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STUDY PROTOCOL

A phase II trial to evaluate the safety and activity of single-agent lenalidomide given as maintenance therapy after response to salvage treatment in patients with relapsed diffuse large B cell lymphoma

[Lenalidomide and DLBCL]

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Date of the Protocol:
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STUDY SYNOPSIS /FLOW CHART

STUDY TITLE	A phase II trial to evaluate the safety and activity of single-agent lenalidomide given as maintenance therapy after response to salvage treatment in patients with relapsed diffuse large B cell lymphoma (DLBCL)
COORDINATOR STUDY SITE	Unit of Lymphoid Malignancies Division of OncoHematological Medicine Department of OncoHematology San Raffaele Scientific Institute Via Olgettina 60-20132 Milan
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STUDY OBJECTIVES **Primary objective**: **Secondary objectives:** **Primary Endpoint:** **Secondary Endpoints:**	 - To explore the efficacy of lenalidomide monotherapy given as maintenance therapy following salvage chemotherapy in patients with relapsed or refractory DLBCL - To evaluate the safety of Lenalidomide maintenance therapy in this setting. - To provide data about the three DLBCL subgroups according to immunohistochemical profile. - To investigate whether specific genetic alterations amenable to distinct DLBCL subtypes add prognostic information on DLBCL patients survival. One-year progression free survival Overall survival (OS), response rate (RR), Adverse Event

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	(AE) and Serious AE reporting

INCLUSION CRITERIA	- Age ≥ 18 years - Biopsy-proven DLBCL at first or second relapse following previous combination chemotherapy regimen ± rituximab, including high-dose chemotherapy supported by autologous stem cell transplantation - Partial response or complete remission to second- or third-line chemotherapy (ICE or DHAP/DHAOx or MINE regimen) + rituximab - ECOG performance status score ≤ 3 - Female of childbearing potential (FCBP) must demonstrate to practice a proper contraception to avoid any pregnancy risk during the study and at least 28 days after the discontinuation of the study - Male subjects must agree to practice a proper contraception during any sexual contact with females childbearing potential -
EXCLUSION CRITERIA	- CNS involvement - TTP <3 months after previous line of treatment - Use of experimental drugs during salvage chemotherapy - Severe concomitant illnesses / medical conditions (e.g. impaired respiratory and/or cardiac function, uncontrolled diabetes mellitus) - Active infectious disease - HIV positivity - HBV-DNA or HCV-RNA positivity - Impaired liver function (Bilirubin >2 x upper normal limit; ALT/AST/GGT > 3 x upper normal limit) at one month from salvage chemotherapy conclusion - Impaired renal function (creatinine clearance <50 ml/min) at one month from salvage chemotherapy

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	conclusion - Absolute neutrophil count (ANC) <1000/µL - Platelet count <75.000 /mm^3 - Hemoglobin <9 g/dL - Non-co-operative behaviour or non-compliance - Psychiatric diseases or conditions that might impair the ability to give informed consent - Pregnant or lactating females -
STUDY MEDICATION	Patients, eligible for the study, will enter the treatment phase and receive single-agent lenalidomide 25 mg once daily for 21 days out of 28, as maintenance treatment after the end of salvagechemotherapy for 24 cycles, unless treatment is discontinued earlier due to disease progression or unacceptable toxicity.. Dose reductions of study drug will be made in case of adverse events when reported as correlated and when clinical appropriate.

STATISTICS/DESIGN Design:	Simon's two-stage optimal design will be used. The null hypothesis that the true 1-year PFS is 30% will be tested against a one-sided alternative. In the first stage, 15 patients will be accrued. If there are 5 or fewer patients progression-free at one year in these 15 patients, the study will be stopped. Otherwise, 32 additional patients will be accrued for a total of 47. The null hypothesis will be rejected if 19 or more patients progression-free at one year are observed in 47 patients. This design yields a type I error rate of 5% and power of 80% when the true 1-year PFS is 50%.
Number of patients:	47
Timelines:	Anticipated start: July 2009 Recruitment period: July 2009 – December 2015 Final report: December 2016

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LIST OF ABBREVIATIONS / DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AST (SGOT)	Asparate transaminase (serum glutamic oxaloacetic transaminase)
β-hCG	Beta-human chorionic gonadotropin hormone
β2M	Beta-2 Microglobulin
BUN	Blood urea nitrogen
CBC	Complete blood count
CR	Complete remission
CRF	Case report form
CT	Computed tomography
CTC	Common toxicity criteria
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for Evaluation of Medicinal Products
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
CC-5013	(lenalidomide)
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMiD	Immunomodulatory drug
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MedDRA	Medical Dictonary for RegulatoryActivities
MITT	Modified Intent-to-Treat
MR	Magnetic Resonance
NCI	National Cancer Institute
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PR	Partial remission
SAE	Serious adverse event
SD	Stable disease

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SOP	Standard Operating Procedure
TSH	Thyroid stimulating hormone
TTF	Time to treatment failure
TTP	Time to progression
ULN	Upper limit of normal
WBC	White blood cell count

