Clinical Protocol

Prospective multicenter dose finding phase II pilot trial to evaluate efficacy and safety of treatment with Lenalidomide plus R-CHOP21 (LR-CHOP21) for elderly patients with untreated Diffuse Large B-Cell Lymphoma (DLBCL).

STUDY DRUG CC-5013
Study ID LR-CHOP21;Phase II
REAL07 Revlimid in Elderly Aggressive Lymphoma
Versione 2 emendamento 1 del 10 gennaio 2008

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Date: 10 January 2008

1.1 INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

Investigator's Signature Date

Name of Investigator (Typed or Printed)

Institution, Address*

Phone Number*

Investigator-Sponsor Signature* Date
(where required)

Name of Coordinating Investigator (Typed or Printed)

Institution

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

2. SYNOPSIS

OVERVIEW OF STUDY DESIGN

This is a prospective, multicenter dose finding phase II trial designed to determine the maximum tolerated dose (MTD) of combination therapy of Lenalidomide and R-CHOP, with a fixed dose of R-CHOP and to evaluate the safety and efficacy of the combination of Lenalidomide, Rituximab and CHOP chemotherapy in elderly patients with untreated Diffuse Large B-Cell Lymphoma (DLBCL) or Follicular grade IIIb Lymphoma.

OBJECTIVES:

PRIMARY OBJECTIVES

- To evaluate the feasibility and safety of a treatment regimen including Lenalidomide plus Rituximab-CHOP (LR-CHOP) through the definition of the DLT of Lenalidomide when delivered in combination with R-CHOP
- To evaluate the response rate of LR-CHOP in elderly patients with DLBCL at diagnosis at the MTD of Lenalidomide.

SECONDARY OBJECTIVES

To evaluate long term efficacy of LR-CHOP with Lenalidomide delivered at the MTD in elderly patients with DLBCL at diagnosis.

STUDY ENDPOINTS

PRIMARY ENDPOINTS

- Evaluation of feasibility and toxicity of the regimen according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.
- Definition of Dose Limiting Toxicity (DLT) considered as the maximum dose inducing any Grade $\geq$ 3 non-hematologic toxicity, or a delay > 15 days of planned cycle date.
- Complete Response and Overall Response Rate;

SECONDARY ENDPOINTS

- 2-year OS and EFS
- Impact of LR-CHOP on immunologic reconstitution by analyzing both T cell and B-cell subsets
- Relationship between response to treatment and available baseline biologic factors. Such biologic factors will include histopathogenesis (GC vs activated B-cell), translocations, presence of immunoglobulin ongoing somatic hypermutation, presence of oncogene aberrant somatic hypermutation. Biological studies will be detailed on a specific Appendix

STUDY POPULATION:

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study:

INCLUSION CRITERIA

1. Understand and voluntarily sign an informed consent form
2. Able to adhere to the study visit schedule and other protocol requirements
3. Histologic subtypes as follows:
   CD20 positive Diffuse large B-Cell lymphoma
   CD20 positive Follicular grade IIIb
4. Age 60-80
5. Untreated patients. In patients with bulky mass or systemic symptoms or compressive disease or rapidly progressive adenopathies a pre-study treatment is allowed with steroids and/or a single dose of Vincristine 1.4 mg/mq (max 2) in the seven days prior the start of the study treatment
6. Measurable and/or evaluable disease
7. Ann Arbor stage II, III, IV
8. International Prognostic Index at low-intermediate, intermediate-high, high risk (2/3/4-5)
9. Adequate haematological counts: ANC > 1.5 x 10^9/L and platelet count > 75 x 10^9/L unless due to bone marrow involvement
10. Conjugated bilirubin up to 2 x UNL.

11. Alkaline phosphatase and transaminases up to 2 x UNL.
12. Creatinine clearance > 50 ml/min.
13. HIV negativity
14. HCV negativity
15. HBV negativity or patients with HBVcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative
16. Cardiac ejection fraction (MUGA scan or echocardiography) > 45%
17. Non peripheral neuropathy or CNS disease. Non testicular Lymphoma
18. Life expectancy > 6 months.
19. Performance status ≤ 2 according to ECOG scale.
20. Comprehensive geriatric assessment (CGA) as outlined in Appendix 15 showing absence of any impairment in activity of daily living (ADL), of any condition defining a geriatric syndrome, and of any grade 4 comorbidity or of more than three grade 3 comorbidities according to CIRS-G scale
21. Disease free of prior malignancies for ≥ 3 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "insitu" of the cervix or breast
22. Females of childbearing potential (FCBP) must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

    - **Before starting study drug:**

    Female Subjects:

        - FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study

drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

During study participation and for 28 days following discontinuation from the study:

All Subjects:

- No more than a 28-day supply of study drug will be dispensed at a time.

Female Subjects:

- FCBP with regular cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood.

- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

- Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen.

- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, study drug must be immediately discontinued.

EXCLUSION CRITERIA

1. Lymphoblastic Lymphoma
2. Burkitt Lymphoma
3. Non Hodgkin lymphoma CD 20 negative
4. Mantle Cell Lymphoma
5. Follicular Non Hodgkin Lymphoma grade I-II-IIIa
6. Primitive mediastinal diffuse large B cell lymphoma with only mediastinal involvement
7. International Prognostic Index at low risk (1)
8. Has known or suspected hypersensitivity or intolerance to Rituximab
9. History of evolutive malignancy within the last 3 years other than squamous cell and basal cell carcinoma of the skin or carcinoma in situ of the cervix or breast
10. Extensive radiation therapy, systemic chemotherapy, or other antineoplastic therapy before enrollment within 3 years before the start of treatment
11. Exposure to Rituximab prior to study entry

12. Have received an experimental drug or used an experimental medical device within 4 weeks before the planned start of treatment. Concurrent participation in non-treatment studies is allowed, if it will not interfere with participation in this study
13. CNS disease (meningeal and/or brain involvement by lymphoma) or Testicular involvement
14. DVT in the last year
15. History of clinically relevant liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances
16. Uncontrolled diabetes (if receiving antidiabetic agents, subjects must be on a stable dose for at least 3 months before first dose of study drug
17. Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure (Attachment 5, NYHA Classification of Cardiac Disease), uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis
18. Creatinine clearance < 50 ml/min
19. Presence of major neurological disorders
20. HIV positivity
21. HBV positivity with the exception of patients with HBVcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative
22. HCV positivity
23. Active opportunistic infection
24. Comprehensive geriatric assessment (CGA) as outlined in Appendix 15 showing presence of any impairment in activity of daily living (ADL), of any condition defining a geriatric syndrome, and of any grade 4 comorbidity or of more than three grade 3 comorbidities according to CIRS-G scale
25. Any other co-existing medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent

BIOSTATISTICAL ANALYSIS

Diffuse large B-Cell lymphoma are currently treated with Rituximab-CHOP chemotherapy with a 5-yr EFS of 54% in elderly patients (>60 yrs). This figure drops at 41% at 5 years in patients with intermediate-high and high risk IPI score. Thus, at least 40-45% of the patients progress or relapse in the first three years off treatment.

A strong rationale exist in favor of the introduction of Lenalidomide in the context of Rituximab supplemented schedules currently employed in DLBCL.

In particular: a) a high proportion of patients still fail R-CHOP; b) Lenalidomide has proven activity in DLBCL; 3) there is strong preclinical evidence that Lenalidomide might be synergistic with drugs employed in R-CHOP, particularly Rituximab; 4) Lenalidomide might be combined with Doxorubicin and Vincristine with acceptable side effects.

DOSE FINDING

PURPOSE

Open-label dose finding study to determine the maximum tolerated dose (MTD) of combination therapy of Lenalidomide and R-CHOP, with a fixed dose of R-CHOP, in elderly patients with untreated Diffuse Large B-Cell Lymphoma.

ENDPOINTS

Primary: adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Secondary: complete response and overall response rate.

TREATMENT SCHEDULE

Patients will be enrolled into four dose level of Lenalidomide (5 mg; 10 mg; 15 mg and 20 mg) in combination with R-CHOP. Lenalidomide will be administered at D1-D14.

The R-CHOP schedule will be repeated every 21 days:

Rituximab 375 mg/sqm D 0 or 1

Cyclophosphamide 750 mg/sqm iv D1

Doxorubicin 50 mg/sqm iv D1

Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)
Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5

DEFINITION OF DOSE LIMITING TOXICITY

DLT is defined as the occurrence of any grade $\geq$ 3 non-hematologic toxicity, or a delay > 15 days from planned cycle date observed during the first two cycles.

Trial design and dose allocation rule

The design of this dose-finding phase I clinical trial is chosen to assess the maximum tolerated dose (MTD) of Lenolidamide when administered in combination with Rituximab-CHOP chemotherapy in the treatment of elderly patients with untreated Diffuse Large B-Cell Lymphoma (DLBCL) or Follicular grade IIIb Lymphoma. The MTD is defined as the dose that achieves a dose-limiting toxicity (DLT) in 33% of patients.
Four dose levels are tested, namely 5, 10, 15 and 20 mg. The continual reassessment method (CRM) (O'Quigley et al, 1990; Garrett-Mayer, 2006; O'Quigley and Zohar, 2006) is used as the dose allocation rule in the trial. It is based on a mathematical modelling of dose–DLT relationship, iteratively updated using Bayes theorem along the trial, as follows. First, before trial onset, prior opinions about DLT probability at each dose level are elicited from expert clinicians on the basis of their personal experience and on literature. These initial guesses, which relied on the opinion of participating clinicians, were fixed at 0.15, 0.20, 0.25, and 0.30, respectively.
The uncertainty in this dose–DLT relationship is incorporated into a prior. Then, the first three included patients are administered the second dose level (10 mg). After the enrollment of the first three patients, accrual continues, with grouped inclusions of three patients per dose level. Then, on the basis of observed responses (DLT or not), DLT probabilities of all dose levels are updated using Bayes theorem. The dose level associated with an updated DLT probability close to 33% is recommended to be administered to the next patient cohort. All this process is re-run until the fixed sample size (N=25) is reached, or in case of fulfilled stopping criteria measuring futility of trial continuation (Zohar and Chevret, 2001).

PHASE II

Primary endpoint:

Overall Response Rate (ORR)

Design:

Phase II study – Simon's two-stage Minimax Design, since it is the design that minimizes the expected sample size given a 'bad' response rate

Parameter specifications:

- Standard proportion of ORR: p0= 0.7
- Minimum required ORR for the new regimen: p1= 0.85
- alpha= 0.05
- power= 0.8

Sample size:

49 subjects (total)
23 will be accrued during DOSE FINDING
26 during PHASE II

Stopping rules:

Given that the 'true' response probability is 70%, there is a 56.01% probability of ending the trial during stage 1, with an expected sample size for the trail of 20.58.
However, if the 'true' response probability is 85%, there is only a 4.63% probability that the trial will be stopped in stage 1.
If 16/23 or fewer responses are observed during the first stage then the trail is stopped early.
If 39/49 or fewer responses are observed by the end of the trail, then no further investigation of this regimen is warranted.
Patients enrolled at the MTD during the first phase study will be consider as part of the Phase II trial.

