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® capsules		
Name of Active Ingredient: Lenalidomide		

Title of Study:
Double Blind Randomized Phase III Study of Lenalidomide (Revlimid®) Maintenance Versus Placebo in Responding Elderly Patients with Diffuse Large B-cell Lymphoma and Treated with R-CHOP in First Line

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Investigators: A list of investigators and their institutional affiliations is provided in Appendix 16.1.4.

Study center(s): Subjects were randomized at 129 study centers in France, Belgium, Switzerland, Austria, Spain, Portugal, Poland, Israel, and Australia.

Publications (reference):
jco.2017.72.6984

Studied period (years): Date first patient enrolled: 14 April 2009 Data cutoff date: 30 September 2019 Overall survival update: 30 September 2019	**Phase of development:** 3

Trial registry number(s):
ClinicalTrials.gov identifier: NCT01122472
EudraCT number: 2008-008202-52

Objectives:
The primary objective was to determine the benefit estimated by the progression-free survival (PFS) associated with lenalidomide maintenance compared with placebo in responding subjects treated with rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for diffuse large B-cell lymphoma (DLBCL).

The secondary objectives were to assess:

- Percentage of subjects who converted from partial response (PR) to complete response (CR)
- Efficacy according to the response to R-CHOP
- Overall survival (OS) in both groups of subjects (with and without lenalidomide maintenance)
- Progression-free survival on next line treatment (PFS2), event-free survival (EFS), and EFS at
- 24 months
- Safety of lenalidomide in maintenance

Methodology:
This study was an ongoing multinational, multicenter, double-blind, randomized Phase 3 study of (or 10 mg/day for subjects with creatinine clearance [CrCl] between 30 and 60 mL/min) on Days 1 to 21 in 28-

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day cycles for 24 months (maximum of 26 cycles) in subjects 60 to 80 years old diagnosed with CD20+ DLBCL who responded (PR or CR) to first-line induction treatment with R-CHOP. The phases of this study included an induction treatment phase, a randomized maintenance treatment phase, and a follow-up phase.

Subjects could have registered to participate in the study at either of 2 time points:

- At the time of initial diagnosis before their first cycle of treatment with R-CHOP
- After first-line treatment with R-CHOP if subjects had achieved at least a PR or a CR

All subjects (independent of time of registration) had at least 6 and up to 8 cycles of R-CHOP-14 or R-CHOP-21 (i.e., R-CHOP for 14-day or 21-day intervals, respectively) **or** 6 cycles of R-CHOP-14 or R-CHOP-21 followed by 2 cycles of rituximab alone (1 dose on Day 1 of each cycle) in accordance with local preference. Response assessments after the induction phase were performed on all subjects (independent of time of registration) between 3 weeks (21 days) and 8 weeks (56 days) after Day 1 of the last cycle of R-CHOP or the last dose of rituximab alone.

After evaluation of response at the end of the induction phase, subjects with at least a PR were randomized in a 1:1 ratio to receive either lenalidomide or placebo according to the following stratification factors:

- Country
- Local assessment of response to R-CHOP (PR or CR)

After consent was obtained, all subjects responding (i.e., PR or CR) to induction treatment with R-CHOP were randomized and given maintenance treatment with lenalidomide or placebo starting within 12 weeks (84 days) after Day 1 of the last cycle of R-CHOP or the last dose of rituximab alone. The study drug (lenalidomide or placebo) was administered at a starting dose of 25 mg/day (or 10 mg/day for subjects with CrCl between 30 and 60 mL/min) on Days 1 to 21 in 28-day cycles for 24 months (maximum of 26 cycles).

In addition to response evaluation, regular safety assessments were performed throughout the study, including physical examinations; clinical laboratory evaluations; monitoring of adverse events (AEs), secondary primary malignancies, and concomitant medications; and bone marrow evaluation, as necessary.

Relapse/progression was determined as per the Cheson, 2007 criteria. Progressive disease was assessed based on computerized tomography (CT) scan, histologic documentation, or clinical measurable tumor, and not on positron emission tomography (PET) finding only.

Follow-up assessments were conducted at each follow-up visit every 6 months for at least 3 years from the last dose of study drug (for any subject) in the study.

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

Planned: 621 subjects
Enrolled: 796 subjects
Randomized: 650 subjects

The study randomized 650 subjects, more than planned, as recruitment at diagnosis was allowed until the number of randomized subjects was obtained.

