Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med 2018;379:934-47. DOI: 10.1056/NEJMoa1805104

Supplementary Appendix

Supplement to: Morschhauser F, Fowler NH et al. Rituximab plus either lenalidomide or chemotherapy in follicular lymphoma

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RELEVANCE
Rituximab Lenalidomide Versus ANy ChEmotherapy

A PHASE 3 OPEN-LABEL RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE (CC-5013) VERSUS RITUXIMAB PLUS CHEMOTHERAPY FOLLOWED BY RITUXIMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA

Statistical Analysis Plan

Version 1, November the 16th 2012

Document History:

VERSION #	EFFECTIVE DATE	AUTHOR	MODIFICATION DESCRIPTION	Affected paragraphs
1	16NOV2012			

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1 INVESTIGATIONAL PLAN

1.1 Overall study design

This multicenter, open-label study is designed to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma. The study is divided into the Screening Period, Treatment Period, and Follow-up Period.

1.2 Study objectives

1.2.1 Primary objective

The primary objective of the study is to compare the efficacy of rituximab plus lenalidomide to rituximab plus chemotherapy followed by Rituximab in patients with previously untreated follicular lymphoma. Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the Independent Review Committee (IRC) using the IWG (Cheson, 1999) criteria.

1.2.2 Secondary objectives

The secondary objectives of the study are:

- To compare the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab using other parameters of efficacy:
  - Event Free Survival (EFS),
  - Time to Next Anti-Lymphoma Treatment (TTNLT),
  - Overall Survival (OS).
- To compare the safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab.

2 EVALUATION CRITERIA

2.1 Co-Primary efficacy endpoints

2.1.1 Complete Response (CR/CRu) Rate at 120 weeks

The tumor response data will be assessed by the IRC using the IWG (Cheson 1999) criteria. Based on the CT/MRI schedule, any assessments in a time window of 120 weeks ± 4 weeks have been qualified as the 120 weeks assessments. If two or more assessments are performed in this time window, the assessment with the least favorable response will be used.

Discontinuation Rules:

- If a patient discontinues the treatment prior to this time window due to disease progression, that patient is classified as a non-responder at 120 weeks.
- If a patient whose disease was not progressed prior to this time window does not have any tumor assessments in this time window, that patient is also considered as a non-responder for this primary endpoint.
- If a patient discontinues the treatment prior to this time window due to any other reasons, the CT/MRI assessments should continue as scheduled until disease progression.

2.1.2 Progression Free Survival (PFS)

The disease progression status will be assessed by IRC using the IWG (Cheson 1999) criteria.

PFS is defined as the time from randomization into the study to the first observation of documented disease progression or death due to any cause. If a patient has not progressed or died, PFS will be censored at the time of last visit with adequate assessment. If a patient received other anti-cancer treatment for follicular lymphoma before progression, the CT/MRI assessments should continue as scheduled until disease progression or death which will be counted as events.

2.2 Secondary efficacy endpoints

The following secondary efficacy endpoints will be analyzed using appropriate statistical methods.

2.2.1 Event Free Survival (EFS)

EFS will be measured from the date of randomization to the date of first documented progression, relapse, and initiation of a new anti-lymphoma treatment or death by any cause. Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

2.2.2 Time to Next Anti-Lymphoma Treatment (TTNLT)

TTNLT will be measured from the date of randomization to the date of first documented administration of any new anti-lymphoma treatment (chemotherapy, radiotherapy, radio-immunotherapy, immunotherapy). Patients continuing in response or who are lost to follow-up will be censored on their last visit date. Patients who died (due to any cause) before having received a new anti-lymphoma treatment will be included in the statistical analysis with death being counted as an event.

2.2.3 Overall Survival (OS)

The OS will be measured from date of randomization to the date of death. Patients who die, regardless of the cause of death, will be considered to have had an event. Patients who withdraw consent for the study will be considered censored at the time of withdrawal. Patients who complete the study and

are still alive at the time of the clinical data cut-off date will be censored. All patients who were lost to follow-up prior to the clinical data cut-off date will also be considered censored at the time of last contact.

3 STATISTICAL METHOD

3.1 Analysis Sets

3.1.1 Enrolled population

The Enrolled population is defined as all patients enrolled in the study.

3.1.2 Intent to Treat (ITT) population

The ITT population is defined as all patients who are randomized into the trial, regardless of whether they received study treatment or not.
The ITT population will be used for the primary efficacy analysis. Patients will be analyzed according to the treatment arm to which they are initially assigned.

3.1.3 Modified ITT (mITT) population

The mITT population is defined as all randomized patients who have received at least one dose of study drug, have confirmed diagnosis of follicular lymphoma with no prior systemic treatment for lymphoma, have baseline and at least one post-baseline tumor assessment for efficacy.
The efficacy analysis will also be performed on the mITT population as supportive evidence and/or sensitivity analysis. Patients will be analyzed according to the treatment arm to which they are initially assigned.

3.1.4 Per Protocol (PP) Population

The PP population is defined as all patients included in the ITT population with no major protocol deviations. Major protocol violations wil be defined during the datacleaning review meetings which occurred before each analysis.
The PP population will be used to ensure the robustness of the results obtained with the ITT population and the mITT population. It will be therefore used to support the primary efficacy analysis.

3.1.5 Safety population

The safety population is defined as all patients who have received at least one dose of study drug. The safety population will be used for all safety analysis. Patients will be analyzed according to the treatment which they actually received.

3.2 Statistical Approaches for control of Alpha

The secondary efficacy endpoints are EFS, TTNLT, and OS.
In order to control an overall two-sided 0.05 study-wise Type I error rate, a fixed-sequence gate-keeping procedure will be employed to interpret the analysis results of these three secondary efficacy endpoints in the order of EFS, TTNLT, and OS. The step of analyzing these 3 secondary endpoints will be as follows:

- **Step 1**: If the result of EFS analysis fails to reach the 2-sided 0.05 significance level, no efficacy claims will be made for these three secondary endpoints. If the p-value from the EFS analysis ≤ 0.05, the efficacy claim for EFS will be made, and further testing will be performed in the Step 2.
- **Step 2**: If the result of TTNLT analysis fails to reach the 2-sided 0.05 significance level, no efficacy claims will be made for the remaining two secondary endpoints. If the p-value from the TTNLT analysis ≤ 0.05, the efficacy claim for TTNLT will be made, and further testing will be performed in the Step 3.
- **Step 3**: If the result of OS analysis fails to reach the 2-sided 0.05 significance level, no efficacy claim will be made for the OS endpoints. If the p-value from the OS analysis ≤ 0.05, the efficacy claim for the OS be made

The analysis of secondary endpoints will be performed at the end of study when the PFS analysis is performed.

3.3 Interim analyses

For the co-primary endpoint of the complete response (CR/CRu) rate at 120 weeks, two interim analyses for futility are pre-planned.
The first interim analysis will be performed when the first 200 patients have their response assessments done at 6 months of treatment or have had disease progression prior to this timepoint.
The second interim analysis will be performed when the first 200 patients have their response assessments done at 120 weeks or have had disease progression prior to this timepoint.
The intention of these two interim futility analyses is to assess risk-benefit and ensure patient safety. The proposed futility boundaries are non-binding. The results of these two futility analyses will be reviewed by the independent DMC to make recommendation of go/no go. There is no plan to claim efficacy superiority based on these interim results, therefore, no Type I error rate adjustment is needed.
As similarly defined for the primary efficacy endpoint, any assessments in a time window of 24 weeks ± 4 weeks are qualified as the 6 months assessments. If two or more assessments are performed in this time window, the assessment with the least favorable response will be used.