Losses to follow-up:

Assuming a 5% losses for any reasons, the total number of patients to be enrolled is 52.

TREATMENT SCHEDULE AND DOSES

Patients will be enrolled into different cohorts with different dose levels of Lenalidomide: 5 mg; 10 mg; 15 mg and 20 mg in accordance with statistical design.

FIRST DOSE LEVEL:

- **Rituximab 375 mg/sqm D 0 or 1**
- **Cyclophosphamide 750 mg/sqm iv D1**
- **Doxorubicin 50 mg/sqm iv D1**
- **Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)**
- **Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5**
- **Revlimid 5 mg/day D1-D14**

Repeated every 21 days

SECOND DOSE LEVEL

- **Rituximab 375 mg/sqm D 0 or 1**
- **Cyclophosphamide 750 mg/sqm iv D1**
- **Doxorubicin 50 mg/sqm iv D1**
- **Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)**
- **Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5**
- **Revlimid 10 mg/day D1-D14**

Repeated every 21 days

THIRD DOSE LEVEL

- **Rituximab 375 mg/sqm D 0 or 1**
- **Cyclophosphamide 750 mg/sqm iv D1**

- **Doxorubicin 50 mg/sqm iv D1**
- **Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)**
- **Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5**
- **Revlimid 15 mg/day D1-D14**

Repeated every 21 days

FOURTH DOSE LEVEL

- **Rituximab 375 mg/sqm D 0 or 1**
- **Cyclophosphamide 750 mg/sqm iv D1**
- **Doxorubicin 50 mg/sqm iv D1**
- **Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)**
- **Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5**
- **Revlimid 20 mg/day D1-D14**

Repeated every 21 days

Patient at risk for CNS involvement according to SIE guidelines (appendix 10) should receive prophylaxis with Methotrexate 12 mg IT for four doses (Day 0 or Day 1 Cycles 1-4).

In patients with bulky mass or systemic simptoms or compressive disease or rapidly progressive adenopathies a pre-study treatement is allowed with steroids and/or a single dose of Vincristine 1.4 mg/mq (max 2) in the seven days prior the start of the study treatment.

SECOND AND THIRD COURSE as the first one:

For patients enrolled in the dose-finding phase of the study a real-time assessment of the development of dose-limiting toxicities after the second course is warranted in order to enable the dose allocation of the subsequent cohort of three patients

Clinical response will be assessed after the first three courses of therapy.

Patients with responsive disease (CR, PR) will proceed to further three courses of therapy with the same schedule and doses.

Patients with progressive disease, stable disease or severe toxicity after the first three courses of therapy will be withdrawn from the study.

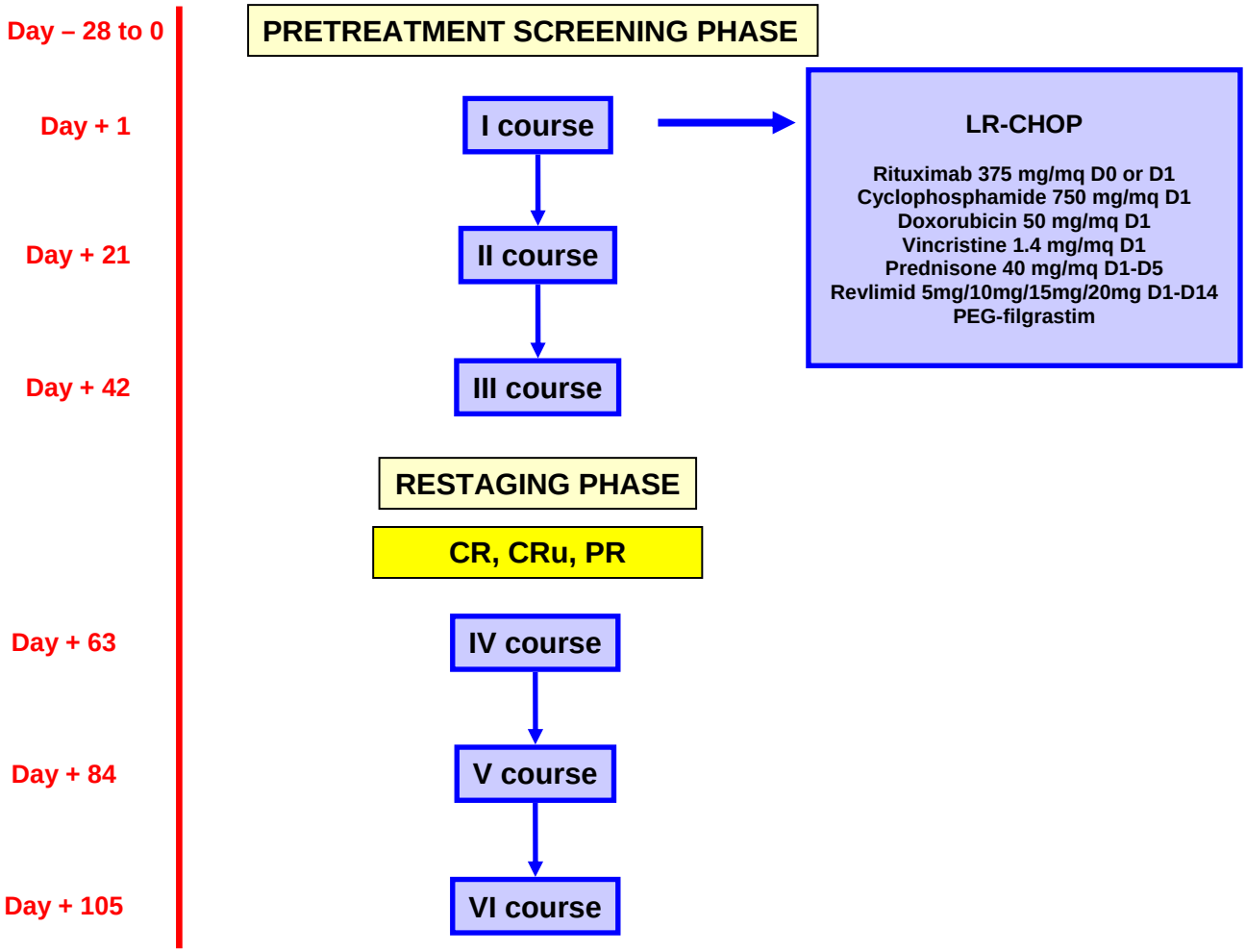
Patients with progressive disease at any time will be withdrawn from the study.

FOURTH, FIFTH AND SIXTH COURSE as the first one:

Clinical response will be assessed two months after the completion of the whole therapy.

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

The study design is presented in the figure below:



3.SCHEDULE OF STUDY ASSESSMENT

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6. INTRODUCTION

Diffuse large B-cell lymphoma is the most common lymphoma subtype accounting for approximately 30% of all lymphomas[1]. It often occurs in elderly patients with median age of incidence of 60 years[2-4.] This neoplasm has an aggressive behaviour and a rapidly fatal outcome if left untreated. Since the introduction of second-generation chemotherapy regimens a proportion of patients with DLCL have been successfully cured. In particular, the golden standard of the "pre-Rituximab age" i.e. the CHOP regimen delivered every 21 days (CHOP-21) is consistently able to obtain disease eradication in approximately 40% of patients[5]. This result has not been improved by the so-called third generation schedules, and the potential advantage of autologous transplantation as first line treatment is highly controversial[6-9]. The only Rituximab-free treatment which appeared to clearly improve the outcome of DLBCL patients has been the dose-dense delivery of CHOP every 14 instead of every 21 days (so called CHOP-14)[10].

Despite their clinical value, all the approaches based on chemotherapy intensification are more suitable for young patients and do not represent the optimal approach to improve the outcome of elderly patients[6-9]. On the other hand the inclusion of Rituximab in the treatment schedule has significantly improved both EFS and OS in elderly patients with DLBCL. According to Coiffier[11] et al the 2-year EFS of 41% with CHOP alone improved up to 58% in patients treated with R-CHOP.

Despite this major advance a high proportion of elderly patients with DLBCL still progress or relapse and eventually die of their disease. The three-year EFS projection of the study from Coiffier et al[11] suggests that this number still approaches 50% even in the Rituximab era. Thus, further improvements of the R-CHOP schedule are sought. One of the most promising new agents in the lymphoma field are radioconjugates in particular Y-90 Ibritumomab Tiuxetan[12-13]. This agent is highly effective both in indolent and aggressive lymphomas[12-13]. However, its delivery requires experienced nuclear medicine facilities, and it is not easily available at small peripheral Institutions which treat the great bulk of elderly lymphoma patients. Alternatively the addition of other effective drugs to standard R-CHOP may be an effective option for the treatment of elderly patients with DLBCL that need to be investigated.

6.1 Lenalidomide pre-clinical studies

Lenalidomide, belongs to a proprietary class of Celgene compounds called IMiDs®. IMiDs®, of which Thalidomide is the parent compound, have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF[14.]. In addition, Lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production[15]. Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity[16].

Although the exact antitumor mechanism of action of Lenalidomide is unknown, a number of mechanisms are postulated to be responsible for Lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis[17]. In addition, Lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone.

In addition, Lenalidomide has direct activity against lymphoid cells and is able to induce apoptosis or G1 growth arrest. Most notably in the lymphoma field Lenalidomide has shown strong synergy with Rituximab, by exerting a strong positive effect on antigen dependent cellular citotoxicity[18]

6.2 Clinical experience in multiple mieloma

As far as toxicity issues are concerned most of our experience arises from MM studies, which include not only single agent but also combination studies as well as a large bulk pharmacokinetic data. Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg,

25mg, and 50mg). Plasma Lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. No plasma accumulation was observed with multiple daily dosing. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg[19]. A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of Lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma. All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent Lenalidomide. The experience of combining Lenalidomide with chemotherapy arise from a phase I/II trial of Liposomal doxorubicin (Doxil®), vincristine, dexamethasone (DVd) and Lenalidomide in heavily pre-treated relapsed/refractory multiple myeloma patients is ongoing. The MTD of Lenalidomide was 10mg on Days 1-21 in combination with Doxil® 40mg/m2 IVPB on Day 1, vincristine 2mg IVP on Day 1 and dexamethasone 40mg PO on Days 1-4 cycled every 28 days. All patients received amoxicillin, acyclovir and aspirin 81mg prophylactically. The dose limiting toxicity with Lenalidomide 15mg on Days 1-21 in combination with DVD was sepsis/septic shock[20].

6.3 Clinical experience in myelodysplastic syndromes (MDS)

An exploratory trial in 43 MDS patients with transfusion dependent or symptomatic anemia was conducted at the University of Arizona. Patients received Lenalidomide at doses of 25mg or 10mg per day, or of 10mg on Days 1-21, repeated every 28 days. All patients had had no response to erythropoietin or had a high endogenous erythropoietin level. Response rates were similar across the 3 dose schedules used. Responses were observed in 24 patients overall (56%) including 21 patients with a major response and 20 patients with sustained transfusion independence. Patients with a major response reached a median hemoglobin level of 13.2 grams per deciliter, with a corresponding 5.3 grams per deciliter median increase from baseline. After a median follow-up of 81 weeks, the median duration of major response had not been reached and was more than 48 weeks. Of 20 patients with karyotypic abnormalities, 10 (50%) patients had a complete cytogenetic remission. The response rate was highest in patients with a clonal interstitial deletion involving chromosome 5q31.1 (10 out of 12, 83%). Neutropenia and

thrombocytopenia were the most common adverse events, and resulted in dose delays or reductions in 25 patients (58%).