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1. Introduction

1.1 Non Hodgkin's Lymphoma and diffuse large B-cell lymphoma (DLBCL)

The non-Hodgkin's lymphomas (NHLs) comprise a heterogeneous collection of lymphoproliferative malignancies, which are most common in people aged over 55 years. DLBCL is the most common type of NHL, accounting for approximately 30% of all new patients. Follicular lymphoma (FL) is the second most common NHL sub-type, and accounts for a further 22% of cases. While the incidence of most other cancers is decreasing, that of NHL is increasing steadily. During the 1970's and 1980's, worldwide NHL incidence rose by 3–4% per year. This rise has slowed in the 1990s, but an annual increase of 1–2% is still being recorded[1].
NHL occurs more commonly in males, and whites are affected more often than blacks. The incidence of NHL increases with age. NHL is known to be associated with chronic inflammation diseases such as Sjögren syndrome, Celiac disease, and rheumatoid arthritis. Immune suppression has also been associated with an increased risk of developing lymphoma[2] Following a solid organ transplant, the risk of lymphoma is associated with the duration of immunosuppression and the drugs and dosages used. In addition, infections with the human immunodeficiency virus (HIV) have been associated with a significantly elevated risk of NHL.
The correct diagnosis today for DLBCL is done following the World Health Organization (WHO) classification, considering that this is still a heterogenous group including lymphomas with a wide variety of morphologic appearances, protein-expression patterns, and gene-expression patterns. For example, patients with DLBCL can be divided into at least 3 clinically relevant groups using gene-expression profiling. These include the germinal-center type, the activated B-cell type, and mediastinal large B-cell lymphoma. A few patients will not easily be classified into these categories. Mediastinal large B-cell lymphoma represents less than 10% of all large B-cell lymphomas, occurs primarily in young women, and always presents with a mediastinal mass. The gene-expression profile is similar to that seen in classical Hodgkin disease. The other 2 types of DLBCL, and those not easily classified, have a median age at presentation in the 60s, a male predominance, and can present at essentially any site in the body.
DLBCL can be seen after histologic transformation of most other types of B-cell lymphoma. This is particularly frequent in patients with follicular lymphoma and is recognized clinically in up to 50% of patients. In general, patients with DLBCL seen after histological transformation have a poorer response to therapy and prognosis than those with a de novo appearance, particularly if the patient were treated for the preceding lymphoma[3].

1.2 Lenalidomide

Lenalidomide (REVLIMID®; Celgene Corp., NJ, USA) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs). It offers potential benefit over the first commercially available IMiD, thalidomide, in terms of both safety and efficacy in human subjects. The key to its therapeutic potential lies in the fact that it has multiple mechanisms of action, which act to produce both anti-inflammatory and anti-tumor effects. These effects are thought to be contextual in that they depend on both the cell type and the triggering stimulus. To date, lenalidomide has been associated with TNF-α inhibitory, T cell

costimulatory, and antiangiogenic activities[4-6]. Preclinical studies have documented that Lenalidomide has several immunomodulatory effects:

- co-stimulation of T cells thus enhancing Th1 type cellular immunity and NK cell-mediated cytotoxicity[7]
- inhibition of regulatory T cells, thereby reducing the suppression of $CD4^+$ T cell activity in NHL
- enhancement of antibody-dependent cellular cytotoxicity in Rituximab-treated NHL cell lines[8]

and have shown other mechanisms which could explain its effects in NHL:

- Inhibition of NHL cell proliferation, possibly through the Akt cell-survival pathway[9]
- Inhibition of angiogenesis, including reduction of endothelial cell migration[10]

Lenalidomide is marketed in the United States for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk Myelodysplastic Syndrome (MDS) associated with a deletion 5q- cytogenetic abnormality with or without additional cytogenetic abnormalities and for patients with relapsed or refractory Multiple Myeloma (MM) in combination with dexamethasone[11-13]. Lenalidomide is also marketed in the European Union for use in combination with dexamethasone as a treatment for patients with MM who have received at least one prior therapy.
Lenalidomide is being investigated as treatment for various oncology indications, including non-Hodgkin's lymphoma, chronic lymphocytic leukaemia (CLL)[14] and solid tumors. It is also being explored as a treatment for inflammatory conditions, including chronic regional pain syndrome. While many of the studies are ongoing, results from controlled and uncontrolled studies in subjects with and MDS are available.
In the MDS study 148 patients received lenalidomide, the most frequent Grade 1-4 adverse events reported were; thrombocytopenia (61.5%), neutropenia (58.8%), pruritus (41.9%), rash NOS (35.8%), and diarrhea NOS (48.6%). The most frequently observed Grade 3 and 4 adverse events regardless of relationship to study drug treatment were neutropenia (53.4%) and thrombocytopenia (50%)[13].
A total of 691 patients (346 patients in the lenalidomide/dexamethasone arms and 345 in the placebo/dexamethasone arms) were treated in the two pivotal MM studies[11,12]. Most adverse events and Grade 3/4 adverse events were more frequent in the patients who received the combination of lenalidomide/dexamethasone. The most common Grade 1-4 adverse events in the lenalidomide/dexamethasone treatment groups were constipation (38.7%), fatigue (38.4%), insomnia (32.1%), muscle cramps (30.1%), and diarrhea NOS (29.2%), The most frequently observed Grade 3 and 4 adverse events reported in patients treated with lenalidomide/dexamethasone groups were neutropenia Grade 3 (17.3%), Grade 4 (3.8%) and thrombocytopenia Grade 3 (9%), Grade 4 (1.2%). Thrombotic or thromboembolic events were reported more frequently in patients treated with lenalidomide/dexamethasone groups (13%) compared to the placebo/dexamethasone groups (3.8%).

Patients with relapsed/refractory CLL have limited therapeutic options and the addition of novel agents with alternative mechanisms of action is needed. Based on the encouraging data from Chanan-Khan et al.[14], a multicenter study is validating the potential therapeutic role of lenalidomide in the treatment of CLL.