Discontinuation rules:

- If a patient discontinues the treatment prior to this time window due to disease progression, that patient is classified as a non-responder at 6 months.
- If a patient discontinues the treatment prior to this time window due to any other reasons, the CT/MRI assessments should continue as scheduled until disease progression.
- If a patient whose disease was not progressed prior to this time window does not have any tumor assessments in this time window, that patient is also considered as a non-responder for this endpoint.

3.3.1 First futility analysis

For the first futility analysis, possible results of the CR/CRu rate at 120 weeks for 644 patients will be simulated according to the following assumptions. The simulated results will then be analyzed to establish the first futility boundary.
Based on the PRIMA study results, the following assumptions are made for simulations:

1. For the first 100 patients in the control arm when their response data at 6 months are observed, their observed CR/CRu rate at 6 months is estimated approximately 58% to 62%, and their observed ORR is approximately 88% to 92%.
2. In the control arm, among the patients who have CR/CRu observed at 6 months there will be a 0.75 probability for them to remain in CR/CRu at 120 weeks, and among the patients who have PR observed at 6 months there will be a 0.50 probability for them to convert to CR/CRu at 120 weeks.
3. For the next 222 patients in the control arm whose response data at 6 months have not been observed yet at the first futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be (the observed CR/CRu rate at 6 months from the first 100 patients) x 0.75 + (the observed PR rate at 6 months from the first 100 patients) x 0.50.
4. For the first 100 patients in the experimental arm when their response data at 6 months are observed, their observed CR/CRu rate and PR rate at 6 months estimated in a wider range for the purpose to establish the first futility boundary.
5. In the experimental arm, among the patients who have CR/CRu observed at 6 months there will be a 0.90 probability for them to remain in CR/CRu at 120 weeks, and among the patients who have PR observed at 6 months there will be a 0.60 probability for them to convert to CR/CRu at 120 weeks.
6. For the next 222 patients in the experimental arm whose response data at 6 months have not been observed yet at the first futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be (the observed CR/CRu rate at 6 months from the first 100 patients) x 0.90 + (the observed PR rate at 6 months from the first 100 patients) x 0.60.

The Table 1 below shows the likelihood of achieving a superiority result based on the observed CR/CRu rates at 6 months for the first 200 patients. The futility boundary of the first futility analysis is that if the observed CR/CRu ratio (experimental arm/control arm) at 6 months is 0.80 or lower, the trial should be recommended to stop considering both the efficacy and safety outcome.

Table 1: 1st Futility Analysis Simulation Results

Observed CR/CRu Rate Ratio (experimental arm / Control arm) **at 6 Months, N=200 pts**	Conditional Power: Average Likelihood of Achieving Statistically Significant Results at α = 0.05 Level on CR/CRu at 30 months (N=644 pts)
0.88	**11.99%**
0.85	**5.58%**
0.82	**0.86%**
0.80	**0.21%**
0.75	**0.01%**
0.70	**0%**

3.3.2 Second futility analysis

For the second futility analysis, possible results of the CR/CRu rate at 120 weeks for 644 patients will be simulated according to the following assumptions. The simulated results will then be analyzed to establish the second futility boundary.

1. For the first 100 patients in the control arm when their response data at 120 weeks are observed, their observed CR/CRu rate at 120 weeks is estimated approximately 60% to 66%.
2. For the next 222 patients in the control arm whose response data at 120 weeks have not been observed yet at the second futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be equal to the observed CR/CRu rate at 120 weeks from the first 100 patient.
3. For the first 100 patients in the experimental arm when their response data at 120 weeks are observed, their observed CR/CRu rate at 120 weeks is estimated in a wider range for the purpose to establish the second futility boundary.
4. For the next 222 patients in the experimental arm whose response data at 120 weeks have not been observed yet at the second futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be equal to the observed CR/CRu rate at 120 weeks from the first 100 patient.

The Table 2 below shows the likelihood of achieving a superiority result based on the observed CR/CRu rates at 120 weeks for the first 200 patients.
The futility boundary of the second futility analysis is that if the observed CR/CRu ratio (experimental arm/control arm) at 120 weeks is 0.98 or lower, the trial should be recommended to stop based on this efficacy and safety outcome.

Table 2: 2nd Futility Analysis Simulation Results

Observed CR/CRu Rate Ratio (experimental arm / Control arm) **at 120 Weeks, N=200 pts**	Conditional Power: Average Likelihood of Achieving Statistically Significant Results at α = 0.05 Level on CR/CRu at 30 months (N=644 pts)
1.08	**23%**
1.06	**14%**
1.04	**7%**
1.02	**2.2%**
1.00	**1%**
0.98	**0.45%**
0.96	**0.14%**

3.4 Descriptive variables

Descriptive statistics for the evaluation parameters will be presented in summary tables, by treatment arm.
Quantitative variables will be summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles will also be presented when considered relevant.
Qualitative variables will be described in terms of frequencies of each response category and frequencies converted into percentages of the number of patients examined (of non-missing).

3.5 Survival variables

Censored data will be 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 will be calculated (if reached) with 95% CIs.
Response rates will be expressed as percentages with their 95% Exact Clopper Pearson Confidence Interval limits.

3.6 Handling of missing or off-schedule efficacy data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed.

3.7 Software

All outputs will be produced using SAS version 9.2 and AdClin version 3.2.2.

4 ANALYSIS PLAN

4.1 Study Summary

Study Summary will be performed on the Enrolled Population (cf §3.1.1).

4.1.1 Patients description

- Number of patients by treatment arm
- Number of patients by country in Total and according to treatment arm
- Number of cycles performed (induction / maintenance) according to treatment arm
- Number of patients by Follow-up visit according to treatment arm

4.1.2 Study dates

- First / Last Date of inclusion
- Last Visit Last Patient
- Study Duration

4.2 Study patients

4.2.1 Disposition of patients

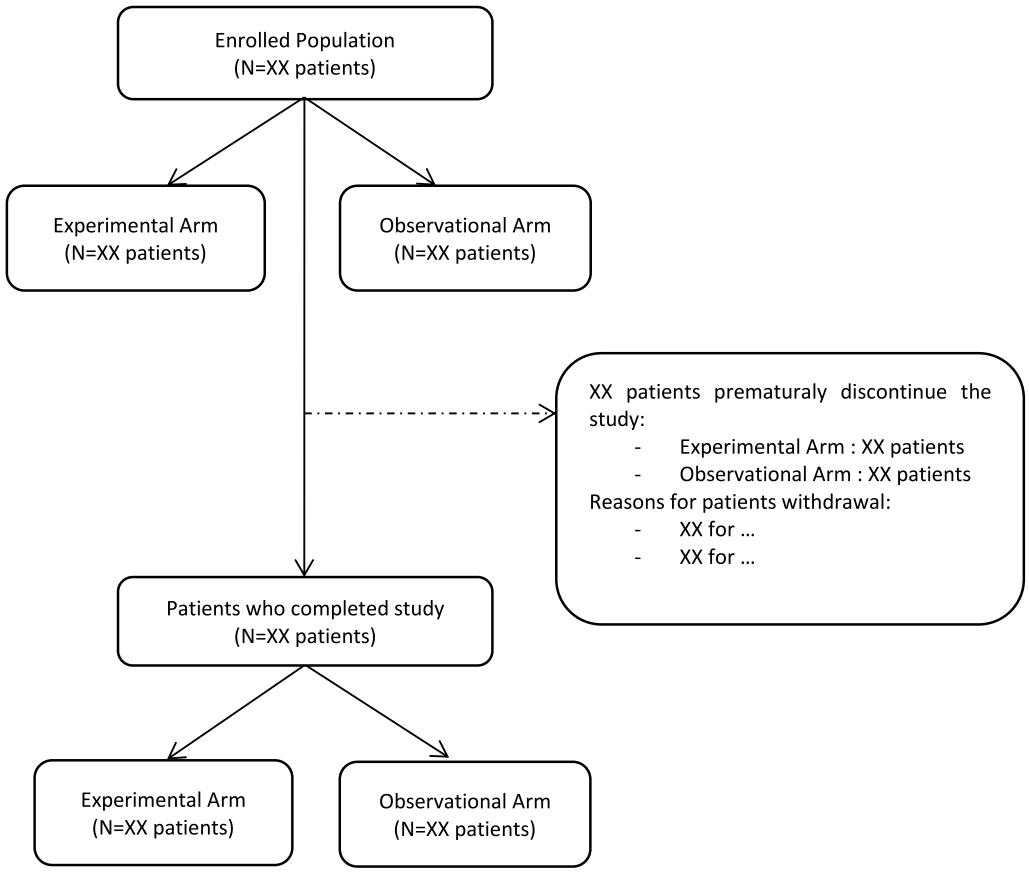
The number of patients enrolled and withdrawn will be displayed in a table.
The reasons for withdrawal from study will be summarized.