Diagnosis and main criteria for inclusion:

Males and female subjects 60 to 80 years at the time of registration with histologically proven CD20+ DLBCL (WHO classification 2008) or with de novo transformed DLBCL from low-grade lymphoma

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(i.e., follicular, other low-grade lymphomas); or CD20+ B-cell lymphoma with intermediate features between DLBCL and Burkitt or with intermediate features between DLBCL and classical Hodgkin lymphoma; or CD20+ follicular lymphoma Grade 3B; or CD20+ aggressive B-cell lymphoma unclassifiable.

Subjects had to be untreated with chemo-radiotherapy for lymphoma if they registered before first-line treatment with R-CHOP, and had to have reached CR or PR (Cheson, 2007) after first-line treatment with at least 6 and up to 8 cycles of R-CHOP-14 or R-CHOP-21 and been previously untreated with radiotherapy for lymphoma if they registered after response evaluation to first-line treatment with RCHOP.

Subjects were also required to have Eastern Cooperative Oncology Group performance status ≤ 2, age adjusted International Prognostic Index (aaIPI) ≥ 1 at the time of initial diagnosis, minimum life expectancy of 3 months, and the following laboratory values at screening:

- Absolute neutrophil count ≥ 1000 × 106/L and platelets ≥ 60,000 × 106/L, unless these abnormalities were related to bone marrow infiltration
- Aspartate transaminase ≤ 5 × upper limit of normal (ULN); alanine transaminase ≤ 5 × ULN; total bilirubin ≤ 1.5 × ULN; unless related to disease involvement
- CrCl ≥ 30 mL/min

Test product, dose, and mode of administration:

Lenalidomide was supplied as 5-, 10-, 15-, 20-, and 25-mg capsules for oral administration.

Duration of treatment:

Treatment with lenalidomide or placebo was administered in 28-day cycles until disease progression, unacceptable toxicity, or treatment discontinuation for any other reason, for up to 24 months (maximum of 26 cycles).

Reference therapy, dose, and mode of administration:

5-, 10-, 15-, 20-, and 25-mg placebo capsules matched to the test treatment were used in the study.

Criteria for evaluation:

The primary analysis populations for this study were:

- The maintenance full analysis set (FAS-Maintenance), which included all subjects who were formally randomized to the maintenance phase of the trial regardless of whether or not they received maintenance therapy (following the principle of intent-to-treat).
- The maintenance safety set (SS-Maintenance), which included all subjects who received at least 1 dose of maintenance treatment.

Efficacy:

The primary efficacy endpoint was PFS, as assessed by a blinded independent response committee (IRC). The final PFS analysis was to be performed when a total of 160 progression/death events (according to the IRC) had been reached, or, at the latest, when a median follow-up of 5 years had been achieved. The primary analysis of PFS was conducted on the FAS-Maintenance, using the Food and Drug Administration (FDA) censoring rules.

Secondary efficacy endpoints included PFS based on investigator assessment, OS, EFS, PFS2, response rate at the end of maintenance treatment, percentage of subjects who converted from PR to CR, and quality of life.

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Safety:
Safety endpoints included toxicities (worst grade by subject, grade by cycle), treatment-emergent AEs (TEAEs), treatment-emergent serious AEs (SAEs), treatment-emergent AEs leading to death, clinical laboratory results, physical examination, and vital signs. The primary analysis population for safety was the SS-Maintenance.

Statistical methods:

Efficacy analyses:
The primary analysis of PFS used an unstratified 2-sided log-rank test (overall alpha level of 5%) based on data from the independent assessments by the IRC. Estimates of the treatment effect were expressed as hazard ratios including 2-sided 95% confidence intervals (CIs). In addition, Kaplan-Meier estimates of median PFS as well as PFS rates at 1, 2, and 3 years after randomization with 95% CIs were reported.
In addition, a log-rank test stratified by country and by response to induction therapy (CR versus PR) was performed to account for the stratified randomization.
Sensitivity analyses of PFS were conducted using European Medicines Agency (EMA) censoring rules and other analysis populations.
An interim analysis on OS was to be performed with O'Brien-Fleming boundary conditional on successful demonstration of superiority on PFS. A final OS analysis was performed when there were cumulative of 167 deaths. Sequential gate keeping approach and alpha spending function were used to adjust for multiplicity.
For non-recurrent time-to-event analyses, censored data were presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points with 95% CIs. The median time-to-event endpoints were calculated (if reached) with 95% CIs. Secondary time-to-event endpoints were analyzed by using the same tests and significance levels as the primary endpoint.
For PFS2, the recurrent event approach based on Prentice, Williams and Peterson (PWP) models were also used to take account of first and second progressions.
Response rates at the end of maintenance therapy and percentage of subjects who converted from PR to CR were expressed with 95% CIs according to the Pearson-Clopper method and compared using a chi-square test.
For the QoL analysis, the global health score was used as the primary QoL outcome, and the physical functional score and the fatigue item were used as secondary outcomes. Statistical tests were performed in an exploratory manner. The difference between the lenalidomide arm and the placebo arm was statistically significant if the 2-sided p-value from the Wilcoxon-Mann-Whitney test was ≤ 0.05 in favor of the lenalidomide arm.