Celgene Corporation sponsored a multicenter trial (MDS-003) of 148 MDS patients with a clonal interstitial deletion involving chromosome 5q31.1. Lenalidomide was given at a dose of 10mg on Days 1-21, repeated every 28 days, to 44 patients, and at a dose of 10mg daily to the other 104 patients. Transfusion independence was achieved in 93 patients (64%), with a median hemoglobin increase of 3.9g/dl. Cytogenetic response was achieved in 76% of transfusion independent patients with 55% achieving a cytogenetic complete response. Pathologic complete response was documented in 32 out of 110 (29%) evaluable patients. With a median follow-up of 9.3 months, the median response duration had not been reached. Neutropenia (39%) and thrombocytopenia (35%) were the most common adverse events requiring dose delays or reductions.

Another Celgene sponsored trial (MDS-002) in patients with low to intermediate-1 risk MDS enrolled 215 patients, of whom, 166 were documented to have low to intermediate-1 risk MDS. Among the patients with documented low to intermediate-1 risk MDS, 84 patients (51%) responded to treatment. Transfusion independence was achieved in 54 patients (33%) and 30 patients (18%) achieved a minor response, defined as a 50% or greater decrease in blood transfusion requirement. The median duration of transfusion-independence was 41 weeks. The median baseline hemoglobin level was 8.0g/dl, which increased by 3.2g/dl in responding patients. Among 20 patients evaluable for cytogenetic response, 9 patients (45%) experienced a cytogenetic remission.

6.4 Clinical experience in solid tumors

Twenty patients with varying types of solid tumors (13 with malignant melanoma, 2 each with carcinoma of the pancreas and non-small-cell lung cancer [NSCLC], 1 each with renal carcinoma, breast carcinoma, and carcinoid-unknown primary) were enrolled in a Phase 1 study of Lenalidomide conducted at the St. George Hospital, London, UK. This was a non-randomized, open-label with-in patient dose-escalation design, where patients started on 5 mg/day for 7 days and then increased their dose every 7 days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks on therapy.

Investigators at the NCI have enrolled 20 patients, including 18 patients with recurrent high-grade gliomas and 2 with other refractory CNS malignancies (1 recurrent atypical meningioma and 1 multiple recurrent spinal hemangioblastomas) into a phase I trial of Lenalidomide given on Days 1 through 21 every 28 days. Treatment has been well tolerated with 1 grade 2 myelosuppression as the only toxicity > grade 1.

In an ongoing phase I trial in patients with refractory metastatic cancer conducted through the NCI, 12 patients with metastatic androgen independent prostate cancer have been enrolled. Lenalidomide was administered in daily doses of 5mg (3 patients), 10mg (3 patients) and 20mg (6 patients). Dose limiting toxicity was seen at 20mg/day (1 grade 3 thrombosis and 1 grade 3 hypotension). Stable PSA values for at least 8 weeks were observed in 6 patients.

In a phase III, multi-center, randomized parallel group study comparing two dose regimens of Lenalidomide, 293 patients with malignant melanoma were enrolled. Subjects were randomized to receive treatment with Lenalidomide at a dose of 5 mg per day orally for 28 days or to 25 mg per day orally for 21 days with a 7 day rest (28 day cycle). Treatment continued until the patient developed disease progression or intolerable adverse events occurred. Interim analysis failed to show an advantage of one regimen over the other with respect to survival. Analyses of response rates are pending. The toxicity profile was similar in both dose groups and the most frequent adverse events were fatigue, seen in 32% of patients, followed by nausea and diarrhea, seen in 24% and 20% of patients respectively. Neutropenia and thrombocytopenia were seen in 2.4% and 2.0% of patients respectively. Grade 3 and 4 toxicities were seen infrequently (<15%).

A second phase III randomized trial compared a Lenalidomide dose of 25 mg daily orally for 21 days with a 7 day rest (28 day cycle) to placebo in patients with metastatic melanoma. Three hundred and five patients enrolled on this study and a preplanned interim analysis failed to demonstrate a survival advantage. Response rates are being analyzed. The toxicity profile was favorable and similar to the previous phase III study.

6.5 Clinical experience in Lymphoma and other CD20+ tumors

The largest experience with Lenalidomide in CD20+ tumors arise from the study from Chanan-Khan et al[21] in chronic lymphocytic leukemia. In this phase II trial 45 patients with relapsed or refractory CLL were treated with Lenalidomide at the dose of 25 mg on a 21 every 28 days

schedule. In patients with evidence of disease progression Rituximab was added. Toxicity in this patient population was similar to that seen in MM and is shown in table 1. No unexpected toxicity was seen in patients undergoing Lenalidomide + Rituximab.

Toxicity	**Grade 1 and 2**		**Grade 3 and 4**	
	No.Patients	**%**	**No. Patients**	**%**
Fatigue	29	73	4	10
Somnolence	1	3	0	0
Constipation	12	30	0	0
Neuropathy	3	8	0	0
Pulmonary thromboembolism	0	0	2	5
Rash	16	40	1	3
Flare reaction	20	50	3	8
Pedal edema	6	15	0	0
Diarrhea	13	33	0	0
Tumor lysis syndrome	0	0	2	5
Hematologic				
Thrombocytopenia	13	33	18	45
Neutropenia	3	8	28	70
Anemia	18	45	7	18
Infections	7	18	2	5
Febrile neutropenia	0	0	6	15

At the 2006 ASH meeting additional experiences in the field has been reported. Wiernik et al[22] have employed Lenalidomide as single agent for the treatment of relapsed/refractory aggressive and indolent lymphoma with the classical 21 every 28 days schedule. Toxicity was mainly haematological. In this trial 32 patients with aggressive lymphomas were treated with a 32% objective response rate.

Most frequently reported adverse events reported during clinical studies with Lenalidomide in oncological and non-oncological indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulites, atrial fibrillation, congestive heart failure, myocardial

infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures. Complete and updated adverse events are available in the Investigational Drug Brochure.

6.6 INDICATIONS AND USAGE:

Revlimid® (Lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

6.7 ADVERSE EVENTS

Most frequently reported adverse events reported during clinical studies with Lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulites, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When Lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, adriamycin) and erythropoeitin the risk of thrombosis is increased.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

7. OBJECTIVES

7.1 PRIMARY OBJECTIVES

- To evaluate the feasibility and safety of a treatment regimen including Lenalidomide plus Rituximab-CHOP (LR-CHOP) through the definition of the DLT of Lenalidomide when delivered in combination with R-CHOP
- To evaluate the response rate of LR-CHOP in elderly patients with DLBCL at diagnosis at the MTD of Lenalidomide.

7.2 SECONDARY OBJECTIVES

To evaluate long term efficacy of LR-CHOP with Lenalidomide delivered at the MTD in elderly patients with DLBCL at diagnosis.

8. STUDY ENDPOINTS

8.1 PRIMARY ENDPOINTS

- Evaluation of feasibility and toxicity of the regimen according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.
- Definition of Dose Limiting Toxicity (DLT) considered as the maximum dose inducing any Grade $\geq$ 3 non-hematologic toxicity, or a delay > 15 days of planned cycle date.
- Overall response rate

8.2 SECONDARY ENDPOINTS

- 2-year OS and EFS
- Impact of LR-CHOP on immunologic reconstitution by analyzing both T cell and B-cell subsets
- Relationship between response to treatment and available baseline biologic factors. Such biologic factors will include histopathogenesis (GC vs activated B-cell), translocations, presence of immunoglobulin ongoing somatic hypermutation, presence of oncogene

aberrant somatic hypermutation. Biological studies will be defined and detailed as soon as possible.

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN

This is a prospective, multicenter dose finding phase II trial designed to determine the maximum tolerated dose (MTD) of combination therapy of Lenalidomide and R-CHOP, with a fixed dose of R-CHOP and to evaluate the safety and efficacy of the combination of Lenalidomide, Rituximab and CHOP chemotherapy in elderly patients with untreated Diffuse Large B-Cell Lymphoma (DLBCL) or Follicular grade IIIb Lymphoma.

DOSE FINDING PHASE

The design of this dose-finding phase clinical trial is chosen to assess the maximum tolerated dose (MTD) of Lenolidamide when administered in combination with Rituximab-CHOP chemotherapy in the treatment of elderly patients with untreated Diffuse Large B-Cell Lymphoma (DLBCL) or Follicular grade IIIb Lymphoma. The MTD is defined as the dose that achieves a dose-limiting toxicity (DLT) in 33% of patients.

Four dose levels are tested, namely 5, 10, 15 and 20 mg. The continual reassessment method (CRM) (O'Quigley et al, 1990; Garrett-Mayer, 2006; O'Quigley and Zohar, 2006) is used as the dose allocation rule in the trial. It is based on a mathematical modelling of dose–DLT relationship, iteratively updated using Bayes theorem along the trial, as follows. First, before trial onset, prior opinions about DLT probability at each dose level are elicited from expert clinicians on the basis of their personal experience and on literature. These initial guesses, which relied on the opinion of participating clinicians, were fixed at 0.15, 0.20, 0.25, and 0.30, respectively.

The uncertainty in this dose–DLT relationship is incorporated into a prior. Then, the first three included patients are administered the second dose level (10 mg). After the enrollment of the first three patient, accrual continues, with grouped inclusions of three patients per dose level Then, on the basis of observed responses (DLT or not), DLT probabilities of all dose levels are updated using Bayes theorem. The dose level associated with an updated DLT probability close to 33% is recommended to be administered to the next patient cohort. All this process is re-run until the

fixed sample size (N=25) is reached, or in case of fulfilled stopping criteria measuring futility of trial continuation (Zohar and Chevret, 2001).

PHASE II

Phase II study – Simon's two-stage Minimax Design, since it is the design that minimizes the expected sample size given a 'bad' response rate

Parameter specifications are: Standard proportion of ORR: p0= 0.7; Minimum required ORR for the new regimen: p1= 0.85; alpha= 0.05; power= 0.8

Sample size: 49 subjects (total), 23 will be accrued during the first PHASE and 26 during PHASE II

Stopping rules:

Given that the 'true' response probability is 70%, there is a 56.01% probability of ending the trial during stage 1, with an expected sample size for the trail of 20.58.

However, if the 'true' response probability is 85%, there is only a 4.63% probability that the trial will be stopped in stage 1.

If 16/23 or fewer responses are observed during the first stage then the trail is stopped early.

If 39/49 or fewer responses are observed by the end of the trail, then no further investigation of this regimen is warranted.

Patients enrolled at the MTD during the dose finfing Phase study will be consider as part of the Phase II trial.

Assuming a 5% losses for any reasons, the total number of patients to be enrolled is 52.

The study is divided in 3 phases:

1. **A pretreatment (screening) phase** of approximately 28 days Patients will be evaluated before enrolment in the study as required according the staging rules.