Patient disposition will be based on the all-patient population and tabulated for the following categories:

- Total number of patients enrolled;
- Number (percentage) of patients completing the study;
- Number (percentage) of patients prematurely withdrawn from study;
- Primary reason for premature withdrawal;
- Time between date of randomization and premature withdrawal
- Period of premature withdrawal

The following figure will be displayed :

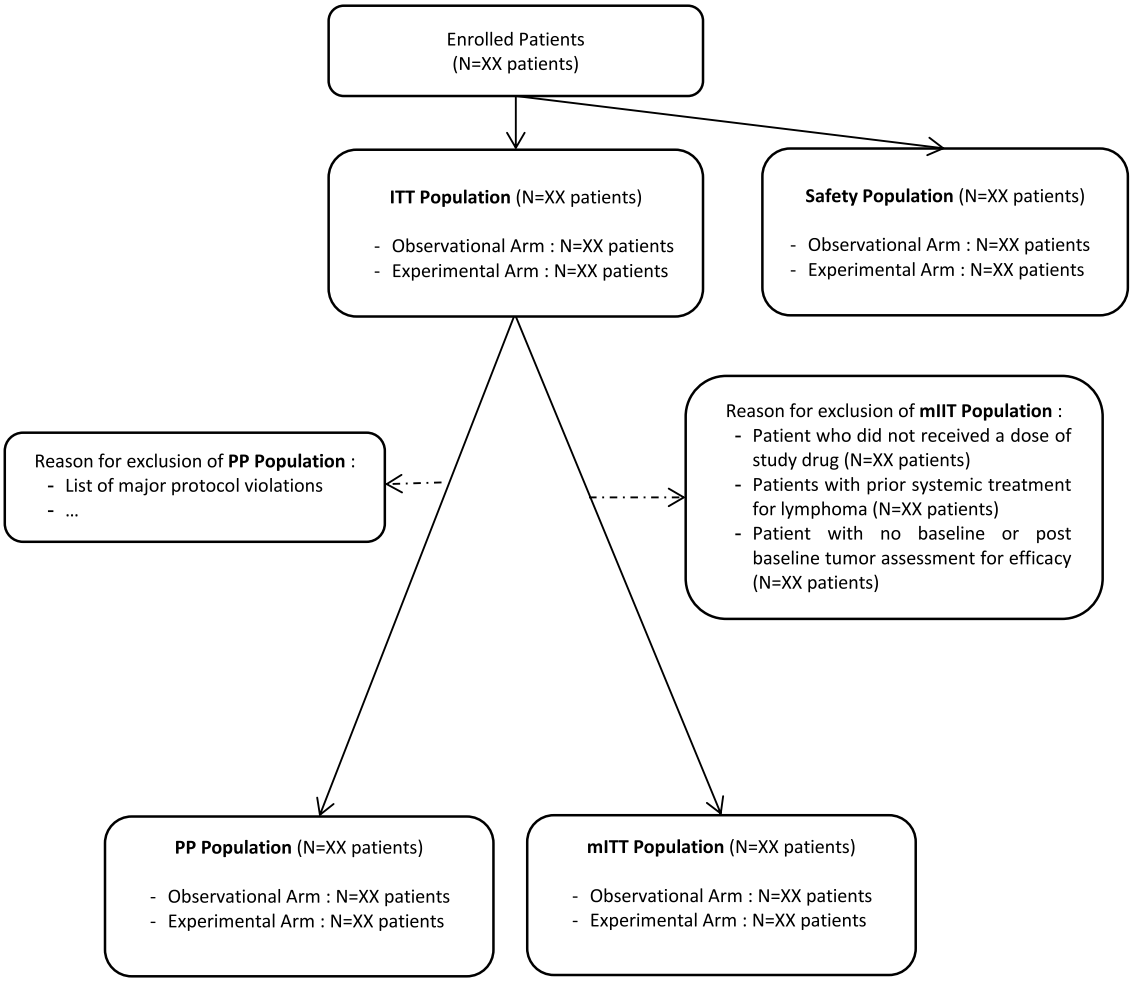
Figure 1 : Disposition of patients



4.2.2 Analysis Sets

- Number of patients in each population described in the section § 3.1 will be displayed by treatment arm and in total
- Listing of patients excluded from each population will be displayed

Figure 2: Analysis Sets



4.3 Protocol deviations

Protocol deviations will be reviewed during a blind review meeting and the list of major protocol deviations will be defined during this meeting.
Protocol deviations occurring before drug administration will be separated from those occurring after drug administration.
A data review plan which describs the criteria that need to be checked will be performed. The detailed description of the decision taken during this blind review meeting will be described in a blind review report.
Description of the protocol deviations will be performed on the ITT population.
The following description will be performed:

- At least one protocol deviation : Yes / No
- At least one protocol deviation before drug administration (at inclusion): Yes / No
- At least one protocol deviation after drug administration (during the study) : Yes / No

4.3.1.1 Protocol deviations before drug administration

Protocol deviations before drug administration are the following :

- Non respect of the inclusion/exclusion criteria
- Patients misrandomized : a patient will be considered as misrandomized if the treatment received do not correspond to treatment planned during the randomization phase.
- …

The following description will be performed :

- At least one protocol deviation before drug administration (Yes/No) : count
- For each inclusion and exclusion criteria (Yes/No): count.

Listing of patients with at least one protocol deviation before drug administration describing: patient identification, treatment arm, each deviation.

4.3.1.2 Protocol deviations after drug administration

Protocol deviations after drug administration are the following :

- …

The following description will be performed :

- At least one protocol deviation after drug administration (Yes/No) : count
- For each deviation (Yes/No): count.

Listing of patients with at leats one protocol deviation before drug administration describing: patient identification, treatment arm, each deviation.

4.3.1.3 Major protocol deviations

The list of major protocol deviations will be listed during the blind review meeting (date to be defined).
Major protocol deviation are the following:

- …

The following description will be performed :

- At least one major protocol deviations (Yes/No) : count

Listing of patients with at least one major protocol deviation: patient identification, treatment arm, each deviation.

4.4 Demographic and other baseline characteristics

The following items will be described on ITT population according to treatment arm.

