2. SYNOPSIS

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Revlimid		
Name of Active Ingredient: Lenalidomide		

Title of Study:

Sub-cutaneous Rituximab-miniCHOP versus Sub-cutaneous Rituximab-miniCHOP + lenalidomide (R2-miniCHOP) in Diffuse Large B Cell lymphoma for patients of 80 years old or more.

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Co-coordinating Investigator : Dr Lucie OBERIC, Institut Universitaire du Cancer Toulouse-Oncopole, Toulouse

Study site(s) and countries:
71 study centers in France and Belgium.

Publications (reference):

DOI: 10.1200/JCO.20.02666 Journal of Clinical Oncology 39, no. 11 (April 10, 2021) 1203-1213.

Studied period (years): Date first subject first visit: 20 August 2014 Date last subject completed: 07/02/2021 Data cutoff date: 07/02/2021	**Phase of development:** 3

Trial registry number(s):
ClinicalTrials.gov identifier: NCT02128061
EudraCT number: 2013-000450-22

Objectives:

Primary:

Primary endpoint of the study was to compare the efficacy of R2-miniCHOP (Sub-cutaneous Rituximab-miniCHOP + lenalidomide) and R-miniCHOP (Sub-cutaneous Rituximab-miniCHOP) in patients of 80 years old or more with not previously treated CD20+ diffuse large B-cell lymphoma as measured by the overall survival (OS).

Secondary:

Secondary endpoints were:

- To evaluate the efficacy and the safety of R2-miniCHOP as measured by the PFS (Progression Free Survival), EFS (Event Free Survival), the DoR (duration of response), the DFS (disease free survival), response rate at the end of the treatment, the additional toxicities
- To evaluate the simplified scale prognostic impact (IADL, MNA, G8, CIRS-G)
- To assess the quality of life before and after treatment

Methodology:

This study was a multicentric, phase III, open-label, randomized (1:1) trial evaluating the efficacy of R2-miniCHOP in patients aged of 80 years or more with non-previously treated CD20+ diffuse large B-cell

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lymphoma, Ann Arbor stage II to IV with a performance status ECOG from 0 to 2.

Subjects were to be eligible for screening once the subject had approved and signed the informed consent form. In the Screening Phase, the subject was to undergo baseline assessments of their disease and other assessments up to 14 days before first dose of study drug, except for imaging exams and biopsies (up to 28 days before first dose of study drug). Subject eligibility was based on local pathology diagnosis. Upon completion of the required assessments in the Screening Phase and fulfillment of the eligibility criteria, subjects were included. Treatment should start as soon as possible after randomization. A pathological review for diagnosis was mandatory to confirm the B cell lymphoma histology. Outcome of the central pathology confirmation was not required for entry into the study. Response assessment included review of computed tomography (CT) scans, bone marrow (BM), examination, laboratory tests, and clinical examination according to International Working Group (IWG) response criteria for non-Hodgkin lymphoma (NHL).

All subjects were to be followed in the Follow-up Phase for PFS and OS with clinic visits every 3 months for the first 2 years, every 6 months until the end of the study. Once the subjects had been discontinued from study drug, they were to be followed for progression of disease or relapse, lymphoma treatments, and death.

The final analysis was realized when the number of 79 events has been reached, and the actualization was performed 3 years after the last drug administration to the last patient included. All data available at the scheduled time of final analysis were to be used for these subjects.

Number of subjects (planned, enrolled, and analyzed):

Planned: 250 subjects
Enrolled: 249 subjects
Analyzed: 249 subjects (ITT set) / 241 subjects (safety set)

Diagnosis and main criteria for inclusion:

Male or female adult (aged 80 years old or older) subjects with histologically proven CD20+ DLBCL not previously treated. Eligibility criteria included stages II-IV, measurable disease, a revised International Prognostic Index (IPI) score of 1 or higher, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or lower. The exclusion criteria were known CNS lymphoma or meningeal involvement, cardiac dysfunction assessed by isotopic or echotomographic measure, or renal insufficiency assessed by creatinine clearance lower than 40mL/min (MDRD formula).

Test product, dose, and mode of administration:

Lenalidomide was supplied in labelled blister. Each capsule contains 10mg or 5mg of Lenalidomide.

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Subjects were treated with Lenalidomide on an outpatient basis. Oral Lenalidomide was initiated on day 1 of cycle 1 at a dose of 10 mg daily and was continued for 14 days in each 21-day cycle. Treatment was continued as tolerated for 6 cycles.

Duration of treatment:

Subjects were to receive study drugs for up to 6 cycles, or until unacceptable toxicity developed, or progression, or voluntary withdrawal.