2. **A prospective multicenter treatment phase**. Patients will be enrolled into different cohorts with different dose levels of Lenalidomide: 5 mg, 10 mg,15 mg and 20 mg according to the method previously described. The investigator will assess patient response to therapy using efficacy measurements and disease response criteria. Patients will be evaluated through this phase for possible toxicities and delays in dosing. Dose adjustments will be made as required according to dose modification rules. Patients will be treated with six courses of therapy with a twenty day rest period between them. At the end of the 3° course all enrolled patients will be evaluated for tumor response. All patients with responsive disease (CR, Cru, PR) will receive the remaining 3 courses of treatment at the same schedule and doses.

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

3. **A follow-up phase**. Patients will be followed for disease progression and survival until the end of the study which is expected to be 24 months after completing the treatment by the last patients enrolled into the study

9.2 DESIGN RATIONALE

Based on previous considerations we believe that a strong rationale exist in favor of the introduction of Lenalidomide in the context of Rituximab supplemented schedules currently employed in DLBCL. In particular: a) a high proportion of patients still fail R-CHOP[11]; b) Lenalidomide has proven activity in DLCL-B[22]; 3) there is strong preclinical evidence that Lenalidomide might be synergistic with drugs employed in R-CHOP, particularly Rituximab[18]; 4) Lenalidomide might be combined with doxorubicin and vincristine with acceptable side effects20. We thus here propose a phase I-II dose escalating trial to explore feasibility, toxicity and efficacy of a Lenalidomide supplemented R-CHOP regimen (LR-CHOP). The first part of the study will investigate feasibility safety and tolerability of increased doses of Lenalidomide in the context of the R-CHOP regimen. When the Dose Limiting Toxicity (DLT) will be established a cohort of patients will be treated at Maximum Tolerated Dose (MTD) to preliminary establish treatment effectiveness. The primary efficacy analysis of the second phase of the study will be the evaluation of complete response observed after LR-CHOP. The study will be designed according to the 2 stage design of phase II clinical trials of Simon et al in order to optimize the number of patients to be enrolled and to stop the study in case of responses less than expected.

Diffuse large B-Cell lymphoma are currently treated with Rituximab-CHOP chemotherapy with a 5-yr EFS of 54% in elderly patients (>60 yrs). This figure drops at 41% at 5 years in patients with intermediate-high and high risk IPI score.[23] Thus, at least 40-45% of the patients progress or relapse in the first three years off treatment. Although Rituximab-CHOP regimen represents a step forward to cure in DLBCL patients, there is a need to find new effective regimen to treat these patients.

9.3 STUDY POPULATION

Male and women patients, $\geq$ 60 years old and $\leq$ 80 are eligible for this clinical trial if they have Diffuse Large B-Cell Lymphoma or Follicular grade IIIb Lymphoma in first line treatment.
Specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

9.4 INCLUSION AND EXCLUSION CRITERIA

9.4.1 INCLUSION CRITERIA

1. Understand and voluntarily sign an informed consent form
2. Able to adhere to the study visit schedule and other protocol requirements
3. Histologic subtypes as follows:
   CD20 positive Diffuse large B-Cell lymphoma
   CD20 positive Follicular grade IIIb
4. Age 60-80
5. Untreated patients. In patients with bulky mass or systemic simptoms or compressive disease or rapidly progressive adenopathies a pre-study treatement is allowed with steroids and/or a single dose of Vincristine 1.4 mg/mq (max 2) in the seven days prior the start of the study treatment
6. Measurable and/or evaluable disease
7. Ann Arbor stage II, III, IV
8. International Prognostic Index at low-intermediate, intermediate, high risk (2/3/4-5)
9. Adequate haematological counts: ANC > 1.5 x 10^9/L and platelet count > 75 x 10^9/L unless due to bone marrow involvement

10. Conjugated bilirubin up to 2 x ULN.
11. Alkaline phosphatase and transaminases up to 2 x ULN.
12. Creatinine clearances > 50 ml/min.
13. HIV negativity
14. HCV negativity
15. HBV negativity or patients with HBVcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative
16. Cardiac ejection fraction (MUGA scan or echocardiography) > 45%
17. Non peripheral neuropathy or CNS disease. Non testicular Lymphoma
18. Life expectancy > 6 months.
19. Performance status ≤ 2 according to ECOG scale.
20. Comprehensive geriatric assessment (CGA) as outlined in Appendix 15 showing absence of any impairment in activity of daily living (ADL), of any condition defining a geriatric syndrome, and of any grade 4 comorbidity or of more than three grade 3 comorbidities according to CIRS-G scale
21. Disease free of prior malignancies for ≥ 3 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "insitu" of the cervix or breast
22. Females of childbearing potential (FCBP) must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

    - **Before starting study drug:**

    Female Subjects:

        - FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second

pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

During study participation and for 28 days following discontinuation from the study:

All Subjects:

- No more than a 28-day supply of study drug will be dispensed at a time.

Female Subjects:

- FCBP with regular cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood.

- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

- Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen.

If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, study drug must be immediately discontinued.

9.4.2 EXCLUSION CRITERIA

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

1. Lymphoblastic Lymphoma
2. Burkitt Lymphoma
3. Non Hodgkin lymphoma CD 20 negative
4. Mantle Cell Lymphoma
5. Follicular Non Hodgkin Lymphoma grade I-II-IIIa
6. Primitive mediastinal diffuse large B cell lymphoma with only mediastinal involvement
7. International Prognostic Index at low risk (1)
8. Has known or suspected hypersensitivity or intolerance to rituximab
9. History of evolutive malignancy within the last 3 years other than squamous cell and basal cell carcinoma of the skin or carcinoma "insitu" of the cervix or breast
10. Extensive radiation therapy, systemic chemotherapy, or other antineoplastic therapy within 3 years before enrollment
11. Exposure to Rituximab prior to study entry

12. Have received an experimental drug or used an experimental medical device within 4 weeks before the planned start of treatment. Concurrent participation in non-treatment studies is allowed, if it will not interfere with participation in this study
13. CNS disease (meningeal and/or brain involvement by lymphoma) or Testicular involvement
14. DVT in the last year
15. History of clinically relevant liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances
16. Uncontrolled diabetes (if receiving antidiabetic agents, subjects must be on a stable dose for at least 3 months before first dose of study drug
17. Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure (Attachment 5, NYHA Classification of Cardiac Disease), uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis
18. Creatinine clearances < 50 ml/min
19. Presence of major neurological disorders
20. HIV positivity
21. HBV positivity with the exception of patients with HBVcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative
22. HCV positivity
23. Active opportunistic infection
24. Comprehensive geriatric assessment (CGA) as outlined in Appendix 15 showing presence of any impairment in activity of daily living (ADL), of any condition defining a geriatric syndrome, and of any grade 4 comorbidity or of more than three grade 3 comorbidities according to CIRS-G scale
25. Any other co-existing medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent

9.5 TREATMENTS

9.5.1. TREATMENT ASSIGNMENTS

The amount (in mg) of Lenalidomide to be administered will be determined based on planned schema by group of study. The amount (in mg) of Rituximab to be administered will be determined based on body surface area (BSA) using a standard calculation provided in Attachment 8, Suggested Body Surface Area Calculation. Instructions including calculation of the subject's dose, preparation and handling of the RITUXIMAB infusion are provided in Attachment 4, Instructions for the Preparation and Handling of RITUXIMAB Injections.
Study drug will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s).

9.5.2. DOSING REGIMENS

Patients will be enrolled into different cohorts with different dose levels of Lenalidomide: 5 mg; 10 mg; 15 mg and 20 mg in accordance with statistical design.

FIRST DOSE LEVEL:

- **Rituximab 375 mg/sqm D 0 or 1**
- **Cyclophosphamide 750 mg/sqm iv D1**
- **Doxorubicin 50 mg/sqm iv D1**
- **Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)**
- **Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5**
- **Revlimid 5 mg/day D1-D14**

Repeated every 21 days

SECOND DOSE LEVEL

- **Rituximab 375 mg/sqm D 0 or 1**
- **Cyclophosphamide 750 mg/sqm iv D1**

- **Doxorubicin 50 mg/sqm iv D1**
- **Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)**
- **Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5**
- **Revlimid 10 mg/day D1-D14**

Repeated every 21 days

THIRD DOSE LEVEL

- **Rituximab 375 mg/sqm D 0 or 1**
- **Cyclophosphamide 750 mg/sqm iv D1**
- **Doxorubicin 50 mg/sqm iv D1**
- **Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)**
- **Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5**
- **Revlimid 15 mg/day D1-D14**

Repeated every 21 days

FOURTH DOSE LEVEL

- **Rituximab 375 mg/sqm D 0 or 1**
- **Cyclophosphamide 750 mg/sqm iv D1**
- **Doxorubicin 50 mg/sqm iv D1**
- **Vincristine 1.4 mg/sqm iv D1 (maximum dose 2 mg total)**
- **Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5**
- **Revlimid 20 mg/day D1-D14**

Repeated every 21 days

Patient at risk for CNS involvement according to SIE giudelines (appendix 10) should receive prophylaxis with Methotrexate 12 mg IT for four doses (Day 0 or Day 1 Cycles 1-4).

In patients with bulky mass or systemic simptoms or compressive disease or rapidly progressive adenopathies a pre-study treatement is allowed with steroids and/or a single dose of Vincristine 1.4 mg/mq (max 2) in the seven days prior the start of the study treatment.

SECOND AND THIRD COURSE as the first one:

For patients enrolled in the dose-finding phase of the study a real-time assessment of the development of dose-limiting toxicities after the second course is warranted in order to enable the dose allocation of the subsequent cohort of three patients

Clinical response will be assessed after the first three courses of therapy.

Patients with responsive disease (CR, PR) will proceed to further three courses of therapy with the same schedule and doses.

Patients with progressive disease, stable disease or severe toxicity after the first three courses of therapy will be withdrawn from the study.

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

FOURTH, FIFTH AND SIXTH COURSE as the first one:

Clinical response will be assessed two months after the completion of the whole therapy.

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

9.5.3 RECOMMENDED CONCOMITANT THERAPY

During treatment are recommended as concomitant therapy:

- PEG-filgrastim 6 mg 48 hours after chemotherapy CHOP
- Cotrimoxazole BACTRIM 3 tablets/week (or 1 x 2/day per two days/week) or Pentamidine aerosol every 15 days in patients with Bactrim allergy or in patients with G6PD deficiency throughout the treatment and consolidation phase
- In patients with Ab antiHBcAg +, Ab antiHBsAg +/- prophylaxis against hepatitis B reactivation with Lamivudine 100 mg/die from the start of the treatment to one year after the end of the treatment
- Low-weight heparin (Enoxaparin 4000 UI or Nadroparin 0.4 ml) as DVT prophylaxis

- Acceptable method of birth control at the same time (one highly effective method and one additional effective method) (cfr attachment 12)

All concomitant medications for medical conditions other than B-NHL are permitted, as clinically indicated

All supportive therapies other than anti-cancer treatment needed for the management of patients enrolled in this study are permitted

9.5.4 PERMITTED CONCOMITANT THERAPY

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

- Antiviral prophylaxis with acyclovir 800-1200 mg at day since the beginning of therapy is strongly recommended in patients with herpes virus infection riactivation
- Additional prophylaxis with levofloxacine or ciprofloxacine and fluconazole/itraconazole will be administrated in case of neutropenia $<1.0 \times 10^9$/l.