1.3 Lenalidomide and NHL

Over the last five years, the anti-CD20 monoclonal antibody, Rituximab, has radically changed the treatment of B cell NHL, and has become a component of salvage therapy in the follicular lymphoma setting. Several large scale prospective randomized trials have demonstrated prolongation of remissions when Rituximab is added to first line CHOP therapy (cyclophosphamide, doxorubicin, vincristine and prednisone)[15]. Despite this major advance a high proportion of elderly patients with DLBCL still progress or relapse and eventually die of their disease[2]. The three-year EFS projection of the study from Coiffier et al[15]. suggests that this number still approaches 50%. The prognosis is even poorer for patients relapsing following treatment with standard chemotherapy for aggressive non-Hodgkin's lymphoma. High-dose chemotherapy and autologous stem cell transplantation is a potentially curative approach for these patients, but many patients are not eligible for this approach due to age and/or comorbidities. Salvage chemotherapy remains the mainstay of treatment, and is tailored according to disease and patient characteristics, goals of therapy, and patient preference. A number of strategies have been explored to improve the response rate to second-line regimens. Different chemotherapeutic schemes, like DHAP (dexamethasone, cisplatin, and cytarabine)[16], ICE[17] (Ifosfamide, carboplatin, and etoposide), or ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) with or without addition of rituximab are currently used to re-induce remission, and none of them have demonstrated to be superior to the others.

A recent multicentre open label single arm phase II study has shown lenalidomide to be active in patients with relapsed/refractory aggressive NHL[18]. In a series of 46 patients, mostly with DLBCL (n=29) or MCL (n=13), the use of lenalidomide at the dose of 25 mg PO, days 1-21, every 28 days for 52 weeks, until toxicity or progressive disease (same dose as the one used in patients with multiple myeloma), was associated with a tumor control rate of 50%, with acceptable toxicity. Grade 4 adverse events were rare; grade 3 events included neutropenia in 14% of cases, thrombocytopenia in 10% and leukopenia in 8%. In the initial pilot studies, response to lenalidomide was associated with low tumor burden, long interval from prior rituximab and high absolute lymphocyte count[19, 20].

The above mentioned properties and the preliminary results, prompted us to investigate the effects of lenalidomide in the maintenance of response of patients with relapsed or refractory aggressive B-cell lymphoma, treated with second-line chemotherapy and older than 65 years or younger but not eligible for high-dose chemotherapy and autologous transplantation. These patients can achieve a rapid and complete lymphoma regression with second-line therapy but invariably experience relapse, which is the main unfavorable prognostic event.

An active maintenance therapy with an oral drug, with an acceptable safety profile such as lenalidomide, could contribute to prolong significantly time to progression and, possibly, overall survival of this patient population.

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2. Study objectives and endpoints

2.1 Primary objective

- To explore the efficacy of lenalidomide monotherapy given as maintenance after at least a partial response (PR) to a second- or third-line chemo-immunotherapy in patients with relapsed DLBCL

2.2 Secondary objectives

- To evaluate the safety of Lenalidomide maintenance therapy in this setting.
- To explore the efficacy of lenalidomide in the different DLBCL prognostic subtypes (see item 6.1.3)
- To investigate, when possible, whether the classification of DLBCL subtypes and the expression of specific candidate genes can provide prognostic information about the efficacy of lenalidomide in DLBCL subtype's

2.3 Primary endpoint

- One-year progression free survival (PFS)

2.4 Secondary endpoints

- Overall survival (OS), response rate (RR), adverse events (AE) and serious adverse events (SAE) rate

3 Overall study design

3.1 Type of study

This is an open label, single-arm, multicentre phase II trial evaluating the maintenance treatment of oral lenalidomide monotherapy given to patients with relapsed DLBCL who presented at least a PR to a second- or third-line therapy.
A total number of 47 eligible patients will be enrolled in the protocol and receive Lenalidomide 25 mg for 21 days every 28 days, until clinical appropriate. These subjects will be continuously monitored for safety, disease status and survival.

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3.2 Schedule and timelines

- Anticipated start of recruitment: July 2009
- Anticipated stop of recruitment: July 2013
- Final report: July 2014

4. Selection of study population

4.1 Inclusion criteria

- Age ≥ 18 years
- Patients affected by histologically-proven DLBCL at first or second relapse following previous combination chemotherapy regimen ± rituximab, including high-dose chemotherapy supported by autologous stem cell transplantation
- Partial response (PR) or complete remission (CR) to a second- or third-line salvage chemotherapy, including the following regimens: R-DHAP (rituximab, dexametasone, high-dose cytarabine, cisplatinum), R-DHAOx (rituximab, dexametasone, high-dose cytarabine, oxalyplatinum), R-ICE (rituximab, ifosfamide, carboplatin, etoposide), R-MINE (rituximab, methotrexate, ifosfamide, vinorelbine, etoposide)
- ECOG performance status score ≤ 3
- Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:
  - Female subjects of childbearing potential[†] must:
    1.1 Understand that the study medication could have a potential teratogenic risk
    1.2 Agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study drug, throughout study drug therapy (including dose interruptions) and for 4 weeks after the end of study drug therapy, even if she has amenorrhoea. This applies unless the subject commits to absolute and continued abstinence confirmed on a monthly basis. The following are effective methods of contraception*
      1.2.1 Implant**
      1.2.2 Levonorgestrel-releasing intrauterine system (IUS)**
      1.2.3 Medroxyprogesterone acetate depot
      1.2.4 Tubal sterilisation

[†] A female subject or a female partner of a male subject is considered to have childbearing potential unless she meets at least one of the following criteria: Age ≥50 years and naturally amenorrhoeic for ≥ 1 year (amenorrhoea following cancer therapy does not rule out childbearing potential), premature ovarian failure confirmed by a specialist gynaecologist, previous bilateral salpingo-oophorectomy or hysterectomy, XY genotype, Turner's syndrome or uterine agenesis.

