1. TITLE PAGE

Investigational Product:	Lenalidomide
Protocol No./Study No.:	R2-CHOP
EudraCT No.:	2007-007698-22
Study Title:	A Phase IB/II study of escalating doses of Revlimid in association with R-CHOP (R2-CHOP) in the treatment of B-cell lymphoma

Development Phase:	IB/II
Indication:	B-cell Lymphoma, CD 20 positive : • Mantle cell, Marginal zone, follicular • Histological transformation from low grade to high grade • Diffuse large B cell

Date First Patient enrolled:	06-Jan-2009
Date Last Patient Last Visit:	23-Nov-2015
Report Date:	21-Dec-2017
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Coordinating Investigator:	Pr Hervé TILLY Centre Henri Becquerel rue d'Amiens 76038 Rouen France ☎: +33(0) 2 32 08 22 00 herve.tilly@chb.unicancer.fr

2. SYNOPSIS

Name of Sponsor/Company: Centre Henri Becquerel	*(For National Authority Use only)*
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Name of Active Ingredient: Lenalidomide	

Title of Study:
A Phase IB/II study of escalating doses of Revlimid in association with R-CHOP (R2-CHOP) in the treatment of B-cell lymphoma

Coordinating Investigator:
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Study Centers:
Sixteen LYSA centers in France.
Coordinating center: LYSARC (The Lymphoma Academic Research Organisation), Centre Hospitalier Lyon Sud, Secteur Sainte Eugénie (Pavillon 6D), 69495 Pierre Bénite Cedex, France.

Publications:
Lenalidomide In Combination With R-CHOP (R2-CHOP) In Patients With High Burden Follicular Lymphoma: Phase 2 Study. Tilly H, Morschhauser F, Casasnovas O, Molina T, Mounier N, Salles G, Le Gouill S, Bologna S, Tournilhac O, Cabecadas J, Bouabdallah R, Gabarre J, Lamy T, Haioun C. ASH 2013 Abstract #248.
Phase 1b study of lenalidomide in combination with rituximab-CHOP (R2-CHOP) in patients with B-cell lymphoma. Tilly H, Morschhauser F, Salles G, Casasnovas RO, Feugier P, Molina TJ, Jardin F, Terriou L, Haioun C, Coiffier B.Leukemia. 2013 Jan;27(1):252-5. doi: 10.1038/leu.2012.172. Epub 2012 Jun 26.

Studied Period (years):		**Phase of Development:**
Date of first patient enrolled:	06-Jan-2009	IB/II
Date of last patient last visit :	23-Nov-2015	
Study duration (per patient):	6.8 years	

Primary Objective:
The primary objective of the Phase IB part of the study is to determine the recommended dose (RD) of lenalinomide (Revlimid) when administered in association with R-CHOP.

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

Secondary Objectives:

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

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

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

The Phase II part of the study is an efficacy study of the association of the recommended dose of

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lenalinomide associated with R-CHOP 21 in a selected population of patients with follicular lymphoma.	
Number of Patients: A total of 110 evaluable subjects were planned to be enrolled in the study: about 30 patients for the Phase I_B part and 80 patients in the Phase II part.	
Inclusion criteria: • Phase IB: Patients with one of the following B-cell Lymphoma, CD 20 positive: o Mantle cell, Marginal zone, follicular o Histological transformation from low grade to high grade o Diffuse large B cell • Phase II: Patients with follicular lymphoma, WHO grade 1, 2 or 3a with at least one of the following signs requiring initiation of treatment: o Bulky disease according to the GELF criteria: nodal or extra-nodal mass >7cm in its greater diameter o B symptoms o Elevated serum LDH or beta 2-microglobulin o Involvement of at least 3 nodal sites (each >3cm) o Symptomatic spleen enlargement o Compressive syndrome o Pleural or peritoneal effusion • Aged from 18 to 70 years • WHO performance status 0, 1 or 2 • Signed inform consent • Life expectancy of ≥ 90 days (3 months). • Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL not more than 3 days from the start of study drug and must either commit to continued abstinence from heterosexual intercourse (and confirmed on a monthly basis) or begin one effective method of birth control, at least four weeks before she starts taking lenalidomide, and maintain that method throughout the entire duration of study drug therapy (including dose interruptions), and for four weeks after the end of study treatment with lenalidomide, even if she has amenorrhea. FCBP must also agree to pregnancy testing at least every three weeks and must be counseled at a minimum of every three weeks about pregnancy precautions and risks of fetal exposure. • Men must agree not to father a child and agree to use a condom throughout study drug therapy, during any dose interruption, and for one week after cessation of study drug therapy, if their partner is pregnant or of child bearing potential. Men must also agree not to donate semen during study drug therapy and for one week after end of study drug therapy. Men must be counseled at a minimum of every 4 weeks about pregnancy precautions and risks of fetal exposure. • All subjects must abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy. • Agree not to share study drug with another person and to return all unusued study drug to the investigator. † A female patient is considered to have childbearing potential unless she meets at least one of the following criteria 1) Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (amenorrhoea following cancer therapy does not rule out childbearing potential); or 2) Premature ovarian failure confirmed by a specialist gynaecologist or 3) Previous bilateral salpingo-oophorectomy, or hysterectomy, or 4) XY genotype, turner	

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syndrome, uterine agenesis.

Exclusion criteria:

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

Investigational Product:

Lenalidomide: provided by Celgene in bottles of 28 capsules of 5 mg or 10 mg.
Lot numbers: 10F0283, 10F0287, 11F0032 and 11F0216.