Platelets and red blood cell transfusion are allowed, if needed.

Immunoglobulin assay is advisable once a month during the therapy with immunoglobulin replacement in case of IgG level < 0.3-0.5 gr/dl and frequent infectious events. Packed red cells and platelets transfusions will be given with filtered and irradiated products in case of Hb < 8 g/dL or Plts $< 10 \times 10^9$/L. Erytropoietin therapy is allowed according to ASH/ASCO guidelines.

Bowel care is recommended to prevent costipation and should be administrered per standard practice.

Antiemetic agents.

Premedication for rituximab infusion with paracetamol and diphenhydramine should be considered before each infusion of rituximab, because it may reduce infusion reactions.

9.5.5 PROHIBITED CONCOMITANT THERAPY

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

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

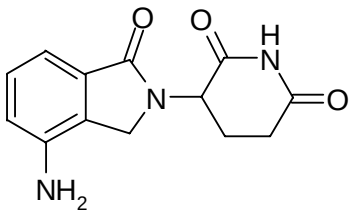
Any experimental agent

10. STUDY DRUG MATERIAL AND MANAGEMENT

10.1 LENALIDOMIDE DESCRIPTION

REVLIMID® (Lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for Lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

REVLIMID® (Lenalidomide) is available in 5 mg and 25 mg capsules for oral administration. Each capsule contains Lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

Clinical pharmacology:

Mechanism of Action:

The mechanism of action of Lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, Lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of yclooxygenase-2 (COX-2) but not COX-1 in vitro.

Pharmacokinetics and Drug Metabolism:

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of Lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters:

Distribution:

In vitro (^{14}C)-Lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of Lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of Lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

10.2 SUPPLIER(S)

Celgene Corporation will supply Lenalidomide.

10.3 DOSAGE FORM

Lenalidomide will be supplied as 5 mg capsules for oral administration.

10.4 PACKAGING

Drug will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules to last for 14 days of dosing. Study drug must be dispensed in the original packaging with the label clearly visible**. Only one 28 day supply maybe provided to the patient each cycle.**

10.5 LABELING

Lenalidomide investigational supplies are dispensed to the patient's in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear name.

10.6 RECEIPT OF STUDY DRUG

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file.

10.7 STORAGE

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.
The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

10.8 UNUSED STUDY DRUG SUPPLIES

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules.

11. DOSE MODIFICATION OR INTERRUPTION

Before each dose of study drug, the subject will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 3.0 (see Attachment 9).

CHOP dose modification

Patients will start LR-CHOP every 21 days if Neutrophils > 1.5 x 10^9/L and Platelets > 75 x 10^9/L.

- If Neutrophils are < 1.5 x 10^9/L and/or Platelets < 75 x 10^9/L: LR-CHOP must be delayed (after 7 days, on Day +28).
- If Neutrophils > 1.5 x 10^9/L and Platelets > 75 x 10^9/L on Day +28 LR-CHOP will be performed with no change in dose.
- If Neutrophils < 1.5 x 10^9/L and/or Platelets < 75 x 10^9/L on Day + 28, LR-CHOP will be delayed (after 7 Days, on Day +35).
- If Neutrophils < 1.5 x 10^9/L and/or Platelets < 75 x 10^9/L on Day + 35, the treatment plan will be discontinued (withdrawal of the study, failure).
- Dose modification for sensory neuropathy. No modification as long as neuropathy does not affect function. Any decrease of function (grade 3/4) would lead to dose reduction of vincristine by 50%. If grade 4 toxicity persists after reduction of vincristine by 50%, vincristine may be eliminated from subsequent cycles.
- Prednisone dose may be decreased by 50% or discontinued if patients have increase in serum glucose to > 300 mg/dl, or other psychological disturbances such as psychosis or anxiety attacks.

RITUXIMAB dose modification

Rituximab administration and dose modification must follow labeling instructions and guidelines. Please refer to the approved product label for instructions.

Patients who develop severe infusion reactions should have rituximab infusion discontinued and supportive care measures as medically indicated (e.g. fluids, vasopressors, oxygen, bronchodilators, acetaminophen , etc.) In most cases, the infusion can be resumed at 50% reduction rate (e.g. from 100 mg/hr to 50 mg/hr (when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events, and whose with high numbers of circulating malignant cells (>25 x 10^9/l) with or without evidence of high tumor burden.

REVLIMID Dose Modifications

In case of hematological toxicity the same rules will apply also for Lenalidomide delivery i.e.

- If Neutrophils are < 1.5 x 10^9/L and/or Platelets < 75 x 10^9/L: LR-CHOP must be delayed (after 7 days, on Day +28)
- If Neutrophils > 1.5 x 10^9/L and Platelets > 75 x 10^9/L on Day +28 LR-CHOP will be performed with no change in dose
- If Neutrophils < 1.5 x 10^9/L and/or Platelets < 75 x 10^9/L on Day + 28, LR-CHOP will be delayed (after 7 Days, on Day +35)
- If Neutrophils < 1.5 x 10^9/L and/or Platelets < 75 x 10^9/L on Day + 35, the treatment plan will be discontinued (withdrawal from the study, failure)

If grade 3 or 4 non-hematologic toxicity will be observed, patient will be withdrawn from the study.

12. ASSESSMENTS

12.1 EFFICACY ASSESSMENT

Overall Response Rate (ORR): Complete Remission, Partial Remission.

A patient is defined as a responder if he has a complete or partial response. Patients without response assessment (due to whatever reason) will be considered as non-responder.

Criteria for evaluation

A modification of the recently published recommendations of an International Workshop to Standardise Response Criteria for Non-Hodgkin´s Lymphomas [Cheson et al., 2007] will be applied. Response criteria will be determined as follows:

Complete response (CR) requires the disappearance of all evidence of disease.

(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative

(b) Variably FDG-avid or PET negative; regression to normal size on CT.

Spleen or liver should be not palpable and any nodules disappeared.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative.

Partial response (PR) requires regression of measuable disease and no new sites of disease.

The decrease in sum of the product of the diameters (SPD) of up to 6 largest dominant masses should be of 50%; no increase in size of other nodes. If nodal masses are FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site. If nodal masses present variably FDG-avid or PET negative; regression on CT should be detected.

Liver or spleen should not be increased in size and their nodules should present a decrease 50% in SPD (for single nodule in greatest transverse diameter). Bone marrow is irrelevant if positive prior to therapy; cell type should be specified.

Stable disease (SD) is defined as a failure to attain CR/PR or PD.

(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET. (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT.

Relapsed disease or PD: Any new lesion or increase by > 50% of previously involved sites from nadir.

Nodal masses. Appearance of a new lesion(s) > 1.5 cm in any axis, 8 50% increase in SPD of more than one node, or 8 50% increase in longest diameter of a previously identifed node > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET

positive prior to therapy.

Spleen, Liver: >50% increase from nadir in the SPD of any previous lesions.

Bone marrow. New or recurrent involvement.

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

Time to treatment failure will be measured from the day of randomization to the date of documented disease progression, relapse or death from any cause.

Progression-free survival will be measured from the first day of recruitment to the date of progressive disease. Responding patients and patients who are lost to follow up will be censored at their last assessment date.

12.2 SAFETY ASSESSMENT

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

Adverse Events

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

Clinical Laboratory Tests

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

Electrocardiogram

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

Physical Examination

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

Safecty and feasibility of treatment: severe hematological toxicities (grade 3-4) expected.

Patients partecipation will include:

- The pretreatment (screening) phase will be 30 days for all laboratory tests and radiographic imaging phase and up to 60 days for bone marrow evaluation. Lymphnode or involved tissue biopsy is mandatory before study entry, it should be performed within 6 months before study entry.
- The treatment phase will extend from the first day of the first course of LR-CHOP to a maximum of 6 courses.
- The follow-up phase will begin after the completion of the sixth course of LR-CHOP. Follow-up will continue until disease progression (PD) is documented, the patient decides to withdraw from the study, death or the study is ended (expected to be 24 months from the date of the last patient's end of therapy).

Hematology results must be available and reviewed by the investigator to evaluate for possible hematological toxicity.

All subjects will be monitored for adverse events throughout the study and for 30 days after the end of treatment.

Screening phase

All patients must satisfy all the inclusion criteria and none of exclusion criteria listed in section 4.2 and 4.3 and sign informed consent before the first dose of study drug can be administrated. Results of procedures performed as part of standard medical care before signing the informed consent may be used as part of the screening evaluation if performed within 28 days of beginning of therapy for laboratory tests and imaging studies, within 60 days for bone marrow biopsy and aspirate and within 6 months for lymphnode biopsy.

- Complete medical history
- Concomitant diseases and treatment
- Recent clinical history (B symptoms)
- Physical examination (size of lymphnodes, sign of organ involvement)
- ECOG performance status
- Bone marrow biopsy and aspirate
- Lymphonode or tissue involved biopsy
- Chest and abdomen computer tomography scan; CT scan of the head and neck at the discretion of the treating physician

- CT scan-PET evaluation (if possible, recommended but not mandatory)
- ECG and echocardiogram or blood pool cardioscintigraphy
- Clinical neurological assessment and eventually EMG
- Hematology (hematocrit, hemoglobin, RBC WBC and differential, Platelets, CD3+, CD4+, CD8+, CD19+, CD20+)
- Blood chemistry (AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, creatinine, Na, K, Ca, P, uric acid, total protein, albumin)
- Coagulation assessment (PTT, PT, ATIII, Ddimero, Fibrinogeno)
- Serum LDH
- Beta-2-microglobulin
- Clearance creatinine
- IgA, IgG, IgM
- HIV
- HBsAg, HbsAb, HBVcAb and HBV-DNA
- HCV
- Immunohistochemical detection of CD20 on lymphoma-cells (lymphnode)
- Lumbar Puncture for determination of cell count, differential, cytologic and cytoflussimetry examination (if possible) of tumor cells; Lumbar Puncture must be performed if neurologically signs of CNS involvement or if patient at risk (see Attachment 10: CNS risk, SIE guidelines and recommendations)
- Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.
- Written informed consent.

Treatment phase

The treatment phase begins on Day 1 of course 1 (total 6 courses) of treatment with study drug and continues until completion of study therapy or discontinuation of treatment with the study drug (end of treatment visit).

Before each course will be evaluated:

- Physical examination
- Hematology (Whole blood cell counts and differential)
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K).

After each course will be evaluated (timing: days 7 to 14):

- Hematology (Whole blood cell counts and differential)
- Blood chemistry (AST, ALT, serum alkaline phosphatase, GGT, total bilirubin, creatinine, Na, K, uric acid).

Patients will be evaluated through this phase for possible toxicities and delays in dosing: dose modification will be made as required according to dose modification rules identified in section 5.2. Patients who discontinued study drug due to toxicity will have end of treatment procedures completed and enter in the follow up phase.

Additional assessments have to be performed according to the local standards and if clinically indicated at the discretion of the treating physician.

