANN ARBOR STAGE**

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

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

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

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

17.5. **BODY SURFACE AREA CALCULATION**

The algorithm to be used in this study is:

\[ BSA = \sqrt{\frac{(Height \ (cm) \times Weight \ (kg))}{3600}} \]

17.6. **PERFORMANCE STATUS CRITERIA**

The following table presents the ECOG performance status scale:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).</td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>

17.7. **BIOLOGICAL SAMPLES**

17.7.1. **Tumor sample**

It is highly important to consider at diagnosis all the possibilities to froze the tumor sample for the analysis of biological prognostic factors:

- fresh sample to send immediately after biopsy to the nearest tumor library
- systematic freezing of part of the biopsy
- new surgical nodal biopsy or true-cut biopsy if none of these conditions have been fulfilled and if possible

This sample will be placed at the GELA tumor library’s network disposal. It will be useful for gene expression (transcriptoma) or protein expression analysis (proteoma).

17.7.2. **Plasma samples for sCD20 and proteomic analysis**

It is highly recommended to take and to freeze a plasma sample before any treatment (included corticosteroids). Practically, it is needed to take 10 ml of blood on EDTA. Sample will be managed:

- by the referent biologist in each center
- it will be centrifuged within 3 hours (3500 revolutions a minute for 10 minutes)
- the plasma will be taken for 500 µl aliquots (2 to 3 aliquots in cryotubes or eppendorf tubes)
- Identification of tubes: The first 3 letters of the name
  The first 2 letters of the first name
  The date of sample
  The name of protocol or the number of registration.
- the aliquots will be stored at –80°C and will be then collected by the GELARC all together in the different laboratories for protein and peptide content analysis

17.7.3. **Samples for DNA genomic analysis of polymorphisms**

It is highly recommended to collect blood samples (10 ml on EDTA) at diagnosis in all patients of each centers participating to the study. Patients with circulating lymphoma cells (detected by cytology in peripheral blood) will be excluded because of possible modifications of polymorphism analysis by some genetic alterations present in tumor cells.

Two options are available:

1) either preparation of a white blood cells dry pellet as described below, to be stored at –80°C (or any appropriate cell purification technique enabling further DNA isolation)
2) or sending the blood tube “paxgene” (provided by the GELARC) directly to Lyon-Sud hospital.

**Centre Hospitalier Lyon Sud**

*Laboratoire de Biologie moléculaire et hématologie – à l’attention de Carole CHARLOT*

*Centre de Biologie Sud – Espace Jacques Monot – Etage 1*

*165 chemin du Grand Revoyet*

*69310 PIERRE BENITE*

- To prepare dry pellet, the 10 ml peripheral blood sample is centrifuged at 2500 rpm (3000 g) for 15 minutes. The plasma layer is removed from the top portion of the interphase using a pipette and
discarded. The white blood cells interface is then removed, and re-suspended in a new tube using a RBC (Red blood cell) lysis solution (for instance 0.15 M NH4CL, 10mM KHCO3). The tube is incubated for 15 to 20 minutes at room temperature, with gentle agitation every 5 minutes, then spun down at 1000g for 10 minutes to pellet white blood cells. A second wash can be eventually performed in a ml tube to adjust the volume for the storage tube. The supernatant is carefully aspirated and the dry pellet is snap frozen in liquid nitrogen or at −80°C until sample collection.

- a clinical department which cannot take advantage of this organization will have the opportunity to send the samples to the Lyon-Sud hospital. The special isolation tubes will be provided and have to be send on the day of collection by regular mail at room temperature.

**Technique to prepare Dry pellet:**

**Technique 1 : Buffy Coat**

- To take a sample of blood (10mL) on EDTA
- To centrifuge at 1800trs/min for 10 minutes
- The white blood cells interface is then removed and re-suspended in a new tube with Phosphate Buffered Saline-pH 7.2 (PBS Buffer)
- To wash cells with PBS (1800 trs/min for 1-2 minutes) 2 washing
- After the second washing, to remove all the supernatant with a pipette
- To keep the dry pellet at -80°C in cryotube or eppendorf
- To identify the tube: The first 3 letters of the name
  - The first 2 letters of the first name
  - The date of sample
  - The name of protocol or the number of registration
- The GELARC will collect these samples at the time of an annual collection of the protocol samples.

**Technique 2 : Ficoll (separation of cells by gradient of density)**

- To take a sample of blood (10mL) on EDTA
- In tube Falcon of 15 or 50 mL, to put the reagent and to add the blood without mixing the two phases
- To centrifuge at 1500trs/min for 20 minutes
- To collect with pipette the ring of white cells.
- To realise 2 washing of cells with PBS (1200rpm for 5 minutes)
- After the second washing, to remove all the supernatant with a pipette.
- To keep the dry pellet at -80°C in cryotube or eppendorf.
- To identify the tube: The first 3 letters of the name
  - The first 2 letters of the first name
  - The date of sample
  - The name of protocol or the number of registration
- The GELARC will collect these samples at the time of an annual collection of the protocol samples.

A specific fax will be sent after each inclusion in the program and will be filled in by the laboratory that have received the sample and sent back to the coordination center in Lyon. The coordination center will be informed on real time about all biopsies taken and about the place of samples storage. This strategy has been validated through the Hodgkin/Cytokines study with a wide participation of clinical centers.

All the samples will be gathered in Lyon following a collect organized one a year (special carrier respecting cold storage). They will be stored at −80°C until DNA extraction. After extraction, the DNA will be stored at + 4°C and will be then delivered to the other laboratories participating to the project (Lyon-Sud, Villejuif, Rouen). After the end of the study, all the remaining samples will be destroyed.

All the samples will be immediately coded after they have been taken:

- First 3 letters of last name
- First 2 letters of name
- The date of sample
- Number of inclusion in study or name of protocol

The complete procedure will remain anonymous all along the biological analysis. Observations will be linked with the GELA clinical database (registered to the CNIL) only after the end of the study. This database contains the main informations about patients participating to the study including demographic data, baseline clinical evaluation, treatment, response to treatment and follow-up (relapse, death). Beyond the period of study monitoring, the database will be actualized every year.