- Demography,
- Prior venous thromboembolic event
- Relevant medical history
- Concomitant treatment at randomization
- Pathological diagnosis
- Clinical examination at screening :
    - Nodal involvement
    - Extra-nodal involvement
    - Bone Marrow Biopsy
    - PET Scan
    - Number of sites used for response evaluation
    - Methods of measurement
- Staging and physical examination
- Female Chilbearing
- Pregnancy tests

4.5 Clinical Examination

The following items will be described on ITT population according to treatment arm for each induction cycle:

- Clinical examination
- Performance status

4.6 Response assessment during the study

The following items will be described on ITT population according to treatment arm.

- Response assessment at 12 weeks
    - Number of sites used
    - Methods of measurement
    - SPD Reduction

for each evaluation timepoint (W24 – W36 – W52 – W76 – W100 - W120…):

- Response assessment
    - Clinical examination
    - Performance status
    - B Symptoms
    - LDH elevated
    - Bone Marrow Biopsy
    - PET San
    - Number of sites used
    - Methods of measurement
    - Response

4.7 Efficacy Analysis

4.7.1 Primary efficacy analyses

The co-primary endpoints are the complete response (CR/CRu) rate at 120 weeks and the PFS. The analyses of the co-primary efficacy endpoints will be based on the ITT population. Analysis based on the mITT population will be considered as supportive.

4.7.1.1 Complete Response Rate

The number and percent of patients with complete response (CR/CRu) at 120 weeks will be presented according to treatment arm.
The primary analysis of the complete response will be performed using a stratified Cochran-Mantel-Haenszel (CMH) test to adjust for possible confounding effects of the stratification factors:

- FLIPI score (0-1 vs 2 vs 3-5),
- Age (> 60 vs ≤ 60),
- Longest diameter of the largest node (> 6 vs ≤ 6 cm).

The experimental arm will be declared superior if the two-sided p-value from a chi-square test is ≤ 0.05 in favor of the experimental arm. If the experimental arm is declared superior than the control arm on this endpoint, the study will still continue to collect data for the PFS analysis.

An un-stratified test will be performed as a sensitive/supportive analysis.

4.7.1.2 Progression Free Survival

PFS will be compared between the two treatment arms when the required 456 progression/relapse/death events are observed.
The Kaplan-Meier estimates of PFS function will be provided.
If a patient has a missing or incomplete CT scan, all other available CT scans or MRIs of the patient will still be used for the analysis.
PFS evaluation wil be done using a stratified log rank test. The stratification factors will be those used for the randomization:

- FLIPI score (0-1 vs 2 vs 3-5),
- Age (> 60 vs ≤ 60),
- Longest diameter of the largest node (> 6 vs ≤ 6 cm).

The experimental arm will be declared superior if the two-sided p-value from a stratified log-rank test is ≤ 0.05 in favor of the experimental arm.
Conventionally, hazard ratio with two-sided 95% confidence interval (CI) will be estimated using the Cox proportional hazards model. But the treatment effect will be determined by the p-value, not by this 95% CI.

An un-stratified log-rank test will be performed as a supportive analysis and subgroup analysis for PFS will be performed as appropriate.

Censoring rules used for the primary PFS analysis:

Situation	Date of Progression or Censoring	Outcome
Death before 1st PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Progression	Date of tumor assessment which revealed the progression	Progressed
Death or progression after more than one missed visit	Date of death or date of tumor assessment which revealed the progression	Progressed
No baseline tumor assessment	Randomization	Censored
No progression, nor death	Date of last visit	Censored
Treatment discontinuation for undocumented progression	Date of last visit	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit	Censored
Treatment discontinuation for new anticancer treatment started	Date of last visit	Censored
Treatment discontinuation for lack of efficacy	Date of last visit	Censored
Lost to Follow-up	Date of last visit	Censored

In order to evaluate the robustness of the primary PFS analysis a sensitivity analysis will be performed. The censoring rules for sensitivity analysis are defined hereafter:

- PFS using only well documented and verifiable progression events

Situation	Date of Progression or Censoring	Outcome
Death or progression after more than one missed visit	Date of death or date of tumor assessment which revealed the progression	Progressed
Progression documented between scheduled visits	Date of last assessment of measured lesions	Progressed
Death before 1st PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
No baseline tumor assessment	Randomization	Censored
Death or progression after more than one missed visit	Date of last assessment of measured lesions	Censored
No progression, nor death	Date of last assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last assessment of measured lesions	Censored
Treatment discontinuation for new anticancer treatment started	Date of last assessment of measured lesions	Censored
Treatment discontinuation for lack of efficacy	Date of last assessment of measured lesions	Censored
Lost to Follow-up	Date of last visit	Censored

4.7.2 Secondary efficacy analyses

4.7.2.1 Event Free Survival (EFS)

EFS analysis will be performed on ITT population according to statistical methods defined in section §3.5.

Censoring rules used for the EFS analysis:

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Randomization	Censored
Progression documented between scheduled visits	Date of tumor assessment visit	Not Censored
Treatment discontinuation for new anti-lymphoma treatment started	Date of permanent treatment discontinuation	Not Censored
Death	Date of death	Not Censored
No progression, nor death nor Treatment discontinuation for new anti-lymphoma treatment started	Date of last visit	Censored
Lost to Follow up	Date of last information	Censored

4.7.2.2 Time to Next Anti-Lymphoma Treatment (TTNLT)

TTNLT analysis will be performed on ITT population according to statistical methods defined in section §3.5.

Censoring rules used for the TTNLT analysis:

Situation	Date of Progression or Censoring	Outcome
Death	Date of death	Not Censored
Administration of any new anti-lymphoma treatment (chemotherapy, radiotherapy, radio-immunotherapy, immunotherapy)	Date of first administration of the treatment	Not Censored
Lost to Follow up	Date of last information	Censored
No Death nor new administration of any new anti-lymphoma treatment	Date of last visit	Censored

4.7.2.3 Overall Survival (OS)

OS analysis will be performed on ITT population according to statistical methods defined in section §3.5.

Censoring rules used for the OS analysis:

Situation	Date of Progression or Censoring	Outcome
Death for any cause	Date of death	Not Censored
Lost to Follow up	Date of last information	Censored
Patient alive	Date of last visit	Censored

4.7.3

4.7.3 Progression / Relapse

- Patients presenting with progression/relapse
- Progression/relapse involvement
- Progression/relapse documentation
- Examination used to evaluate progression/relapse
- Progression/relapse - FLIPI
- Progression/relapse - Treatments
- Progression/relapse : response after additional treatments

4.8 Safety analysis

Safety analysis will be performed on the Safety population according to statistical method defined in the section §3.4. No statistical test will be performed.
All descriptive tables will be perfoemd according to treatment arm.

- Treatment intake Duration (months) in total
- Number of cycles performed during induction / maintenance phase

4.8.1 Extent of exposure to trial medication

- Dose of Lenalidomide received and Time between first and last intake
- For each phase (induction and maintenance) and by treatment arm
    - Time between cycle
    - Dose of Rituximab
    - Dose Intensity of Rituximab
- For Control Arm :
    - Induction Chemotherapy administration

4.8.2 Total Dose Taken

- For Experimental arm:
    - Rituximab
    - Lenalidomide
- For Control Arm :
    - Rituximab
    - Cyclophosphamide
    - Vincristine
    - Prednisone
    - Doxorubicin
    - Bendamustine

4.8.3 Dose reduction of Lenalidomide

4.8.4 Adverse Events

- At least one AE
- Number of AE by patient
- Characteristic of AEs
- Grades increase/decrease
- AE by SOC and PT for all AE and for AE related to:
    - Lenalidomide
    - Rituximab
    - Induction Chemotherapy
- Deaths due to AE

4.8.5 Serious Adverse Events

- Same description for AE will be pefomed for SAE
- Listing of Serious Adverse event

4.8.6 Deaths

- Number of patients who died
- Cause of death
- Disease staus at death
- Listing of patients who died

4.8.7 Clinical Laboratory / Serologies / Vital signs

Clinical laboratory measurements, serologies and vital signs will be described on Safety population in total and according to statistical method defined in section § 3.4 by treatment arm.