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1.2.5 Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses

1.2.6 Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

* Combined oral contraceptive pills are not recommended. If a subject was using combined oral contraception, she must switch to one of the methods above. The increased risk of VTE continues for 4 to 6 weeks after stopping combined oral contraception.

**prophylactic antibiotics should be considered at the time of insertion particularly in patients with neutropenia due to risk of infection

1.3 Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 IU/ml not more than 3 days from the start of study medication once the subject has been on effective contraception for at least 4 weeks. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.

1.4 Agree to have a medically supervised pregnancy test every 4 weeks including 4 weeks after the end of study treatment, except in the case of confirmed tubal sterilization. These tests should be performed not more than 3 days before the start of next treatment. This requirement also applies to women of childbearing potential who practice complete and continued abstinence

- Male subjects must

1.5 Agree to use condoms throughout study drug therapy, during any dose interruption and for one week after cessation of study therapy if their partner is of childbearing potential and has no contraception.

1.6 Agree not to donate semen during study drug therapy and for one week after end of study drug therapy.

- All subjects must

1.7 Agree to abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy.

1.8 Agree not to share study medication with another person and to return all unused study drug to the investigator

4.2 Exclusion criteria

- CNS involvement

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- Time to progression < 3 months after the previous line of treatment
- Use of experimental drugs during salvage chemotherapy
- Concomitant malignancies diagnosed in the last five years before patient's registration
- Severe concomitant illnesses / medical conditions (e.g. impaired respiratory and/or cardiac function, uncontrolled diabetes mellitus)
- Active infectious disease
- HIV positivity
- HBV-DNA or HCV-RNA positivity
- Impaired liver function (bilirubin >2 x upper normal limit; ALT/AST/GGT > 3 x upper normal limit) at one month from salvage chemotherapy conclusion
- Absolute neutrophil count (ANC) <1000/μL and/or platelet count <75.000 /mm^3 and/or hemoglobin <9 g/dL
- Pregnant or lactating females
- Impaired renal function (creatinine clearance <50 ml/min) at one month from salvage chemotherapy conclusion
- Non-co-operative behaviour or non-compliance
- Psychiatric diseases or conditions that might impair the ability to give informed consent
- Pregnant or lactating females:

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene S.r.l., *drugsafety-italy@celgene.com* or Tel. +0039-02-91434340, Fax +0039-02-63471119 or Celgene Drug Safety Department in the US at: +1 800 640 7854 immediately by phone and facsimile using the Pregnancy Reporting Form.

The female should be referred to a physician specialized or experienced in teratology for further evaluation and counseling.

The Investigator(s) will follow the female subject until completion of the pregnancy, and must notify the Celgene S.r.l, *drugsafety-italy@celgene.com or Tel.* +39-02-91434340 *or Fax* +39-02-63471119 of the outcome of the pregnancy as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (i.e., report the event to the Celgene S.r.l, *drugsafety-italy@celgene.com or Tel.* +39-02-91434340 by telephone and *Fax* +39-02-63471119 facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, the Celgene S.r.l, *drugsafety-italy@celgene.com or Tel.* +39-02-91434340 should be advised by telephone and *Fax* +39-02-63471119 fac-simile within 24 hours of the Investigator's knowledge of the event.

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(s) suspects is related to the in utero exposure to the study drug should also be reported to the Celgene S.r.l, *drugsafety-italy@celgene.com or Tel.* 0039-02-91434340 by telephone and *Fax* +39-02-63471119 facsimile within 24 hours of the Investigators' knowledge of the event.

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

4.3 Removal of patients from therapy / study

4.3.1 Regular termination of study participation

The participation of the patient in the study is regularly terminated:

1. In case of death or in case of lymphoma failure
2. Discontinuation of study drug due to toxicity or adverse event

4.3.2 Premature termination of study participation

The patient may drop out of the clinical study at any time without stating reasons. This may not have any negative consequences for the patient's further treatment.

Possible reasons for withdrawal of the patient are:

- Withdrawal of the patient's consent
- Further participation assessed by the investigator to be unacceptable / intolerable
- Pregnancy
- Lack of co-operation/compliance of the patient
- Occurrence of new diseases that could influence the treatment efficacy, for which the study medication is contraindicated or that are treated with a medication that is not permitted as a concomitant medication.
- Reconsideration of the risk/benefit ratio, in consensus with Ethical Committee and Independent Safety Monitoring Committee

The reason for both regular and premature termination should be recorded in the CRF and in the subject's medical records.

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5 Treatment Plan

5.1 Treatment

After the documentation of PR or CR after salvage chemo-immunotherapy, patients will receive lenalidomide 25 mg daily orally for 21 days every 28 days for 2 years (24 cycles). This maintenance therapy will start after one month from salvage chemotherapy conclusion. The duration of period between the end of chemotherapy and the beginning of maintenance treatment can be variable according to the achievement of the acceptable haematological and biochemical parameters. This interval could be prolonged until the patient will be considered eligible for the trial, within 2 months.