AFTER COURSE 3:

- Physical examination (size of lymphnodes, signs of organ involvement)
- ECOG performance status
- Hematology (hematocrit, hemoglobin, RBC WBC and differential, Platelets, CD3+, CD4+, CD8+, CD19+, CD20+)
- Blood chemistry (AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, creatinine, Na, K, Ca, P, uric acid, total protein, albumin)
- Serum LDH
- Beta-2-microglobulin
- IgA, IgG, IgM
- Bone marrow biopsy (Should be performed only if it was abnormal at baseline visit)

- Chest and abdomen computer tomography; CT of the head and neck at the discretion of the treating physician
- CT scan-PET (if possible)
- Bone marrow biopsy and aspirate (Should be performed only if it was abnormal at baseline visit)
- Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.

All patients with disease in CR or PR will continue the trial and will be treated with 3 courses of therapy with the same drug doses and assessment.

All patients in NR, SD, PD or with severe toxicity will be considered out of study and the therapy with the study drug will be discontinuated

Follow phase

The follow up phase begins with the end treatment visit that will be performed one month after the last dose of study drug is administrated.

The end treatment visit will include end of treatment procedures and collection of adverse events during the month after the last dose of study drug administration : in this visit will be evaluated:

- Physical examination (size of lymphnodes, signs of organ involvement)
- ECOG performance status
- Hematology (hematocrit, hemoglobin, RBC WBC and differential, Platelets, CD3+, CD4+, CD8+, CD19+, CD20+)
- Blood chemistry (AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, BUN, creatinine, Na, K, Ca, P, uric acid, total protein, albumin)
- Serum LDH
- Beta-2-microglobulin
- IgA, IgG, IgM

- Bone marrow biopsy and aspirate (Should be performed only if it was abnormal at baseline visit)
- Chest and abdomen computer tomography; CT of the head and neck at the discretion of the treating physician
- CT scan-PET (mandatory)
- Neurological assessment
- Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.

After the completion of the end of treatment evaluation all patients will enter in the follow up phase. The follow up phase will end in case of dead or progressive disease.

During the follow up phase will be evaluated:

Every 2 months:

- Physical examination (size of lymphonodes, sign of organ involvement)
- Recent clinical history (B symptoms)
- ECOG performance status
- Hematology (hematocrit, hemoglobin, RBC WBC and differential, Platelets)
- Blood chemistry (AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, BUN, creatinine, Na, K, Ca, P, uric acid, total protein, albumin)
- Serum LDH
- Additional assessments if necessary

At months 6, 12, 18 and 24:

- Recent clinical history (B symptoms)
- Physical examination (size of lymphonodes, sign of organ involvement)
- ECOG performance status
- Chest and abdomen computer tomography or CT-scan PET; CT of the head and neck at the discretion of the treating physician
- Hematology (hematocrit, hemoglobin, RBC WBC and differential, Platelets, CD3+, CD4+, CD8+, CD19+, CD20+)

- Blood chemistry (AST, ALT, serum alkaline phosphatase, gGT, total bilirubin, BUN, creatinine, Na, K, Ca, P, uric acid, total protein, albumin)
- Serum LDH
- Beta-2-microglobulin
- IgA, IgG, IgM
- Bone marrow biopsy and aspirate (Should be performed only if it was abnormal at baseline visit)
- Additional assessments if necessary according to the local standards and if clinically indicated at the discretion of the treating physician.

13. PROTOCOL AMENDMENTS/DEVIATIONS

13.1 PROTOCOL AMENDMENTS
13.2 PROTOCOL DEVIATIONS

14. DATA MANAGEMENT

14.1 STUDY MONITORING AND AUDITING

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

15 BIOSTATISTICAL ANALYSIS

15.1 INTRODUCTION

Diffuse large B-Cell lymphoma are currently treated with Rituximab-CHOP chemotherapy with a 5-yr EFS of 54% in elderly patients (>60 yrs). This figure drops at 41% at 5 years in patients with intermediate-high and high risk IPI score. Thus, at least 40-45% of the patients progress or relapse in the first three years off treatment.

A strong rationale exist in favor of the introduction of Lenalidomide in the context of Rituximab supplemented schedules currently employed in DLBCL.

In particular: a) a high proportion of patients still fail R-CHOP; b) Lenalidomide has proven activity in DLCL-B; 3) there is strong preclinical evidence that Lenalidomide might be

synergistic with drugs employed in R-CHOP, particularly Rituximab; 4) Lenalidomide might be combined with doxorubicin and vincristine with acceptable side effects.

15.2 PURPOSE

This is a prospective, multicenter dose finding phase II trial designed to determine the maximum tolerated dose (MTD) of combination therapy of Lenalidomide and R-CHOP, with a fixed dose of R-CHOP and to evaluate the safety and efficacy of the combination of Lenalidomide, Rituximab and CHOP chemotherapy in elderly patients with untreated Diffuse Large B-Cell Lymphoma (DLBCL) or Follicular grade IIIb Lymphoma.

DOSE FINDING PHASE

Open-label dose finding study to determine the maximum tolerated dose (MTD) of combination therapy of Lenalidomide and R-CHOP, with a fixed dose of R-CHOP, in elderly patients with untreated DLCL-B.

ENDPOINTS

Primary: adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Secondary: complete response and overall response rate.

TREATMENT SCHEDULE

Patients will be enrolled into four dose level of Lenalidomide (5 mg; 10 mg; 15 mg and 20 mg) in combination with R-CHOP. Lenalidomide will be administered at D1-D14.

The R-CHOP schedule will be repeated every 21 days:

Rituximab 375 mg/sqm D 0 or 1

Cyclophosphamide 750 mg/sqm iv D1

Doxorubicin 50 mg/sqm iv D1

Vincristine 1.4 mg/sqm iv D1 (Maximum dose 2 mg total)

Prednisone 40 mg/sqm orally D1, D2, D3, D4, D5

DEFINITION OF DOSE LIMITING TOXICITY

DLT is defined as the occurrence of any grade $\geq$ 3 non-hematologic toxicity, or a delay > 15 days from planned cycle date observed during the first two cycles.

Trial design and dose allocation rule

The design of this dose-finding phase II clinical trial is chosen to assess the maximum tolerated dose (MTD) of Lenolidamide when administered in combination with Rituximab-CHOP chemotherapy in the treatment of de-novo elderly patients with untreated Diffuse Large B-Cell Lymphoma (DLBCL) or Follicular grade IIIb Lymphoma. The MTD is defined as the dose that achieves a dose-limiting toxicity (DLT) in 33% of patients.

Four dose levels are tested, namely 5, 10, 15 and 20 mg. The continual reassessment method (CRM) (O'Quigley et al, 1990; Garrett-Mayer, 2006; O'Quigley and Zohar, 2006) is used as the dose allocation rule in the trial. It is based on a mathematical modelling of dose–DLT relationship, iteratively updated using Bayes theorem along the trial, as follows. First, before trial onset, prior opinions about DLT probability at each dose level are elicited from expert clinicians on the basis of their personal experience and on literature. These initial guesses, which relied on the opinion of participating clinicians, were fixed at 0.15, 0.20, 0.25, and 0.30, respectively.

The uncertainty in this dose–DLT relationship is incorporated into a prior. Then, the first three included patients are administered the second dose level (10 mg). After the enrollment of the first three patient, accrual continues, with grouped inclusions of three patients per dose level.. Then, on the basis of observed responses (DLT or not), DLT probabilities of all dose levels are updated using Bayes theorem. The dose level associated with an updated DLT probability close to 33% is recommended to be administered to the next patient cohort. All this process is re-run until the fixed sample size (N=25) is reached, or in case of fulfilled stopping criteria measuring futility of trial continuation (Zohar and Chevret, 2001).

PHASE II

Primary endpoint:

Overall Response Rate (ORR)

Design:

Phase II study – Simon's two-stage Minimax Design, since it is the design that minimizes the expected sample size given a 'bad' response rate

Parameter specifications:

- Standard proportion of ORR: p0= 0.7
- Minimum required ORR for the new regimen: p1= 0.85
- alpha= 0.05
- power= 0.8

Sample size:

49 subjects (total)

23 will be accrued during DOSE FINDING PHASE

26 during PHASE II

Stopping rules:

Given that the 'true' response probability is 70%, there is a 56.01% probability of ending the trial during stage 1, with an expected sample size for the trail of 20.58.

However, if the 'true' response probability is 85%, there is only a 4.63% probability that the trial will be stopped in stage 1.

If 16/23 or fewer responses are observed during the first stage then the trail is stopped early.

If 39/49 or fewer responses are observed by the end of the trail, then no further investigation of this regimen is warranted.

Patients enrolled at the MTD during the first Phase study will be consider as part of the Phase II trial.

Losses to follow-up:

Assuming a 5% losses for any reasons, the total number of patients to be enrolled is 52.

SUBJECT COMPLETION/WITHDRAWAL

Completion

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

Discontinuation of Treatment

A patient should be discontinued from study treatment if

- the investigator believes that for safety reasons (e.g., adverse event) it is in the best interest of the subject to stop treatment
- the subject has disease progression at any time
- the subject has no response after the third course of therapy
- The subject has ≥ grade 3 toxicity for > 2 weeks

Withdrawal From the Study

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

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

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

ADVERSE EVENT REPORTING

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

Definitions

Adverse events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the time of signing the informed consent through the end of the designated follow-up period.

Abnormal laboratory values defined as adverse events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.
- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention.
- Is judged by the Investigator(s) to be of significant clinical importance.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Serious Adverse Events (SAE)

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

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

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The severity of adverse events (AEs) will be graded on a scale of 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE). The NCI CTCAE V3.0 can be viewed on-line at the following NCI web site: http://ctep.cancer.gov/reporting/ctc.html. If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event

Grade	Definition
1	**Mild** Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities
2	**Moderate** Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres
3	**Severe** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required
4	**Life-threatening** Immediate risk of death; requires hospitalization and clinical intervention.
5	**Death**

Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

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

Not suspected:	The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Suspected:	The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Serious Adverse Event (SAE) Reporting Report of Adverse Events to Regulatory Authorities and the Ethics Committee

The sponsor will inform relevant Regulatory Authorities and the Ethics Committee:

- of all relevant information about serious unexpected adverse events suspected to be related to the study medication that are fatal or life threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days.
- of all other serious unexpected events suspected to be related to the study medication as soon as possible , but within a maximum of fifteen days of first knowledge by the investigator.

The investigator will inform the sponsor of all SAEs within 24 hours in order that the sponsor can fulfil their regulatory reporting obligations within the required timeframes.

The sponsor will supply Celgene with a copy of all SAEs as they occur regardless of whether or not the event is listed in the reference brochure.

The sponsor will provide Celgene with a copy of the annual safety report at the time of the submission to the regulatory authority and the Ethics Committee.

Table 6: Safety Contact Information

	Safety Phone Number	**Safety Fax/e-mail**
Principal Investigator **PHARMACO VIGILANCE responsible :** **Dr. Alessandro Levis (AL)**	**+39 - 0131-206129**	**+39 - 0131-261029** **email:** **segreteria@iilinf.it**
Celgene S.r.l. **Dr. Roberta Di Menno Di Bucchianico**	**+39 02 72546315** **+39 340/8369630**	**Fax** **+39 02 72546 400** **Email** **drugsafetyitaly@celgene.com**

Sponsor Reporting to Celgene

The sponsor will provide Celgene with a copy of the annual safety report at the time of the submission to the regulatory authority and the Ethics Committee.