Criteria for Evaluation:

Clinical examinations (including vital signs, ECOG performance status) and laboratory safety tests (including complete blood counts, serum chemistries) was be obtained prior to drug administration, and before each cycle of treatment, and up to 30 days after the last study treatment administration.
During the first two cycles of the phase IB, clinical examination and complete blood cell counts were obtained at day 7, day 10 and then every two days (± 1 day) until the absolute neutrophil count reach 1.5 x 109/L and platelet count reach 100 x 109/L.
AEs/SAEs type, severity (according NCI-CTCAE v. 3.0), cycle, duration, seriousness, and relationship to study treatment were assessed. Laboratory abnormalities were assessed according to the NCI-CTCAE v. 3.0.
Tumor assessment (clinical examination, laboratory tests, abdominal and chest CT scan, PET scan, bone

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marrow examination) were performed at baseline, after cycle 4 and three weeks after the last treatment dose. To ensure comparability, baseline and on-study methods for response assessment were performed using identical techniques.

Statistical Methodology:

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

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

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

Safety data and, when available, preliminary efficacy data were used to define dose escalation increments.

The cut-off for main criteria analysis is defined when safety data for the first 2 cycles of R2-CHOP are available for all patients. Then, the cut-off for efficacy data and safety data for cycles 3 to 6 of this part of the study was established at 3 months after the end of treatment for the last patient. A last cut-off occurred 2 years after the last treatment last patient.

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

Cut-off for final analysis occurred one year after last treatment last patient.

Sample Size Determination:

For the phase IB part of the study, sample size is not based on statistical power calculation. The number of dose levels and the emerging dose limiting toxicities determine the sample size. It is anticipated that approximately 30 patients are required to establish the maximum tolerated dose (MTD) and the recommended dose of lenalidomide (Revlimid).

For the phase II part of the study, the sample size calculation is based on Simon's randomized phase II design testing the null hypothesis that the complete response rate is less than or equal to 65% versus the alternative hypothesis that the response rate is greater than or equal to 80%. A total of 73 evaluable provide nominal power of 80% at the nominal one-sided 2.5% significance level. Assuming an estimated drop out of 10%, a total of 80 patients were enrolled.

RESULTS:

Disposition

Overall the Phase IB part study enrolled 28 patients from January 6, 2009 to June 21, 2010 and the Phase II part study enrolled 80 patients from December the 21th, 2010 to January the 25th, 2012.

Twenty seven patients received treatment in Phase IB and were evaluable for DLT assessment: 3 at dose level 5 mg, 3 at dose level 10 mg, 3 at dose level 15 mg, 6 at dose level 20 mg and 11 at dose level 25 mg.

In Phase II part, 80 patients were enrolled and treated. 6 patients withdrawn during treatment (1 toxicity, 2

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consent withdrawal, 1 concurrent illness, 1 insufficient response, 1 other) and 74 patients completed treatment period.

Efficacy

Primary endpoint:

The primary objective for Phase I part was the determination of the Recommended Dose of lenalidomide (Revlimid) in combination with R-CHOP regimen. One patient (17%) at dose level 20mg experienced at least one DLT and 5 patients (42%) at dose level 25mg. The dose of 25 mg was recommended for Phase II with a schedule of dose adjustments for toxicity.

The primary objective for Phase II part was the Complete Response Rate (CR+CRu) at the end of treatment: 74% of patients.

Secondary endpoints:

Secondary efficacy analyses showed:

- Overall Response Rate at the End of Treatment: 93.8%,
- Complete Response Rate at Interim Evaluation According to Cheson: 38.8%,
- Overall Response Rate at Interim Evaluation: 88.8%,
- Progression free survival: 60 patients at 36 months,
- Overall survival: 72 patients at 36 months,
- 17 Patients presenting with Progression/Relapse and Response Duration for these patients was 18.14 months.

Safety

Adverse events

Revlimid in association with R-CHOP was well tolerated in the patient population. In Phase IB part, the most common toxicities during whole treatment were hematological. In Phase II, the most common toxicities during whole treatment were hematological: Hemoglobin (9 patients with grade 3), Neutrophils (52 patients with grade 4 and 9 patients with grade 3), Platelets (10 patients with grade 4 and 18 patients with grade 3) and Febrile neutropenia (1 patients with grade 4 and 5 patients with grade 3). Few patients were concerned by other grade 3 toxicities (no grade 4 was observed): Diarrhea for 4 patients, Vascular for 4 patients, Peripheral neuropathy for 1 patient, and Rash for 2 patients.

The incidence of SAEs was low. A total of 51 serious adverse events (10 in phase IB and 41 in phase II) were reported: 29 patients out of 108 patients experienced SAEs (8 for the phase IB and 21 for the phase II). The Serious Adverse Reactions which occurred more frequently were in the SOC: Infections and infestations (with 8 cases), Neoplams benign, malignant and unspecified (7 cases) and Blood and lymphatic system disorders (5 cases).

Deaths

In Phase IB, no death was reported. In Phase II part, 4 deaths were reported : one due to digestive cancer and three due to Progressive Disease of lymphoma.

Hematology, serum biochemistry, vital signs, clinical examination

There were no clinically important findings that would be unexpected in this patient population.

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CONCLUSIONS: • This phase 2 confirmed the safety of the combination : R2-CHOP regimen yielded a high rate of complete response in patients with high tumor burden follicular lymphoma. • Survival analysis is still immature due to the current short duration of patient follow-up. • The future of this combination will depend on the results of ongoing trials exploring association of Rituximab and Revlimid (R2) as frontline treatment in this population.	
Report Date: *21-Dec-2017*	