5.2 Identity of investigational product

Celgene Corporation will supply 10 mg, 5 mg and 25 mg lenalidomide capsules for oral administration in order to treat patients with the full dose of 25 mg and in case to adjust this dose if any drug related AEs occur.
Lenalidomide will be packaged in bottles containing 21 days of study drug.

5.3 Dose Modification or Interruption

Dose reduction levels are reported on Appendix I.
Subjects will be evaluated for AEs at each visit following the NCI CTCAE (Version 3.0) and used as a guide for the grading of severity:

• Thrombocytopenia will be graded as follows:
− Grade 1 ≥ 75 x 10^9/L and < LLN
− Grade 2 ≥ 50 and < 75 x 10^9/L
− Grade 3 ≥ 25 and < 50 x 10^9/L
− Grade 4 < 25 x 10^9/L

• Hemoglobin will be graded as follows:
− Grade 1 ≥ 10 g/dL and < LLN
− Grade 2 ≥ 8 and < 10 g/dL
− Grade 3 ≥ 6.5 and < 8 g/dL
− Grade 4 < 6.5 g/dL

• Neutropenia will be graded as follows: (ANC/µL)
− Grade 1 ≥ 1500 and < 2000 x 10^9/L
− Grade 2 ≥1000 and < 1500 x 10^9/L
− Grade 3 ≥ 500 and < 1000 x 10^9/L
− Grade 4 < 500 x 10^9/L

5.4 Prior/Concomitant Medications

All medications (prescription and non-prescription), treatments and therapies taken during the treatment with study drug must be recorded on the appropriate CRF.
All the therapies considered necessary for the subject's wellbeing may be administered at the discretion of the Investigator. These therapies may include antibiotics, analgesics, antihistamines, or other medications as well as growth factors and transfusions of red blood cells, platelets, or fresh frozen plasma given to assist in the management of complications associated with NHL or its therapy. To date, no data on a higher risk of thromboembolic complications with lenlidomide in lymphoma patients have been reported. However, antithrombotic prophylaxis could be indicated according to the Institutional guidelines of each center and o the individual risk of the registered patient considering that patients entering into this trial will be older than 65 years and lenalidomide treatment will be long-lasting.

5.5 Prohibited Concomitant Therapy

Concomitant use of other lymphoma therapy or experimental therapies while the subject is on study drug is prohibited.

6 Efficacy and safety variables

6.1 Efficacy measures

6.1.1 Assessment of the disease status

Response to treatment is defined on the basis of International Workshop Response Criteria for non-Hodgkin's Lymphoma (Appendix E).

6.1.2 Survival status

Patient survival status will be determined every four weeks during the study treatment, every four months for three years after, every six months for the following two years and every year after there, until 10-year follow-up completion, progression or death.
In addition to reporting the serious adverse events, patient's deaths must be recorded continuously throughout the study.
Evaluation and documentation of the cause of death must be entered in the CRF.

6.1.3 Central pathology review and cell of origin (COO) characterization

All the registered cases will undergo central pathology review.

Efficacy of the experimental therapy will be analysed stratifying registered patients according to their COO, namely "germinal-centre B cell type" and "activated B-cell type" subgroups. COO will be defined according immunohistochemical results of antibodies raised against CD20, CD3, CD10, bcl-6, MUM-1/IRF4, and bcl-2 molecules, using the Hans algorithm. This is a surrogate practical tool in confirming data generated by gene-expression profiling and could be applied also to tissue microarrays obtained by formalin-fixed, paraffin-embedded (FFPE) clinical cases of DLBCL. The limits in detecting the precise COO by means of immunohistochemistry will be overcome by using a validated gene-expression-profiling-based assay performed on NanoString's nCounter® Analysis System, now available on FFPE pathological material. The correlation between COO in DLBCL subtypes and clinical efficacy will be studied in order to identify genetic predictors of successful response to therapy with lenalidomide.

In order to identify cases of "double expressor lymphomas" and "double hit lymphomas", MYC will be added to the previously mentioned bcl-6 and bcl-2 markers on FFPE samples by immunohistochemistry; these data will enable to select a subgroup of cases suitable for the assessment of MYC and BCL2 genetic abnormalities through FISH technique.

Cereblon (CRBN), a substrate receptor of the E3 ubiquitin ligase complex CRL4CRBN, is the target of lenalidomide. Expression of cereblon will be evaluated in diagnostic tissue samples by immunohistochemistry, through the use of a Celgene anti-CRBN rabbit monoclonal antibody CRBN65. The prognostic value of the expression of CRBN will be assessed on the clinical data from registered patients.

In order to fulfil these aims, diagnostic tissue blocks (tissue block from biopsy performed at relapse is also requested if available) and all the diagnostic, already stained specimens per case should be referred to: Dr. Maurilio Ponzoni, Pathology Unit, IRCCS San Raffaele Scientific Institute, Via Olgettina 60 - 20132, Milano (tel: 02-26432544 – e-mail: ponzoni.maurilio@hsr.it). In the case the blocks will not be available, all stained specimens plus 30 unstained slides, prepared as to undergo antigen retrieval, will be referred for analyses; in the case stained slides and blocks will not be available, one Haematoxylin and eosin plus 40 unstained slides, prepared as to undergo antigen retrieval, will be referred.