4.8.8 Prior Cancer History

Prior cancer history will be described on Safety population in total and according to statistical method defined in section § 3.4 by treatment arm.

- Patient with a prior cancer history
- Type of cancer
- Assessment of prior cancer history
- Prior cancer exams
- Prior cancer history

4.8.9 SPM

SPM will be described on Safety population in total and according to statistical method defined in section § 3.4 by treatment arm.

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Statistical Analysis Plan

Version 3.4, the 22th of November 2017

RV-FOL_GELARC-0683 PROTOCOL	
EudraCT Number	2011-002792-42
ClinicalTrials.gov Identifier	NCT01650701
RV-FOL_GELARC-0683C PROTOCOL	

TABLE OF CONTENT

1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for the protocol **RELEVANCE** titled "*A Phase 3 Open-Label Randomized Study To Compare The Efficacy And Safety Of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Chemotherapy Followed By Rituximab In Patients With Previously Untreated Follicular Lymphoma*." There The study encompasses are two companion studies protocols (RV-FOL-GELARC-0683 sponsored by the Lymphoma Academic Research Organisation [LYSARC] and RV-FOL-GELARC-0683C sponsored by Celgene) and one combined database. The analyses described in this document will be performed on the combined total of patients enrolled under in both study protocols.

The statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy, rationale, and statistical methods to be applied to assess the efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma (FL).

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches for all data analyses before database lock for the analyses of co-primary endpoints (complete response [CR]/CR unconfirmed [CRu] rate at 120 weeks and progression-free survival [PFS]) for all randomized patients. Safety data will be reviewed on an ongoing fashion by the Data Monitoring Committee (DMC; formerly known as the data safety monitoring committee [DSMC]) and Sponsor personnel. The SAP provides additional details concerning the statistical analyses that were originally outlined in the protocol. The analyses described in this document serve the purpose of publication as well as for the Clinical Study Report (CSR). The table shells for the CSR submission are prepared in a separate document to satisfy the regulatory submission requirements.

The SAP will be finalized and signed prior to the clinical database lock.

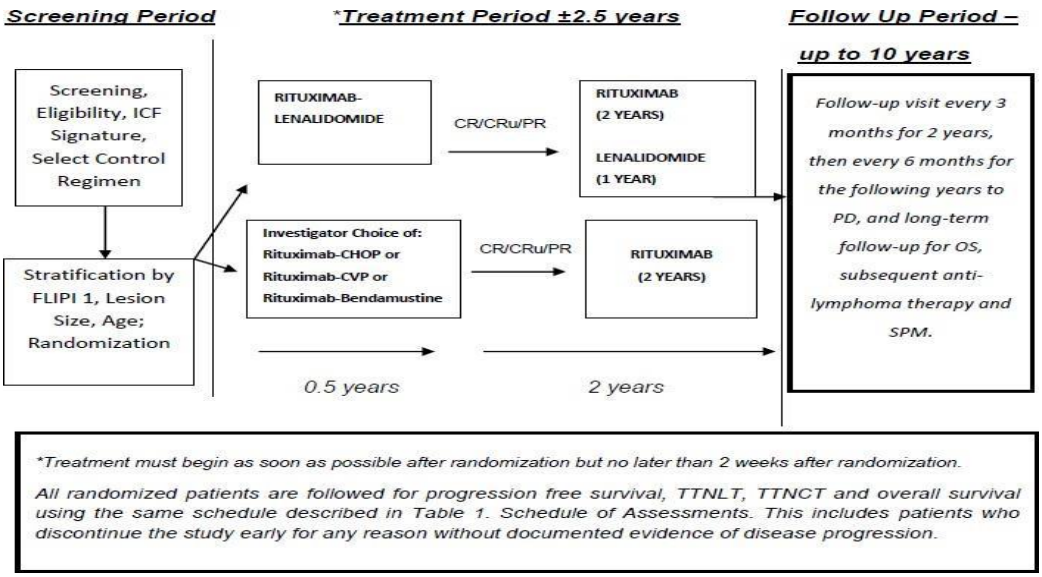
2 INVESTIGATIONAL PLAN

2.1 Overall study design

2.1.1 Study Design

This multicenter, open-label study was designed to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab in patients with previously untreated FL. The study design was divided into the Screening Period, Treatment Period, and Follow-up Period, as shown in the Figure 1.

Figure 1 : Study Design



2.1.2 Study Duration

The duration of the entire study was approximately 12 to 13 years. Patients underwent up to four weeks of screening, received approximately 2.5 years of treatment, and remained up to 10 years of in follow- up. Patients were randomized in a 1:1 ratio to receive either rituximab- plus lenalidomide or Investigator's Choice of R-CHOP, R-CVP, or R-Benda according the following stratification factors:

- FLIPI score (0 to 1 vs 2 vs 3 to 5),
- age (> 60 vs ≤ 60) and
- longest diameter of the largest node (> 6 vs ≤ 6 cm)

2.2 Study objectives

2.2.1 Primary objective

The primary objective of the study was to compare the efficacy of rituximab plus lenalidomide to rituximab plus chemotherapy followed by rituximab in patients with previously untreated FL. Efficacy determination was based upon the co-primary endpoints of complete response/complete response unconfirmed (CR/CRu) rate at 120 weeks and PFS assessed by the Independent Review Committee (IRC) using the International Working Group (IWG) criteria (Cheson, 1999).

2.2.2 Secondary objectives

The secondary objectives of the study were as follows:

- To compare the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab using other parameters of efficacy:
    - Complete response (CR) rate at 120 weeks by IWG 1999,
    - Event Free Survival (EFS) by IWG 1999,
    - Time to Next Anti-Lymphoma Treatment (TTNLT),
    - Overall Survival (OS).
- To compare the safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab.

3 EVALUATION CRITERIA

3.1 Co-primary efficacy endpoints

3.1.1 Complete Response (CR/CRu) Rate at 120 weeks

The tumor response data will be assessed by the IRC using the IWG (Cheson, 1999) criteria.

In order to be sure to have an evaluable response assessment at this timepoint, some imputation rules will be applied. The imputation rules are detailed in the Section §4.7.

3.1.2 Progression Free Survival (PFS)

The disease progression status will be assessed by IRC using the IWG (Cheson 1999) criteria. The primary analysis of PFS is to be based on IRC assessment, however, investigator assessed PFS will also be analyzed as sensitivity/exploratory analyses.

PFS is defined as the time from randomization into the study to the first observation of documented disease progression or death due to any cause. If a subject has not progressed or died, PFS will be censored at the time of last visit with adequate assessment. If a subject received other anti-cancer treatment for FL before progression, the CT/MRI assessments were to continue as scheduled until disease progression or death which will be counted as events.

3.2 Secondary efficacy endpoints

The following secondary efficacy endpoints will be analyzed using appropriate statistical methods.

3.2.1 Complete Response (CR) Rate at 120 weeks

The tumor response data will be assessed by the IRC using the IWG (Cheson, 1999) criteria.