Safety analyses:
The number and percentage of subjects who reported any TEAEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. Summaries were provided for all TEAEs, treatment-related TEAEs, treatment-emergent SAEs, Grade 3 and 4 TEAEs, TEAEs leading to dose reduction, dose interruption, and study drug discontinuation. In addition, exposure-adjusted incidence rate was calculated for selected TEAEs.
Clinical laboratory, vital signs, and electrocardiogram data were summarized using descriptive statistics. Shift analyses of laboratory data by cycle and from baseline to worst on-study value, based on national Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) were produced.

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SUMMARY – CONCLUSION

Study Disposition

The planned enrollment was 621 subjects randomized in a 1:1 ratio to lenalidomide or. A total of 796 subjects were registered, among them 650 were randomized. Only subjects who had either a CR or PR to treatment with R-CHOP (per investigator assessment) were to be randomized in the study. Of the 796 registered subjects, a total of 650 subjects were randomized, including 323 subjects randomized to lenalidomide and 327 to placebo. The majority of randomized subjects were enrolled in France (403 subjects; 62.0%), other countries enrolled between 4 (0.6%; Switzerland) and 54 (8.3%; Belgium) subjects.

In total, 146 registered subjects (17.1%) were not randomized, including 7 subjects (0.9%) who completed R-CHOP therapy but did not respond to induction treatment, and 127 subjects (16.2%) who did not complete 6 to 8 cycles of R-CHOP therapy.

In the lenalidomide arm, 127 subjects (39.3%) completed the maintenance phase (defined as having completed at least 23 months of maintenance therapy) and 196 subjects (60.7%) discontinued treatment. In the placebo arm, 191 subjects (58.4%) completed the maintenance phase, 136 subjects (41.6%) discontinued treatment.

The primary reasons for discontinuation from treatment during the maintenance phase were toxicity (59.2% in the lenalidomide arm vs. 39.0% in the placebo arm), treatment failure (18.4% in the lenalidomide arm vs. 39.7% in the placebo arm), and subject decision (i.e., withdrawal from treatment but not from the follow-up phase; 8.4% in the lenalidomide arm vs. 3.7% in the placebo arm).

Once subjects discontinued treatment, they entered the follow-up phase of the study. Overall, 323 subjects (96.9%) in the lenalidomide arm and 313 subjects (98.8%) in the placebo arm entered the follow-up phase.

Efficacy Results

The primary efficacy endpoint of PFS remain significative in favor of the Lenalidomide in the 2 analyses with a p-value of 0.0153 for the censoring case and 0.0104 with all datas.

Results of sensitivity analyses on PFS including PFS based on central review using different censoring rules and different analysis sets were generally consistent with the primary efficacy results. However, there was no significant difference in PFS based on central review in subjects with centrally confirmed eligible diagnosis who had at least PR at the end of R-CHOP ($p = 0.1625$), for the lenalidomide arm and placebo arm. OS remains not significative with a p-value of 0.2854. PFS2 remains not significative with a p-value of 0.6402. As in 2016 analysis, the EFS is the same as PFS since no randomized patients have initiated a new anti-lymphoma therapy.

Safety Results

In general, the incidence of frequently reported TEAEs (≥ 5% of subjects) was higher in the lenalidomide arm compared with the placebo arm. Similarly, treatment-related TEAEs (lenalidomide, 81.7%; placebo, 48.3%), NCI CTCAE Grade 3 or 4 TEAEs (lenalidomide, 77.0%; placebo, 52.0%), treatment-related NCI CTCAE Grade 3 or 4 TEAEs (lenalidomide, 66.8%; placebo, 32.2%), treatment-related treatment-emergent SAEs (lenalidomide, 15.8%; placebo, 10.8%), TEAEs leading to dose reduction (lenalidomide, 65.8%; placebo, 31.9%), TEAEs leading to dose interruption (lenalidomide, 57.1%; placebo, 34.4%), and