Pregnancies

Pregnancies occurring while subjects are on study drug or within 4 weeks after a subject's last dose of study drug are considered events to be reported immediately to Sponsor and Celgene. 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 must be reported to Sponsor who will inform Celgene immediately of the Investigator's knowledge of the pregnancy by phone and facsimile using an SAE Form.

The Investigator will follow the subject until completion of the pregnancy, and must notify the sponsor and Celgene of the outcome within 5 days or as specified below. The Investigator will provide this information as a follow-up to the initial pregnancy report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted foetus is to be documented], stillbirth, neonatal death, or congenital anomaly), 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 is related to the *in utero* exposure to the study drug should also be reported.

In the case of a live "normal" birth, the Sponsor and Celgene should be advised as soon as the information is available.

Any suspected foetal exposure to Lenalidomide must be reported to Sponsor and Celgene within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

Adverse event updates/IND safety reports

Celgene shall notify the sponsor via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The principle investigator/sponsor will forward this information to other investigators involved in the trial.

The sponsor shall notify the EC and the relevant regulatory authorities of any new significant risks to subjects as required.

Drug Accountability (to be defined)

The clinical investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area or in a locked.

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

16. REGULATORY CONSIDERATIONS

INVESTIGATOR RESPONSIBILITIES

[The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

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

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

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

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

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

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

For protocol amendments that increase subject risk, the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB and Celgene for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be informed about the clinical ongoing of this clinical study. This request should be documented in writing.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2 INFORMED CONSENT

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by IELSG and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before entry into the study, the investigator or an authorized member of the investigational staff must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.

The subject or legally acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry to the study, consent should be appropriately recorded by means of either the subject's or his/her legally acceptable representative's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

Subjects will also be asked to consent to participate in a genetic research component of the study. Refusal to participate will not result in ineligibility for the rest of the clinical study unless participation in genetic testing is required as an inclusion criterion. After informed consent is appropriately obtained, the subject or his/her legally acceptable representative will sign and personally date a separate DNA informed consent form indicating agreement or refusal to participate in the genetic testing. A copy of this informed consent form will be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and personally date and sign the informed consent form after the oral consent of the subject or legally acceptable representative is obtained.

PRIVACY OF PERSONAL DATA

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The investigator-sponsor ensures that the personal data will be

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

Explicit consent for the processing of personal data will be obtained from the participating subject (or his/her legally acceptable representative) before collection of data. Such consent should also address the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

ADMINISTRATIVE REQUIREMENTS

Data Quality Assurance

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

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

Record Retention

The results of the study will be reported in a Clinical study Report generated by the investigator-sponsor and will contain all data from all investigational sites.

Provide identification of any data to be recorded directly on the CRFs (electronic record of data), on site www.epiclin.cpo.it and to be considered to be source data.

On-Site Audits

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

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18. APPENDICES

Appendix 1: performance status scales[24]

The following table presents the Karnofsky performance status scale.

Which of the following descriptions best describes the subject's level of performance at this time:

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

			imminent.
Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.	4	20 10 0	Hospitalisation necessary, very sick, active supportive treatment necessary Moribund, fatal processes progressing rapidly Dead

1 Zubrod, C.G., et al. *Appraisal of Methods for the Study of Chemotherapy of Cancer in Man.* Journal of Chronic Diseases, **11**:7-33, 1960.

2 Oken, M.M., et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group*. Am J Clin Oncol (CCT) 5: 649-655, 1982

3 Karnofsky, D.A., Abelmann, W.H., Craver, L.F., and Burchenal, J.H., *The use of the nitrogen mustards in the palliative treatment of carcinoma*. Cancer (Philad.) **1**:634, 1948.

4 Schag, C.C., Heinrich, R.L., Ganz, P.A., Karnofsky Performance Status Revisited : Reliability, Validity, and Guidelines, Clinical Oncology. 2:187-193, 1984.

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

Appendix 2: WHO CLASSIFICATION FOR lymphoma

B-cell neoplasms	
Precursor B-cell neoplasm	Precursor B-Lymphoblastic leukemia/lymphoma
Peripheral B-cell neoplasm	Chronic lymphocitic leukemia Small lymphocitic lymphoma (SLL) With/without a monoclonal component With/without plasmacytoid differentiation B-cell prolymphocitic leukemia Hairy cell leukemia Lymphoplasmocytoid lymphoma (LPL) or immunocytoma Marginal zone B-cell lymphoma (MZL) Mucosa-associated lymphoid tissue (MALT type lymphoma) *Splenic marginal zone lymphoma (+/- villous lymphocytes)** *Nodal lymphomas (+/- monocytoid B-cells)** Follicular lymphomas (FL) Grade I (<15% centroblasts) Grade II (>15% to 50% centroblasts) Grade III (>50% centroblasts) Mantle cell Lymphoma Diffuse large B-cell Lymphoma (DLCL) Variants: Centroblastic lymphoma; Immunoblastic lymphoma; B-cell lymphoma rich in T-cells; B-cell lymphoma rich in histiocytes; Anaplastic large B-cell lymphoma; Burkitt-like lymphoma; Lymphomatoid granulomatosis Subtypes: Mediastinal lymphoma; Intravascular lymphoma; Serous lymphoma Burkitt's lymphoma/leukemia (BL)

T-cell neoplasms	
Precursor T-cell neoplasm	Precursor T-Lymphoblastic leukemia/lymphoma
Peripheral T/NK-cell neoplasm	Chronic lymphocitic leukemia T-cell chronic lymphocytic leukemia/prolymphocytic leukemia Large granular lymphocyte leukemia T-cell type NK-cell type Mycosis fungoides/Sezary syndrome Peripheral T-cell lymphomas Angioimmunoblastic T-cell lymphoma (AILD)

	Angiocentric lymphoma
	Intestinal T-cell lymphoma (+/- enteropathy-associated)
	Adult T-cell lymphoma/leukemia (ATL)
	Anaplastic large cell lymphoma (ALCL)
	CD30+, T- and null-cell types
	*Anaplastic large cell lymphoma, Hodgkin's like**
Hodgkin's disease	
	*Predominantly lymphocytic nodular Hodgkin's lymphoma**
Classic variant	Predominantly lymphocytic
	With nodular sclerosis
	Mixed-cell
	With lymphocyte depletion
	*Hodgkin-like ALCL lymphoma**
Plasma cell diseases	
	Waldenstrom's macroglobulinemia
	Monoclonal component of uncertain significance
	Plasmacytoma
	Solitary plasmacytoma
	Extra-osseous plasmacytoma
	Multiple Myeloma
	Plasma cell sarcoma
	Plasma cell leukemia

Proliferative diseases due to immunodeficiency	
Hereditary immunodeficiency	Atipical lymphoid proliferation
	Large B-cell lymphoma
After allogeneic transplantation	Polymorfic lymphoproliferative diseases
	Large B-cell lymphoma
	Plasmacytoma
	Peripheral T-cell lymphoma
	Hodgkin's lymphoma
Deficiency due to HIV	Burkitt's and Burkitt-like lymphomas
	Large B-cell lymphoma
	Immunoblastic lymphoma
	Serous lymphoma
* provisional entities	

Appendix 4: dispensing information for rituximab (idec-c2b8)

DESCRIPTION

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

RECOMMENDED PREPARATION AND ADMINISTRATION

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

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

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

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

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

Following the infusion the intravenous line should be kept open for medications, as needed. If there are no complications, the intravenous line may be discontinued after one hour of observation.Dosage: 375 mg/m² body surface

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

2.0 m² 750.0 mg

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

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

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

RITUXIMAB 375 mg/m^2	First dose of 100 mg in saline solution 100 ml
	Second dose (to total dose) mg in saline solution 250 ml

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

Appendix 5: Neurotoxicity Questionnaire[25]

Subjects should complete the following questionnaire.

By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

CONCERNS	***Not at all***	***A little bit***	***Some-what***	***Quite a bit***	***Very much***
I have numbness or tingling in my hands……	*0*	*1*	*2*	*3*	*4*
I have numbness or tingling in my feet……	*0*	*1*	*2*	*3*	*4*
I feel discomfort in my hands…….	*0*	*1*	*2*	*3*	*4*
I feel discomfort in my feet……	*0*	*1*	*2*	*3*	*4*
I have joint pain or muscle cramps……	*0*	*1*	*2*	*3*	*4*
I feel weak all over……	*0*	*1*	*2*	*3*	*4*
I have trouble hearing……	*0*	*1*	*2*	*3*	*4*
I get a ringing or buzzing in my ears……	*0*	*1*	*2*	*3*	*4*
I have trouble buttoning buttons……	*0*	*1*	*2*	*3*	*4*
I have trouble feeling the shape of small objects when they are in my hand……	*0*	*1*	*2*	*3*	*4*
I have trouble walking……	*0*	*1*	*2*	*3*	*4*

Source: FACT/GOG-Ntx, Version 4.0

Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. ***Int J Gynecol Cancer 2003;****13(6):741-8.*

Appendix 6: Creatinine Clearance Calculation

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

In men:

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

In women:

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

Note: Age (in years), weight (in kg), serum-creatinine (in mg/dL)
72 (normalized to 72 kg body weight and a body surface of 1.72 m^2)

Appendix 7: New York Heart Association Classification of Cardiac Disease[26]

The following table presents the NYHA classification of cardiac disease:

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

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

Appendix 8: Suggested Body Surface Area Calculation

BSA should be determined using the appropriate following calculation:

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

OR

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

Appendix 9: NCI Common toxicity criteria

Toxicities evaluation:

International Common Toxicity Criteria (CTC), version 3.0, 12/12/2003.

National Institute of Healt (NIH):

http://ctep.cancer.gov/reporting/ctc.html

Appendix 10: CNS risk, SIE guidelines and recommendations

Prophylaxis of CNS relapse should be performed in patients with involvement of specific extranodal sites such as testes, paranasal sinuses, hard palate, orbit, paravertebral masses and bone marrow.

Prophylaxis of CNS relapse should also be used in patients presenting with a high-intermediate/high IPI score, particularly reflecting the presence of a high level of LDH and involvement of more than one extranodal site.

Prophylaxis should be performed with intrathecal injections of methotrexate at the beginning of each cycle of chemotherapy.

Appendix 12: PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Women of Child Bearing Potential:

Only 2 criteria are allowed for the status of not of childbearing potential, hysterectomy or menopausal for 24 consecutive months. Women of childbearing potential must confirm to the best of their knowledge that they are not pregnant nor intend to become pregnant during the study. They must be informed and understand the risk of birth defects, and agree not to become pregnant while taking Lenalidomide.

Pregnancy Testing Requirements:

Women of childbearing potential must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL). The first should be performed within 10 – 14 days and the second within 24 hours before the start of Lenalidomide therapy. If the subject is pregnant, she cannot take Lenalidomide. The subject must have a pregnancy test done by the doctor every week during the first 4 weeks of treatment. She will then have a pregnancy test every 4 weeks if her menstrual cycles are regular or every 2 weeks if her cycles are irregular. The subject may also need to have a pregnancy test if she misses her period or has unusual menstrual bleeding.