3.2.2 Event Free Survival (EFS)

EFS will be measured from the date of randomization to the date of first documented disease progression, relapse, initiation of a new anti-lymphoma treatment or death by any cause before documented progression or relapse. Responding subjects and subjects who are lost to follow up will be censored at date of last adequate assessment with evidence of no progression.

3.2.3 Time to Next Anti-Lymphoma Treatment (TTNLT)

TTNLT will be measured from the date of randomization to the date of first documented administration of any new anti-lymphoma treatment (chemotherapy, radiotherapy, radio-immunotherapy, immunotherapy). Subjects continuing in response or who are lost to follow-up will be censored on their last visit date if no new anti-lymphoma treatment has been initiated. Subjects who died (due to any cause) before having received a new anti-lymphoma treatment will be censored on their date of death.

3.2.4 Overall Survival (OS)

OS will be measured from date of randomization to the date of death. Subjects who die, regardless of the cause of death, will be considered to have had an event. Subjects who withdraw consent for the study will be considered censored at the time of withdrawal. Subjects who complete the study and are still alive at the time of the clinical data cut-off date will be censored. All subjects who were lost to follow-up prior to the clinical data cut-off date will also be considered censored at the time of last contact.

3.3 Safety Endpoints

Safety endpoints include the following:

- Adverse Events / Serious Adverse Events
- Laboratory results
- Physical examination and Vital signs

3.4 Sample size consideration

Sample size calculation was based on providing adequate power to evaluate treatment effect on the co-primary efficacy endpoints.

The co-primary efficacy endpoints were complete response (CR/CRu) rate at 120 weeks and PFS.

It is hypothesized that the CR/CRu rate at 120 weeks is 60% in the control arm and 72% in the experimental arm. For 90% power to detect this difference with two-sided $\alpha = 0.05$, a total of 644 patients (322 in each arm) are required. The power calculation for the response rates was performed using EAST v5.4 software based on the large sample z-test with unspooled variance estimate.

It was hypothesized that the median PFS is 83 months in the control arm, and there was a 30% increase in the median PFS in the experimental arm (corresponding hazard ratio [HR] of 0.7692). For 80% power to detect this difference with two-sided $\alpha = 0.05$, a total of 456 progression/relapse/death events would be required.

Considering the sample size requirements for both co-primary endpoints, it was planned to enroll a total of approximately 1000 patients into the study.

Therefore, for an enrollment rate of 10 patients per month in the first 6 months, 25 patients per month in the next 11 months, and 30 patients per months thereafter with 6% dropout rate per year, a total of 1000 patients in a 1:1 ratio to the two treatment arms (500 in each arms) was needed, with a 40-month accrual period and up to 10 years follow-up. The analysis of PFS would occur in about 142 months when the required 456 progression/relapse/death events were expected to be observed.

The assumptions used in sample size calculations are derived from available literature, especially from the published results of the PRIMA (Salles, 2011) and STiL studies (Rummel, 2013). For the proposed sample size of N = 1000, it should be noted that any reasonable deviations from these assumptions have limited impact on the power of the test. For example, if the CR/CRu rate at 120 weeks is down to 50% in the control arm instead of 60%, the proposed sample size of 1000 patients would still have roughly 97% power to detect a 12% rate difference. If the median PFS disminishes to 70 months in the control arm instead of 83 months, a total of 456 events to detect a 30% increase in the median PFS is still required, and the only impact is that the study duration will be reduced to 113 months if 1000 patients are to be randomized.

A recent meta- analysis demonstrated that the CR rate at 30 months is well correlated with PFS. The point estimate and corresponding 95% confidence intervals (CIs) for the study-level surrogacy measures R^2_{WLS} and R^2_{Copula} were 0.88 [0.77 to 0.96] and 0.86 [0.72 to 1.00], respectively. The relationship between odds ratio (OR) of CR rate at 30 months and HR of PFS based on weighted least square method is:

$$\log(\mathrm{HR}) = -0.099 - 0.634 * \log(\mathrm{OR})$$

Therefore, it was decided to include a secondary endpoint of the CR rate at 120 weeks by IWG 1999.

The proposed sample size of 1000 patients has 90% power to detect a 10% difference in CR rate at 120 weeks with two-sided (α= 0.05), assuming a 50% CR rate at 120 weeks in the control arm and corresponding to an odds ratio (OR) of 1.5. The power calculation for the response rates is performed using EAST v5.4 software based on the large sample z-test with unpooled variance estimate.

4 STATISTICAL METHOD

4.1 Analysis Sets

4.1.1 Intent- to -treat (ITT) population

The ITT population is defined as all subjects who are randomized into the trial, regardless of whether they received study treatment or not.

The ITT population will be used for the primary efficacy analysis. Subjects will be analyzed according to the treatment arm to which they were initially assigned.

4.1.2 Modified ITT (mITT) population

The mITT population is defined as all randomized subjects who received at least one dose of study drug, have confirmed diagnosis of FL with no prior systemic treatment for lymphoma, have baseline and at least one post-baseline tumor assessment for efficacy.

The efficacy analysis will also be performed on the mITT population as supportive evidence and/or sensitivity analysis. Subjects will be analyzed according to the treatment arm to which they were initially assigned.

4.1.3 Safety population

The safety population is defined as all subjects who received at least one dose of study drug. The safety population will be used for all safety analysis. Subjects will be analyzed according to the treatment which they actually received.

4.2 Statistical Approaches for control of Alpha

The secondary efficacy endpoints are CR rate at 120 weeks, EFS, TTNLT, and OS.

In order to control an overall two-sided 0.05 study-wise Type I error rate, a fixed-sequence gatekeeping procedure will be employed to interpret the analysis results of these secondary efficacy endpoints in the order of CR rate at 120 weeks, EFS, TTNLT, and OS. The step of analyzing these four secondary endpoints is as follows:

- **Step 1**: If the result of CR rate at 120 weeks fails to reach the two-sided 0.05 significance level, no efficacy claims will be made for these secondary endpoints. If the p-value from the CR rate at 120 weeks is ≤ 0.05, the efficacy claim for CR rate at 120 weeks will be made, and further testing will be performed in the Step 2.

Step 2: If the result of EFS analysis fails to reach the two-sided 0.05 significance level, no efficacy claims will be made for the remaining three secondary endpoints. If the p-value from the EFS analysis is ≤ 0.05, the efficacy claim for EFS will be made, and further testing will be performed in the Step 3.

- **Step 3**: If the result of TTNLT analysis fails to reach the two-sided 0.05 significance level, no efficacy claims will be made for the remaining two secondary endpoints. If the p-value from the TTNLT analysis is ≤ 0.05, the efficacy claim for TTNLT will be made, and further testing will be performed in the Step 4.
- **Step 4**: If the result of OS analysis fails to reach the two-sided 0.05 significance level, no efficacy claim will be made for the OS endpoints. If the p-value from the OS analysis ≤ 0.05, the efficacy claim for the OS will be made

For the binary endpoints such as CR/CRu rate at 120 weeks or CR rate at 120 weeks, the analysis will be performed when all randomized subjects have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment.

The analysis of the co-primary endpoint PFS will be performed at 3 timepoints: (i) at the time when the co-primary endpoint CR/CRu rate at 120 weeks is reported, ie, when all randomized patients have had their response assessment at 120 weeks, or have had disease progression or died prior to the 120 week assessment (228 PFS events are expected, ~0.50 information); (ii) at the time when 342 PFS events (ie, ~0.75 information) are observed and recorded in the clinical database; and (iii) at the time when the required 456 PFS events have occurred. In order to control the overall alpha for PFS, an alpha spending function of Gamma Family with parameter -2.5 will be applied. Detailed alpha control method will be described in the Section 5.3.2, Interim analysis for efficacy.