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TEAEs leading to dose discontinuation (35.1%; placebo, 16.1%) were also more frequently reported in the lenalidomide arm compared with the placebo arm.
In both treatment groups, Grade 3 or 4 TEAEs were most frequently reported in the Blood and lymphatic system disorders SOC, with a higher frequency in the lenalidomide arm than in the placebo arm. Frequently reported Grade 3 or 4 TEAEs (≥ 5% of subjects) included neutropenia (54.0% lenalidomide vs. 20.7% placebo), leukopenia (19.6% lenalidomide vs. 8.0% placebo), lymphopenia (14.6% lenalidomide vs. 9.6% placebo), and neutrophil count decreased (5.0% lenalidomide vs. 1.5% placebo). All other Grade 3 or 4 TEAEs were infrequent (with PTs occurring in < 5% of subjects in either treatment arm). In general, the frequency of TEAEs in subjects < 70 years and ≥ 70 years was similar. Differences across sexes were minimal, however the frequency of TEAEs in the Blood and lymphatic system disorders SOC was generally higher in females than in males in both treatment arms.

There were no deaths on treatment in the lenalidomide arm; and no deaths due to toxicity of study drug were reported in the lenalidomide arm at any time during the study. One subject had a TEAE leading to death (cardiac failure; Grade 5) in the lenalidomide arm; the event, assessed by the investigator as unrelated to study drug. In the placebo arm, 2 deaths (0.6% of subjects) were reported on treatment (1 due to lymphoma, 1 due to toxicity to study drug); and 2 deaths due to toxicity of study drug were reported during the study.

Treatment-emergent SAEs were infrequent in this study (≤ 2% of subjects), and were primarily reports of atrial fibrillation, febrile neutropenia, squamous cell carcinoma, cardiac failure, neutropenia, and basal cell carcinoma. In the lenalidomide arm, the most frequent treatment-emergent SAEs were febrile neutropenia and neutropenia, in the placebo arm, basal cell carcinoma was the most frequently reported treatment-emergent SAE.

Invasive and non-melanoma skin cancers (SPMs) were also reviewed in this study. A total of 73 (11.3%) of the 645 subjects experienced ≥ 1 SPM as of the 30 Sep 2019 data cutoff date. Of these, a higher frequency of subjects with SPMs was observed in the placebo arm compared with the lenalidomide arm (12.7% versus 9.9%, respectively). The overall median time to onset of an invasive SPM was 21.4 months (range: 2.0 to 69.7 months) and was longer for the lenalidomide arm compared with the placebo arm (23.0 and 19.1 months, respectively). The median time to onset of a non-melanoma skin cancer was longer for the lenalidomide arm (22.3 months) compared with the placebo arm (13.1 months). Of the 73 subjects who experienced an SPM, 55 remain alive (23 in the lenalidomide arm and 32 in the placebo arm), while 18 died (9 each in the lenalidomide and placebo arms). Of the 18 subjects who died, 10 subjects died due to their SPM (5 subjects each in the lenalidomide and placebo arms), 6 subjects died due to other reasons (4 in the lenalidomide arm and 2 in the placebo arm), and 2 subjects died due to progression of lymphoma (both in the placebo arm).

Conclusions

The results of this study demonstrate that lenalidomide maintenance therapy shows benefit in centralized PFS and has an acceptable safety profile in subjects 60 to 80 years old diagnosed with CD20+ DLBCL who responded (PR or CR) to first-line induction treatment with R-CHOP.

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Lenalidomide has a predictable and generally manageable safety profile in this population, consistent with the known safety profile of the compound.

The population studied, subjects with DLBCL 60 to 80 years old, represents subjects for whom little treatment options are available if they relapse after R-CHOP induction therapy, and for whom optimization of first-line therapy is an important objective. Eligible histologies in this study included DLBCL, FL 3B, and de novo transformed lymphoma. According to local histological diagnosis, 94.1% of subjects in the lenalidomide arm and 95.4% of subjects in the placebo arm had DLBCL; based on central review, subjects with DLBCL represented 69.7% and 71.3%, and subjects having de novo transformed lymphoma, 9.6% and 4.9% of subjects in the lenalidomide and placebo arms, respectively; in each treatment arm, < 1% of subjects had FL 3B, with the remainder of subjects having missing or ineligible diagnosis.

Demographic characteristics were generally well balanced between treatment arms. The median age of subjects was 69.0 years in the lenalidomide arm, and 68.0 years in the placebo arm, and slightly more males were enrolled in the study (56.7% in the lenalidomide arm and 55.0% in the placebo arm). The majority of subjects in both treatment arms had an ECOG score at diagnosis ≤ 2 (95.6% in lenalidomide arm vs. 94.5% in placebo arm), Ann Arbor stage IV (67.5% in both treatment arms), and normal renal function (80.8% and 83.2% of subjects in lenalidomide and placebo arms had creatinine clearance ≥ 60 mL/min at the end of R-CHOP therapy).