Birth Control Methods

If there is ANY chance that the subject can get pregnant, she must either commit to continued abstinence from heterosexual intercourse or begin TWO methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking Lenalidomide. Barrier methods alone (i.e. condoms) are not sufficient. These birth control methods must be used for at least 4 weeks before starting Lenalidomide therapy, all during Lenalidomide therapy and for at least 4 weeks after Lenalidomide therapy has stopped. The subject must be given information about the following acceptable birth control methods:

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

Remember: The subject must use at least one highly effective method and one additional effective method AT THE SAME TIME. However, the doctor may recommend that the subject use two barrier methods for medical reasons. The subject must talk to the doctor before changing any birth control methods she has already agreed to use.

If the subject has sex without birth control or if for any reason she thinks she may be pregnant, she must IMMEDIATELY stop taking Lenalidomide and IMMEDIATELY tell the doctor. If the subject gets pregnant, she must IMMEDIATELY contact the doctor to discuss the pregnancy.

The subject must not breast-feed a baby while she is being treated with Lenalidomide. The subject must NEVER donate blood or ova while she is being treated with Lenalidomide. Lenalidomide does not induce abortion of the fetus and should never be used for contraception.

Men:
The subject must be informed and understand the risk of birth defects, and agrees to use latex condoms every time he has sex with a woman while he is taking Lenalidomide and for 4 weeks after he stops taking the drug even if he has had a successful vasectomy.

The subject must tell the doctor if he has sex with a woman without using a latex condom, or if he thinks for any reason that his partner may be pregnant.

The subject must NOT be a sperm or blood donor while he is being treated with Lenalidomide.

Appendix 13: TIMING OF TREATMENT AND INVESTIGATIONS

	PRETREATMENT PHASE	TREATMENT PHASE							FOLLOW UP					
		I	II	III		IV	V	VI	0	6	12	18	24	
Day	**-28**	**0**	**21**	**42**		**63**	**84**	**105**						
COURSES		1	2	3		4	5	6						
LR-CHOP		X	X	X		X	X	X						
IT CHEMOTHERAPY		X	X	X		X								
History, physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lymphadenectomy (1)	X													
CT's chest, abdomen, pelvis	X				X				X	X	X	X	X	
PET (2)	X				X				X					
Full blood count+differ	X	X	X	X	X	X	X	X	X	X	X	X	X	
Bone marrow aspirate+biopsy (3)	X				X				X	X	X	X	X	
Lumbar puncture(s) (4)	X													
β2-microglobulin	X								X	X	X	X	X	
HIV, HBV, HCV (5)	X													
Biochemestry (6)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Geriatric assessment (CGA) (7)	X													
MUGA or cardiac echo	X													

(1) Lymphadenectomy should be performed within 6 months before study entry; (2) PET mandatory only at final evaluation; (3) Bone marrow mandatory at baseline. Will be repeated only if clinically indicated; (4) Lumbar Puncture for determination of cell count, differential, cytologic and cytoflussimetry examination of CNS liquor; (5) Patients HBVcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative: HbsAg once a month; (6) ESR, Biochemestry including serum clearance Creatinine, AST, ALT, ALP, Bilirubin, albumin, acid uric, LDH.

Appendix 14: Partecipating centers:

TORINO

Hematology — Dr. Umberto Vitolo
SC Ematologia 2 ASO San Giovanni Battista Torino
C.so Bramante 88,
10126- Torino

ALESSANDRIA

Hematology — Dr. Alessandro Levis
Divisione di Ematologia
Osp. SS. Antonio e Biagio
Via Venezia, 18
15100 -Alessandria

AVIANO (PN)

Oncology — Dr. Michele Spina
Divisione di Oncologia Medica A
Centro di Riferimento Oncologico
Via Pedemontana Occ.le, 12
33081 - Aviano (PN)

BARI

Hematology — Prof. Vincenzo Liso
Cattedra di Ematologia
Università Policlinico
P.zza Giulio Cesare, 11
70124 - Bari

BARI

Hematology — Dr. Attilio Guarini
UO Ematologia
IRCCS Istituto Tumori Giovanni Paolo II
Via Hanneman, 10
70124 - Bari

BRESCIA

Hematology — Dr. Giuseppe Rossi
Divisione di Ematologia
Spedali Civili
P.le Spedali Civili, 1
25100 - Brescia

CAGLIARI

Hematology — Dr. Emanuele Angelucci
Divisione di Ematologia
Osp. Businco
Via Jenner, 1
09121 - Cagliari

CANDIOLO (TO)

Hematology — Prof. Massimo Aglietta
Onco-Ematologia
I.R.C.C.
Strada Provinciale, 142
10060 - Candiolo (TO)

MILANO

Hematology	Prof.ssa Enrica Morra Divisione di Ematologia Ospedale Niguarda P.zza Ospedale Maggiore,n°3 Milano

NAPOLI

Hematology	Prof. Bruno Rotoli UO Ematologia II Facoltà di Medicina e Chirurgia Università Federico II Via Pansini, 5 80131 - Napoli

NOVARA

Hematology	Prof. Gianluca Gaidano Divisione di Ematologia Università Avogadro Via Solaroli, 17 28100 Novara

PAVIA

Hematology	Dr. Ercole Brusamolino UO Ematologia Università - Policlinico San Matteo P.le Golgi,2 27100 - Pavia

PERUGIA

Medicin	Prof.ssa Marina Liberati Medicina Interna Università Policlinico Monteluce Via Bonacci Brunamonti, 51 06122 - Perugia

ROMA

Hematology	Dr. Maurizio Martelli Cattedra di Ematologia Policlinico Umberto I Via Benevento, 6 00161 - Roma

TRICASE (LE)

Hematology	Dr. Vincenzo Pavone UO Ematologia Osp. Cardinale Panico Via S. Pio X, 4 73039 - Tricase (LE)

Appendix 15: COMPREHENSIVE GERIATRIC ASSESSMENT

PAZIENTE NON FRAGILE

Arruolabile nel protocollo REAL 07

Deve rispettare tutte le seguenti condizioni:

- Età tra 60 e 80 anni
- Meno di 3 tipi di comorbidità di grado superiore a 3 e nessuno di grado 4 nella scheda di comorbidità (appendice 15a)
- Punteggio non inferiore a 6 della scheda ADL (appendice 15b)
- Assenza di sindrome geriatrica (definizione nell'appendice 15c)

PAZIENTE FRAGILE

(non arruolabile nel protocollo REAL07)

E' sufficiente una delle seguenti condizioni perché si possa classificare come fragile

- Età > 80 anni
- 3 o piu' tipi di comorbidità di grado 3 o anche un solo tipo di grado 4 (appendice 15a)
- Scheda ADL con punteggio < 6 (appendice 15b)
- Presenza di sindrome geriatrica (appendice 15c)

Protocollo REAL 07 Appendice 15a

SCHEDA COMORBIDITA' [CUMULATIVE ILLNESS RATING SCALE FOR GERIATRICS (CIRS-G)]

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PAZIENTE FRAGILE: 3 o piu' categorie di grado 3 oppure 1 di grado 4.

PATOLOGIA CARDIACA(solo cuore)					
IPERTENSIONE(si valuta la severità dell'ipertensione)					
APPARATO VASCOLARE (sia versante venoso che arterioso)					
DIABETE					
APPARATO RESPIRATORIO					
APPARATO DIGERENTE					
FEGATO					
RENE					
ALTRE PATOLOGIE GENITO-URIN.					
APPARATO MUSCOLOSCHELETRICO (muscoli,tegumenti,scheletro)					
SISTEMA NERVOSO (centrale e periferico,esclusa demenza)					
OCCHI-ORL (occhio, orecchio, naso, gola ,laringe)					
SIST.ENDOCRINOMETABOLICO (diabete escluso)					

Legenda

1. **Nessuna menomazione.**
2. **Menomazione lieve** (non interferisce con le normali attività; terapia facoltativa; prognosi eccellente)
3. **Menomazione moderata** (interferisce con le normali attività; terapia necessaria; prognosi buona)
4. **Menomazione grave** (invalidante; trattamento necessario con urgenza; prognosi riservata)
5. **Menomazione molto grave** (può essere letale; terapia di emergenza o inefficace; prognosi grave)

Protocollo REAL 07 Appendice 15b

SCHEDA ADL (Activities of Daily Living)

MISURA DELL'ABILITA'	SI	NO
NEL LAVARSI (spugnatura, vasca da bagno, doccia): non ha bisogno di assistenza o solo per lavarsi di una parte del corpo.	**1**	**0**
NEL VESTIRSI Può indossare gli indumenti e vestirsi senza alcuna assistenza, tranne che per allacciarsi le scarpe.	**1**	**0**
NELL'ESEGUIRE LE FUNZIONI CORPORALI Raggiunge la toilette, ne fa uso conveniente, sistema i vestiti, ed esce senza alcuna assistenza (usa al massimo il bastone come supporto ed eventualmente fa uso di notte della padella o del pappagallo)	**1**	**0**
NEL TRASFERIRSI Entra ed esce dal letto, si alza dalla sedia e si siede senza assistenza (fa uso eventualmente del bastone o di altro supporto)	**1**	**0**
CONTINENZA E' in grado di controllare autonomamente la vescica e l'intestino (senza incidenti occasionali)	**1**	**0**
NELL'ALIMENTARSI Si alimenta senza assistenza (tranne un aiuto nel tagliare la carne o nell'imburrare il pane)	**1**	**0**

PUNTEGGIO TOTALE MASSIMO OTTENIBILE = 6

Protocollo REAL07: appendice 15c

DEFINIZIONE e SCHEDA di SINDROME GERIATRICA

	NO	SI
Demenza	☐	☐
Delirio	☐	☐
Depressione	☐	☐
Incontinenza urinaria o fecale	☐	☐
Osteoporosi	☐	☐
Failure to thrive	☐	☐
Cadute	☐	☐
Neglect and abuse	☐	☐

LEGENDA

Si definisce presenza di sindrome geriatrica la situazione caratterizzata dalla positività per una o più delle situazioni elencate in tabella

Demenza	Diagnosi clinica
Delirio	Se compare in corso di infezioni urinarie o bronchiali banali, o come conseguenza di farmaci che normalmente non lo causano
Depressione	Diagnosi clinica
Incontinenza urinaria o fecale	Se completa e incorreggibile (se per esempio il malato sente il bisogno di urinare o defecare, ma non può raggiungere il bagno per problemi motori come quelli secondari ad artrite, questo non comporta una positività per sindrome geriatrica)
Osteoporosi	Se associata a una frattura
Failure to thrive	Incapacità di guadagnare peso a dispetto di una dieta bilanciata, purché non rientri nell'ambito dei sintomi B da linfoma
Cadute	3 o più al mese
Neglect and abuse	Il malato indossa vestiti sporchi e ha macchie di liquidi organici abitualmente (per più di 2 visite consecutive) oppure ha segni di maltrattamenti

Appendix 16: Response Criteria Cheson 2007

Cheson et al

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.