In order to control the alpha for the other secondary endpoints EFS, TTNLT, and OS, the analysis results of these secondary endpoints will be submitted together with the PFS analysis results and interpretable only after the PFS analysis has reached a statistically significant level.

4.3 Interim analyses

4.3.1 Interim analysis for futility

For the co-primary endpoint of the CR/CRu rate at 120 weeks, two interim analyses for futility are pre-planned:

- The first interim analysis will be performed when the first 200 subjects have had their response assessments done at 6 months of treatment, or have had disease progression or died prior to this timepoint.
- The second interim analysis will be performed when the first 200 subjects have their response assessments done at 120 weeks, or have had disease progression or died prior to this timepoint.

The intention of these two interim futility analyses is to assess risk-benefit and ensure subject safety. The proposed futility boundaries are non-binding. The results of these two futility analyses will be reviewed by the independent DMC to make recommendation of go/no go. There is no plan to claim efficacy superiority based on these interim results ; therefore, no Type I error rate adjustment is needed.

Any assessments in a time window of 24 weeks ± 4 weeks are qualified as the 6 months assessments, and any assessments in a time window of 120 weeks ± 4 weeks are qualified as the 120 weeks assessments. If two or more assessments are performed in this time window, the assessment with the least favorable response will be used.

Discontinuation rules:

- If a subject discontinues the treatment prior to this time window due to disease progression, that subject is classified as a non-responder at 6 months.
- If a subject discontinues the treatment prior to this time window due to any other reasons, the CT/MRI assessments should continue as scheduled until disease progression.
- If a subject whose disease has not progressed prior to this time window and does not have any tumor assessments in this time window, that subject is also considered as a non-responder for this endpoint.

4.3.1.1 First futility analysis

For the first futility analysis, possible results of the CR/CRu rate at 120 weeks for 644 patients will be simulated according to the following assumptions. The simulated results will then be analyzed to establish the first futility boundary.

Based on the PRIMA study results (Salles, 2011), the following assumptions are made for simulations:

1. For the first 100 subjects in the control arm when their response data at 6 months are observed, their observed CR/CRu rate at 6 months is estimated as approximately 58% to 62%, and their observed ORR is approximately 88% to 92%.
2. In the control arm, among the patients who have CR/CRu observed at 6 months there will be a 0.75 probability for them to remain in CR/CRu at 120 weeks, and among the patients who have PR observed at 6 months there will be a 0.50 probability for them to convert to CR/CRu at 120 weeks.
3. For the next 222 subjects in the control arm whose response data at 6 months have not been observed yet at the first futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be (the observed CR/CRu rate at 6 months from the first 100 subjects) x 0.75 + (the observed PR rate at 6 months from the first 100 subjects) x 0.50.
4. For the first 100 subjects in the experimental arm when their response data at 6 months are observed, their observed CR/CRu rate and PR rate at 6 months is estimated in a wider range for the purpose of establishing the first futility boundary.
5. In the experimental arm, among the subjects who have CR/CRu observed at 6 months there will be a 0.90 probability for them to remain in CR/CRu at 120 weeks, and among the subjects who have PR observed at 6 months there will be a 0.60 probability for them to convert to CR/CRu at 120 weeks.
6. For the next 222 subjects in the experimental arm whose response data at 6 months have not been observed yet at the first futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be (the observed CR/CRu rate at 6 months from the first 100 subjects) x 0.90 + (the observed PR rate at 6 months from the first 100 subjects) x 0.60.

Table 1 shows the likelihood of achieving a superiority result based on the observed CR/CRu rates at 6 months for the first 200 subjects. The futility boundary of the first futility analysis is that if the observed CR/CRu ratio (experimental arm/control arm) at 6 months is 0.80 or lower, the trial should be recommended to stop considering both the efficacy and safety outcome.

Table 1: First Futility Analysis Simulation Results

Observed CR/CRu* Rate Ratio (Experimental arm / Control arm) at 6 Months, N=200	Conditional Power: Average Likelihood of Achieving Statistically Significant Results at α = 0.05 Level on CR/CRu at 30 months (N=644)
0.88	**11.99%**
0.85	**5.58%**
0.82	**0.86%**
0.80	**0.21%**
0.75	**0.01%**
0.70	**0%**

CR= Complete Response CRu=CR unconfirmed

4.3.1.2 Second futility analysis

For the second futility analysis, possible results of the CR/CRu rate at 120 weeks for 1000 subjects will be simulated according to the following assumptions. The simulated results will then be analyzed to establish the second futility boundary.

1. For the first 100 subjects in the control arm when their response data at 120 weeks are observed, their observed CR/CRu rate at 120 weeks is estimated as approximately 60% to 66%.
2. For the next 400 subjects in the control arm whose response data at 120 weeks have not been observed yet at the second futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be equal to the observed CR/CRu rate at 120 weeks from the first 100 subjects.
3. For the first 100 subjects in the experimental arm when their response data at 120 weeks are observed, their observed CR/CRu rate at 120 weeks is estimated in a wider range for the purpose to establish the second futility boundary.
4. For the next 400 subjects in the experimental arm whose response data at 120 weeks have not been observed yet at the second futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be equal to the observed CR/CRu rate at 120 weeks from the first 100 subjects.

Table 2 below shows the likelihood of achieving a superiority result based on the observed CR/CRu rates at 120 weeks for the first 200 subjects.

The futility boundary of the second futility analysis is that if the observed CR/CRu ratio (experimental arm/control arm) at 120 weeks is 0.98 or lower, the trial should be recommended to stop based on this efficacy and safety outcome.

Table 2: Second Futility Analysis Simulation Results

Observed CR/CRu* Rate Ratio (Experimental arm / Control arm) at 120 Weeks, N=200	Conditional Power: Average Likelihood of Achieving Statistically Significant Results at $\alpha = 0.05$ Level on CR/CRu at 30 months (N=1000)
1.08	**36.6%**
1.06	**23.8%**
1.04	**13.8%**
1.02	**3.6%**
1.00	**1.4%**
0.98	**0.5%**
0.96	**0.1%**

**CR= Complete Response CRu=CR unconfirmed*

4.3.2 Interim analysis for efficacy

The co-primary endpoint PFS will be analyzed at three timepoints. The first interim analysis will be performed at the time when the co-primary endpoint CR/CRu rate at 120 weeks is reported, ie, when all randomized subjects have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment. The second interim analysis will be performed based on 0.75 information level, ie, when 342 PFS events have been observed and recorded in the clinical database. The final analysis will be performed when the required 456 PFS events have occurred. The timing of the interim analysis and final analysis are based on the IRC-assessed number of PFS events.

In order to control the overall alpha for PFS, an alpha spending function of Gamma Family with parameter -2.5 will be applied. It is estimated that around 228 PFS events (ie, 0.50 information) would occur at the first interim PFS analysis, and 342 PFS events (ie, 0.75 information) are required at the second interim PFS analysis. The final PFS analysis will be performed based on a total of 456 PFS events. A statistically significant treatment effect on PFS will be reached if the two-sided p-value ≤ 0.011 at the first interim PFS analysis, or ≤ 0.019 at the second interim PFS analysis, or ≤ 0.039 at the final PFS analysis.

If the actual number of PFS events greatly deviates from what is expected at the time of interim or final analyses, the p-value interpretation will be adjusted accordingly based on the actual information fraction.