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6.2 Safety measures

6.2.1 Adverse events

6.2.1.1 Adverse Event Definitions and Classifications

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

- *Adverse Event*

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product (Definition per International Conference on Harmonization [ICH]).
This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.
Note: The Investigator collect adverse events starting 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 to be 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 part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

- *Serious Adverse Event*

A serious adverse event (SAE) as defined by ICH is any untoward medical occurrence that at any dose:
- results in death
- is life-threatening (the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- results in persistent or significant disability/ incapacity, or
- is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.
Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.
If an AE is considered serious, both the AE pages of the CRF and the SAE Report form must be completed.
For each SAE, the investigator will provide information on severity , start and stop dates, relationship to (investigational product) study drug, action taken regarding (investigational product) study drug and outcome.

- *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**

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- *UnexpectedAdverse Event*

An adverse event, the nature or severity of which is not consistent with the applicable product information (for an investigational medicinal product, the Investigator's Brochure). *Associated With the Use of the Investigational medicinal product*
An adverse event is considered associated with the use of the investigational product if the attribution is possible, probable, or very likely by the definitions listed in Section 10.1.2.

Attribution Definitions

- Not related.

An adverse event that is not related to the use of the investigational product.

- Doubtful.

An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

- Possible.

An AE that might be due to the use of the investigational product. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

- Probable.

An AE that might be due to the use of the investigational product. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

- Very likely.

An AE that is listed as a possible adverse event reaction, and cannot be reasonably explained by an alternative explanation, e.g., concomitant investigational drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

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.

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

Procedures

All Adverse Events
All AEs, with the exception of progression of systemic AL-amyloidosis, that occur between the first study-related procedures and for 30 days following the last dose of investigational product will be reported. Resolution information after 30 days should also be provided for grade 3 to 4 drug related events. This subset should be followed up until resolution to a grade 1 or better.
Adverse events occurring after 30 days should also be reported if considered related to investigational product.
Clinically relevant changes in laboratory values must be recorded in the adverse event section of the CRF.
All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded in the source document and the CRF. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to the study therapy. All measures required for adverse event management must be recorded in the source document.
The Principal Investigator assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Principal Investigator must report these events to the appropriate Institutional Review Board (IRB) that approved the protocol unless otherwise required and documented by the IRB.

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.

6.2.1.2 Immediate reporting by Investigator to Sponsor and Celgene

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The investigator will inform the sponsor and Celgene of any serious adverse event. This applies to all SAEs, regardless of relationship to the study medication, that occur during the study, those made known to the Investigator(s) within 30 days after a subject's last dose of study drug, and those made known to the investigator(s) at any time that are suspected of being related to the study medication. This must be documented on an SAE form. This form must be completed in English and supplied to Celgene Europe Drug Safety within 24 hours/1 business day or at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up SAE form.
All adverse event reports must include the patient number, age, sex, weight, severity of reaction, relationship to study drug, date and time of administration of test medications and all concomitant medications, and medical treatment provided.

Safety Contact Information

	Safety Phone Number	**Safety Fax/e-mail**
Fondazione S. Raffaele Safety Desk	**+39 02 2643 4289**	**+39 02 2643 4760** **stefania.trinca@hsr.it**
Celgene International Sarl **Att. Drug Safety Department** **Route de Perreux 1** **2017 Boudry** **CH-NE** **24-H Emergency Contact** **Call Centre Direct Telephone** **+41 32729 8476 and follow the instructions in the recorded message**	**+41 32 729 8476**	**Fax : +41 32 729 8409** **drugsafetyeurope@celgene.com**
Celgene S.r.l. **Dr. Roberta Di Menno Di Bucchianico**	**+39 02 91434340** **+39 340/8369630**	**Fax +39 02 63471119** **drugsafety-italy@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 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 Celgene within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form. The pregnancy must also be reported to the sponsor.
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, Celgene should be advised as soon as the information is available.
Any suspected foetal exposure to CC-5013 must be reported to 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 Investigators and 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 AE associated with the use of any other drug in this study that is both serious and unexpected as per the Summary of Product Characteristics for cyclophosphamide and dexamethasone.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

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

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- the events resolves;
- the event stabilizes;
- the event returns to baseline, if a baseline value is available;
- the event can be attributed to agents other than the investigational product or to factors unrelated to study conduct;

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- when it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Data protection

Patient's identity will stay anonymously.

6.2.2 Safety board

An Independent Data Monitoring Committee (IDMC) will review ongoing safety and efficacy data and at the time of the planned analyses to assess benefit-to-risk considerations throughout the study. Additional safety reviews will occur at scheduled intervals agreed upon by the IDMC.

6.3 Monitoring and prophylactic treatment for hepatitis B reactivation

At screening patients will be tested for hepatitis B serologic markers, that is HBsAg, HBsAb, and HBcAb. Patients with positive serologic markers should be tested for viral load dosing HBV-DNA. Patients with detectable levels of HBV-DNA will be excluded. Patients with HBsAg positivity, independently from HBsAb and HBcAb titres, will receive prophylaxis with lamivudine 100 mg/d. It will be started 1-2 weeks before lenalidomide treatment. HBV-DNA will be assessed on day 1 of each course (±7 days of scheduled visit), at the end of lenalidomide (within 7 days after stopping drug), and at 28-day follow-up visit (± 7 days of scheduled visit). Patients with undetectable levels of HBV-DNA and/or with HBsAg negativity, independently from HBsAb and HBcAb titres, will not receive prophylaxis treatment; HBV-DNA will be assessed as above mentioned. Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of lenalidomide. For hepatitis B reactivation definition and management guidelines see following table.