Reference therapy, dose, and mode of administration:

R-miniCHOP was used as reference therapy in this study. Lenalidomide was administered in combination with R-miniCHOP regimen.

Criteria for evaluation:

Efficacy:

Response was assessed at end of treatment (after end of the 6th cycle of treatment or at permanent treatment discontinuation). Assessment of response was based on the International Workshop to Standardize Response criteria for NHL (Criteria for evaluation of response in non-Hodgkin's lymphoma (Cheson 1999 criteria)).

Safety:

Safety assessments included recording of adverse events, clinical laboratory measurements (hematology and serum chemistry, pregnancy), and vital signs. Adverse events included severity graded according to the Common Terminology Criteria for Adverse Events (CTCAE; Version 4.03), causality, dose interruption, dose adaptation, study treatment discontinuation, and death.

Statistical methods:

Analysis Sets

Intent to Treat (ITT) set

The ITT set included all patients having signed the informed consent and randomized regardless of study drug being received or not. Patients were analyzed based on the assigned treatment group at the time of randomization.

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Per Protocol (PP) set

The PP set included all patients included in the ITT set, with no major protocol deviation. Major protocol deviations were defined during the data review meeting before the analysis and described in the Data Review Report.

QoL set

The QoL set was defined as all patients with an evaluable QLQ-C30 at randomization. A QLQ-C30 questionnaire was considered as evaluable if it contains less than 50% of missing data among the 30 items of the questionnaire.

Safety set

Safety set included all patients who took at least one dose of study drug (R-miniCHOP or R2-miniCHOP). Patients were analyzed on the actual treatment received ("as treated").

Efficacy set

The efficacy set included all patients included in the ITT set with histopathological confirmed DLBCL by central review having:

- received at least one dose of study drug (R-miniCHOP or R2-miniCHOP with sub-cutaneous Rituximab)
- for patients in the R2-miniCHOP treatment arm, only patients who correctly switched to Rituximab SC during at least one completed cycle will be included in this set
- baseline tumor assessments
- at least one post baseline tumor assessment

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SUMMARY – CONCLUSION

Study Disposition

In total, from 20 August 2014 to 13 September 2017, 249 patients were enrolled and randomized in standard arm (n=127) or experimental arm (n=122).

Study Population

Among the 249 enrolled patients, 241 patients received treatment (124 patients in the standard arm and 117 in the experimental arm), constituting the safety population.

Efficacy Results

With a median follow-up of 38.9 months, the primary end point of OS was not significantly different between the two arms (HR= 1.10; 95% CI, 0.74 to 1.62; p=0.637). The 2-year OS was 67.9 (95% CI, 58.9 to 75.3) in the R-miniCHOP arm and 66.9% (95% CI, 57.6 to 74.6) in the R2-miniCHOP arm. Among treated patients, 49 (38.6%) deaths occurred in the R-miniCHOP arm (35 for lymphoma progression) and 53 (43.4%) in the R2-miniCHOP arm (28 for lymphoma progression).

No significant difference between the standard arm and experimental arm was observed regarding PFS (HR= 1.07, 95% CI, 0.74 – 1.55, p=0.70) and EFS (HR= 0.976, 95% CI 0.68–1.39, p= 0.89). The ORR assessed by investigators at the end of treatment was 73.2% in the R-miniCHOP arm (95% CI, 64.6% to 80.7%) and 82.8% in the R2-miniCHOP arm (95% CI, 74.9% to 89.0%). 2-year DoR was 68.5% (95% CI; 56.9–77.6) in the standard treatment group compared with 64.5% (95% CI; 53.6–73.5) in the experimental arm (HR= 1.34, 95% CI 0.83–2.14, p= 0.34).

Safety Results

Compared with standard R-miniCHOP results, more patients in the R2-miniCHOP arm had at least one grade 3-4 AEs, due to large amount of grade 3 or 4 neutropenia occurring in this experimental arm. Additionally, more SAEs occurred in the experimental arm and were due to infections. Secondary primary malignancies were reported in similar proportion between both arms but seem to be qualitatively different.

Conclusions

The SENIOR study is the first prospective phase III trial in patients older than 80 years with newly diagnosed DLBCL. The addition of lenalidomide to the R-miniCHOP schema does not improve OS irrespective of GCB/ABC status and results in more AEs. Rituximab delivered subcutaneously was safe and well-tolerated in this very elderly population, showing a similar efficacy with historic IV R-

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miniCHOP data. **Date of the report**: 29 November 2021		