R-CHOP 21 was the most commonly administered induction treatment (91.6% in lenalidomide arm vs 91.1% in placebo arm), with the majority of subjects receiving 8 cycles of R-CHOP 21 (Lenalidomide, 59.4%; placebo, 60.6%); in both lenalidomide and placebo arms, R-CHOP was administered for a mean of 7.4 cycles. Based on investigator assessment, 77.7% of subjects in the lenalidomide arm and 74.6% in placebo arm were in CR at the end of induction therapy, and 21.4% and 25.4% of subjects were in PR in the lenalidomide and placebo arm, respectively. In the maintenance phase, approximately 40% of subjects in each treatment arm reported the use of ASA, which was the most commonly used concomitant medication, followed by paracetamol.

The REMARC study is the first phase 3 trial evaluating maintenance therapy in DLBCL to meet its primary endpoint. The primary efficacy endpoint of PFS based on central review using US FDA censoring rules was statistically significant, with a 27% reduction in the risk of disease progression or death for subjects treated with lenalidomide compared with those treated with placebo (HR = 0.729; 95% CI: 0.551, 0.964; p = 0.026). The PFS was significative in favor of the Lenalidomide in the 2 analyses with a p-value of 0.0153 for the censoring case and 0.0104 with all datas.

In general, results of sensitivity analyses on PFS, including PFS based on central review using different censoring rules and different analysis sets demonstrated a consistent trend of risk reduction with lenalidomide compared with placebo. However, there was no significant reduction in the risk of disease progression or death for investigator assessed PFS using FDA censoring rules.

At the 3 data cutoffs used for this CSR (31 Dec 2015, 31 Oct 2016 and 30 Sep 2019), 98 of 322 subjects and 91 of 323 subjects, respectively, had died across treatment arms. Median OS was not reached in either the lenalidomide arm or the placebo arm. Although OS improved for subjects in the lenalidomide arm at the later data cutoff, there was no significant difference in OS between treatment arms at either data cut point with a p- value of 0.2854. Similarly, there was no significant difference in the likelihood of experiencing second objective PD or death or in the rate of conversion from PR to CR between treatment

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groups. It is not clear why no correlation was observed between OS and PFS, however there is no indication that it could be due to excessive toxicity in the lenalidomide arm.
Subgroup analyses on PFS were performed to determine if subjects with specific demographic or baseline disease characteristics responded differently to lenalidomide treatment. In general, point estimates were < 1, indicating longer PFS for subjects who received maintenance therapy with lenalidomide compared with those who received placebo. However, and in contrast to previous reports of lenalidomide activity in the ABC subtype, no preferential activity of lenalidomide was noted for this subtype in this study.
Results from a multivariate analysis identified treatment, response to induction, and calculated aaIPI at diagnosis as predictors of PFS.
The safety profile of lenalidomide maintenance therapy in subjects 60 to 80 years old with DLBCL was generally consistent with the known safety profile of the compound. The most common TEAEs were hematologic abnormalities (neutropenia, leukopenia, and lymphopenia) and could be managed through dose modifications and supportive therapies; Grade 3 or 4 toxicities reported in ≥ 5% of lenalidomide subjects also included infections and cutaneous reactions. While a difference in the median duration of treatment was noted between treatment arms (14.90 months in the lenalidomide arm and 23.69 months in the placebo arm), this difference in exposure is likely attributable to the fact that protocol versions before Protocol Version 5 did not provide for dose reductions in the case of mild (Grade 1 or 2) or unrelated toxicities, and subjects in the lenalidomide arm may have opted to discontinue treatment as a result of this. Overall, no new safety signals were observed that would warrant additional monitoring or precautions than what are already included in current prescribing information. There were no deaths on treatment (i.e., occurring within 28 days of the last dose of study drug) in the lenalidomide arm; and no deaths due to toxicity of study drug were reported in the lenalidomide arm at any time during the study.
Of note, the frequency of SPMs was similar in the lenalidomide and placebo arms. Treatment-emergent SAEs were infrequent in this study (≤ 2% of subjects); in the lenalidomide arm, the most frequent treatment-emergent SAEs were febrile neutropenia and neutropenia. Other than the expected hematologic effects, lenalidomide therapy had no notable effects on other clinical laboratory results, and there was no indication of cumulative toxicity for any of the clinical laboratory parameters.
The results of this study demonstrate the clinical benefit of lenalidomide as maintenance therapy, with an acceptable safety profile for long-term treatment in subjects with DLBCL 60 to 80 years old.

Date of the report: 18 January 2022