Guidelines for management of hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with positive HBsAg reactivation is defined as: new appearance of measurable HBV-DNA ± ALT elevation x 5 ULN	Treat: Start a second antiviral AND interrupt lenalidomide administration until resolution: • ≤ grade 1 ALT (or baseline ALT, if > grade 1) and • undetectable HBV-DNA levels <u>If resolution occurs within ≤ 28 days:</u> lenalidomide should be re-started at 10 mg/d. If the patient is already receiving 10 mg/d of lenalidomide, according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of lenalidomide. <u>If resolution occurs > 28 days.</u> Patients should discontinue

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	lenalidomide but continue both antiviral therapies at least 4 weeks after last dose of lenalidomide.
For patients with baseline results: Negative HBsAg AND [Positive HBs Ab (with no prior vaccination against HBV), OR positive HBc Ab] _____ reactivation is defined as: New appearance of measurable HBV-DNA	Treat : Start first antiviral medication AND interrupt lenalidomide administration until resolution (undetectable HBV-DNA levels). If resolution occurs within ≤ 28 days: lenalidomide should be re-started at 10 mg/d. If the patient is already receiving 10 mg/d of lenalidomide, according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of lenalidomide. If resolution occurs > 28 days: Patients should discontinue lenalidomide but continue antiviral therapy at least 4 weeks after last dose of lenalidomide.

* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator (grade 4 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Reactivation).

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6.4 Monitoring for hepatitis C virus reactivation

At screening, HCV-RNA will be tested using quantitative RNA-PCR in patients with HCV Ab positivity and in patients with known or suspected past hepatitis C virus infection (including patients with past interferon 'curative' treatment).
Patients with detectable HCV RNA at baseline will be excluded. Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered 'cured') will be monitored for HCV reactivation on Day 1 of every cycle, at end of lenalidomide (within 1 week after stopping study drug), and at 28-day follow-up visit (± 7 days of scheduled visit).
In patients with known past hepatitis C infection with undetectable HCVRNA levels at baseline, reactivation will be defined by the new appearance of detectable HCV-RNA; in this case, lenalidomide must be discontinued.

6.5 Flow chart

6.5.1 Screening

All eligible patients will receive the following assessments:

- Medical history
- Clinical and laboratory evaluation
- Imaging documentation of therapy response (CT, MR, other)
-

6.5.2 Initial examinations

- Informed consent
- Medical history
- Concomitant medications
- Vital signs (pulse, blood pressure, weight and height)
- Physical examination including ECOG Performance Status
- CBC
- Biochemistry: creatinine, uricemia, AST, ALT, GGT, ALP, total and direct bilirubin, LDH, beta2-microglobulin, Nat, Kal, Ca
- HIV, HCV, HBV testing
- Pregnancy test (for FCBP only)

6.5.3 Interim examinations (every week for the first 8 weeks, then every 2 weeks)

- Concomitant medications
- Vital signs (pulse, blood pressure, weight and height)
- Physical examination including ECOG Performance Status
- CBC

- Biochemistry
- Disease status evaluation (contrasted total body CT scan every 4 months)
- AE reports

6.5.4 Post-study surveillance evaluation (until 1 year after lenalidomide discontinuation)

- Concomitant medications
- Vital signs (pulse, blood pressure, weight and height)
- Physical examination including ECOG Performance Status
- CBC
- Biochemistry
- Disease status evaluation
- AE reports

6.5.5 Follow-up (every 4 months for the 2nd to the 4th year; every 6 months for the 5th and 6th , yearly afterward)

- Physical examination including ECOG Performance Status
- CBC
- Biochemistry
- Disease status evaluation (contrasted total body CT scan plus every procedure positive at first relapse (marrow biopsy according to clinical requirements)

7 Data quality assurance

7.1 Quality control

The investigators will assure the monitoring of the clinical study to assure conformance to protocol as well as the completeness, correctness and plausibility of the completed case report forms (CRF).

7.2 Deviation from study protocol

Every deviation from the trial protocol must be specified and documented separately for each patient. The investigator is responsible of discussing the type and extent of deviation as well as the possible consequences for further participation of the patient in the study.

8 Statistical procedures

8.1 Sample size and power consideration

Simon's two-stage optimal design will be used. The null hypothesis that the true 1-year PFS is 30% will be tested against a one-sided alternative. In the first stage, 15 patients will be accrued. If there are 5 or fewer patients progression-free at one year in these 15 patients, the study will be stopped. Otherwise, 32 additional patients will be accrued for a total of 47. The null hypothesis will be rejected if 19 or more patients progression-free at one year are observed in 47 patients. This design yields a type I error rate of 5% and power of 80% when the true 1-year PFS is 50%.

8.2 Efficacy endpoints

8.2.1 Overall survival

It is defined as the time from enrolment to death for any cause. Patients alive at last follow-up will be censored.

8.2.2 Progression-free survival

It is defined as the time from enrolment to progression or relapse of lymphoma (if post-induction disease status was PR or CR, respectively). Patients alive at last follow-up will be censored.

8.2.3 Duration of response

It is defined as the time from induction therapy response documentation and progression or relapse of lymphoma.

8.3 Safety endpoints

8.3.1 Grade 3-4 NCI-CTC AEs

All NCI-CTCAE grade 3-4 will be recorded.

8.4 Efficacy analysis

Efficacy analyses will be performed on the intention-to-treat population that includes all subjects enrolled. Response rate during and after lenalidomide treatment will be provided. Analyses will be performed to characterize PFS, TTP and OS. The Kaplan-Meier procedure will be used to characterize the time-to-event curves in the analyses where there is censoring. Otherwise, summary statistics (mean, standard deviation, median, minimum and maximum) will be provided. Parameters known to be potentially predictive of disease aggressiveness and

likelihood of response to lenalidomide in relapsed or refractory DLBCLs (tumour burden, LDH levels, time from last rituximab, etc) as well as prognostic subtypes (namely "germinal-center B cell type" – GBC - and "activated B-cell type" – ABC) or specific gene expression patterns/genetic signatures amenable to DLBCL subtypes - where available - will be taken into consideration in post-hoc multivariate efficacy analysis.

8.5 Safety analysis

All subjects who receive at least one week of study drug medication will be included in safety analysis. AEs, vital signs measurements, clinical laboratory information and concomitant medications will be tabulated and summarized. Subject incidence rates of all AEs and events requiring the discontinuation of study drug will be tabulated by system class, preferred term, and severity using MedDRA terms and NCI-CTCAE Version 3.0 severity grades. Time to first dose reduction will be summarized for each regimen. Death and clinically important AEs (including tumour lysis and thrombosis) will also be summarized.
All other measurements will be summarized using means, standard deviations, medians, minimum and maximum. Graphical display will be provided where useful in the interpretation of results.

9 Data handling and record keeping

9.1 Definition of source documents and data

All parameters asked for in the case report form (CRF) should be documented in the source documents.

Parameter	Source document
Medical history / patient's eligibility	- patients' charts
Therapy	- patients' charts
Disease status	- patients' charts - histological / radiological / laboratory reports
Adverse events	- patients' charts - laboratory reports - medical reports - nurses documentation

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Physical examination	- patients' charts
Disease response	- patients' charts - histological / radiological / laboratory reports
Survival	- patients' charts, autopsy report if available

For the following parameter, the CRF might be used as source document:
- ECOG Performance Status

9.2 Patient registration

Registration of patients will be performed by responsible investigator of every participating center by sending a fulfilled Registration Form at the attention of the Principal Investigator by fax at **+39 02 2643 4760**.

9.3 Documentation of data in the case report form (CRF)

All relevant data collected during the study for all of the patients enrolled in the study shall be entered in the CRF by the responsible investigator or someone authorised by him in a timely manner so that they are clear and legible. The physician shall confirm the completeness, correctness and plausibility of the data by his signature with the date. The entries shall be made with black ball-point pen.
The properly filled in CRF will remain in the trial centre.

9.4 Data management

The data will be recorded in the CRF designed for this study. All CRF will be checked for completeness, plausibility and compliance with the ICH guidelines and the institutional SOPs.

9.5 Record keeping

The investigator shall arrange for the retention of the patient identification list, the signed informed consent forms and the signed data protection declaration for at least 15 years after the completion or discontinuation of the study. Patient files and other source data shall be kept for the maximum period of time permitted by the hospital.
The sponsor will keep essential documents according to ICH-GCP.

10. Study drug material and management

10.1 Supplier(s)

- Celgene Corporation will supply lenalidomide.

10.2 Dosage form

- Lenalidomide will be supplied as 5mg, 10mg and 25mg capsules for oral administration.

10.3 Packaging

- Lenalidomide will be shipped to the pharmacy at the study site in individual bottles each containing 21 capsules of lenalidomide 5mg, 10mg or 25mg.
    - Patients will be treated for 24 cycles of therapy, unless treatment is discontinued earlier due to disease progression or unacceptable toxicity. At each cycle, patients will be provided with a number of bottles containing lenalidomide 5, 10 or 25mg sufficient to cover 21 days of treatment.

10.4 Special Handling Instructions

Women of childbearing potential should not handle or administer the clinical dosage forms unless they are wearing gloves.

10.5 Labelling

The label for study drug supplied by Celgene will detail Sponsor's name name and address, the protocol number, EudraCT number, product name, dosage form, and strength, medication identification/kit number, dosing instructions, storage conditions, the quantity of study drug contained, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as needed an/or applicable.

10.6 Receipt of study drug

The Investigator 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, and return a copy to Celgene or its representative.

10.7 Storage

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

At the study site, all investigational study drugs will be stored in a double locked, safe area to prevent unauthorized access.

10.8 Unused study drug supplies

Patients will be instructed to return empty bottles or unused capsules. Unused or returned study drug will be destroyed locally in compliance with local pharmacy destruction procedures and drug disposition must be appropriately documented in the study file. If any study drug is lost or damaged, its disposition should be documented in the source documents.

10.9 Record of administration

Accurate records will be kept of all study drug administration (including dispensing and dosing) in the study record files.

11 Formalities / regulatory aspects

11.1 Legal regulations and guidelines

This study will be conducted in conformance with the regulations of the latest versions of the applicable laws, the "Declaration of Helsinki" and the principles of good clinical practice (ICH-GCP).

11.2 Patient insurance

In accordance with the drug regulations, all patients participating in the study have been insured for injury or death.

11.3 Additions / amendments to the study protocol

Substantial additions and changes to the trial protocol require a written amendment. Changes affecting the health of the patient will require another vote by the ethics committee and a new written consent by the patients affected. Celgene is to be notified of all amendments.
Additions and changes made after the start of the trial will be communicated to all study participants in writing together with the date the change becomes effective.

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