4.4 Final analysis

The final analysis will be performed:

- for the co-primary endpoint CR/CRu rate at 120 weeks: when all randomized subjects have had their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment,
- for the co-primary endpoint PFS: when the required 456 progression/relapse/death events have occurred among all randomized subjects.

The secondary endpoint CR rate at 120 weeks will be analyzed when all randomized subjects have had their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment.

4.5 Descriptive variables

Descriptive statistics for the evaluation parameters will be presented in summary tables, by treatment arm.

Quantitative variables will be summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles will also be presented when considered relevant.

Qualitative variables will be described in terms of frequencies of each response category and frequencies converted into percentages of the number of subjects examined (of non-missing).

4.6 Efficacy variables

Time-to-event variables will be 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% confidence intervals (CIs). The median time to event will be calculated (if reached) with 95% CIs.

Response rates will be expressed as percentages with their 95% Exact Clopper Pearson CI limits.

4.7 Handling of missing or off-schedule efficacy data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed in listings.

For analysis of response rate (CR/CRu or ORR) at 120 weeks, imputation rules will be used and are as follows.

Based on the CT/MRI schedule, any assessments in a time window of 120 weeks ± 10 weeks from Cycle 1 day 1 or from randomization (if no treatment) will be qualified as the 120-week(s) assessment(s). This will avoid excluding subjects unnecessarily. If two or more assessments are performed in this time window, the assessment with the least favorable response will be used:

CR/CR status:

1st assessment	2nd assessment	Imputed CR/CRu Status at 120 weeks Assessment
CR/CRu	PR	CR/CRu = “No”
CR/CRu	SD	CR/CRu = “No”
CR/CRu	PD	CR/CRu = “No”
CR/CRu	Not evaluated	CR/CRu = “Yes”
CR/CRu	Death	CR/CRu = “Yes”

In case of the required response assessment at 120 weeks is not performed in the time window, the following imputations rules will therefore be applied for CR/CRu status at 120 weeks and ORR status at 120 weeks:

CR/CRu status:

If the last available response is prior to 120 weeks - 10 weeks assessment	If the first available response is after 120 weeks + 10 weeks assessment (follow-up assessment not included)	Imputed Response at 120 weeks Assessment	Imputed CR/CRu Status at 120 weeks Assessment
CR/CRu	CR/CRu	CR/CRu	CR/CRu = "Yes"
CR/CRu	PR/SD/PD	PR/SD/PD	CR/CRu = "No"
CR/CRu	Not evaluated	Not evaluated	CR/CRu = "No"
PR/SD	CR/CRu	CR/CRu	CR/CRu = "Yes"
PD	CR/CRu	PD	CR/CRu = "No"
PD	SD/PR	PD	CR/CRu = "No"
SD	PR	PR	CR/CRu = "No"
PR	SD	SD	CR/CRu = "No"
SD/PR	Not evaluated	Not evaluated	CR/CRu = "No"
Death	N/A	Death	CR/CRu = "No"

ORR status:

If the last available response is prior to 120 weeks - 10 weeks assessment	If the first available response is after 120 weeks + 10 weeks assessment	Imputed ORR Status at 120 weeks Assessment
CR/CRu/PR	CR/CRu/PR	ORR = "Yes"
CR/CRu/PR	SD/PD	ORR = "No"
SD	CR/CRu/PR	ORR = "Yes"
PD	CR/CRu/PR	ORR = "No"
CR/CRu/PR/SD	Not evaluated	ORR = "No"
Death	N/A	ORR = "No"

For analysis of the secondary efficacy endpoint, response rate (CR) at 120 weeks, imputation rules will be used and are the following.

Based on the CT/MRI schedule, any assessments in a time window of 120 weeks ± 10 weeks from cycle 1 day 1 or from randomization (if no treatment) will be qualified as the 120-week(s) assessment(s). If two or more assessments are performed in this time window, the assessment with the least favorable response will be used.

In case of the required response assessment at 120 weeks is not performed in the time window, the following imputations rules will therefore be applied:

If the last available response is prior to 120 weeks - 10 weeks assessment	If the first available response is after 120 weeks + 10 weeks assessment	Imputed CR Status at 120 Weeks Assessment
CR	CR	CR = "Yes"
CR	CRu/PR/SD/PD	CR = "No"
CRu/PR/SD	CR	CR = "Yes"
PD	CR	CR = "No"
CR/CRu/PR/SD	Not evaluated	CR = "No"
Death	N/A	CR = "No"

For analysis of adverse events and concomitant medications, imputation rules will be used and are the following.

Impute Missing Adverse Event / Prior or Concomitant Medications Start Dates

If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing month with non-missing year

- If the year is **same** as the year of first day on study medication, then the day and month of the start date of study medication will be assigned to the missing fields
- If the year is **prior to** the year of first day on study medication, then 31 December will be assigned to the missing fields.
- If the year is **after** the year of first day on study medication, then 01 January will be assigned to the missing fields.

Missing day only

- If the month and year are **same** as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.
- If the month and year are **before** the year and month of first day on study medication, then the last day of the month will be assigned to the missing day.
- If the month and year are **after** the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.

Missing year

- Not imputed. Included as a treatment-emergent adverse event (TEAE).

Impute Missing Adverse Event / Prior or Concomitant Medications Stop Dates

If the imputed stop date is before the start date then the imputed stop date will be equal to the start date.

Missing month with non-missing year

- If the year of the incomplete stop date is the **same** as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dose date of study medication, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is **after** the year of the last dose date of study medication, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dose date of study medication, then the day of the last dose date will be assigned to the missing day.
-
- If the month and year of the incomplete stop date are **before** the month and year of the last dose date of the study medication, then the last day of the month will be assigned to the missing

day.

- If the month and year of the incomplete stop date are **after** the month and year of the last dose date of study medication, then the first day of the month will be assigned to the missing day.

Missing year

- Not imputed.

4.8 Software

All outputs will be produced using SAS version 9.2 or higher and AdClin version 3.2.2 or higher.

5 ANALYSIS PLAN

5.1 Study Summary

Study Summary will be performed on the ITT Population (cf §4.1.1).

5.1.1 Patients description

- Number of screened subjects
- Number of subjects by treatment arm
- Number of subjects by country in Total and according to treatment arm
- Number of cycles received by treatment period according to treatment arm
- Number of subjects by Follow-up visit according to treatment arm

Treatment periods will be defined as the following 3 periods:

- Treatment period 1 is defined as from the date of the first dose of study drug to the first dose of Cycle 9 (R-CVP and R-CHOP) and Cycle 7 (R-Benda) of rituximab for control arm ; and Cycle 8 of lenalidomide for experimental arm, which is 28 weeks in duration. In treatment period 1, control arm subjects received chemotherapy and rituximab while experimental arm subjects received lenalidomide plus ritxuximab.

- Treatment period 2 is defined as from the Cycle 9 (of rituximab only) through the completion of Cycle 14 for the control arm (R-CVP and R-CHOP) ; from the Cycle 7 (of rituximab only) through the completion of Cycle 12 for the R-Benda arm (control arm); and from Cycle 8 (of lenalidomide dose) through the completion of Cycle 18 for the experimental arm. Treatment period 2 is 48 weeks in duration. In treatment period 2, control arm subjects received rituximab monotherapy while experimental arm subjects received lenalidomide and rituximab.

- Treatment period 3 is defined as from the Cycle 15 (of rituximab only) through the completion of Cycle 20 for the control arm (R-CVP and R-CHOP); from the Cycle 13 (of rituximab only) through the completion of Cycle 18 for the R-Benda arm (control arm); and from Cycle 19 (of lenalidomide dose) through the completion of Cycle 24 (4 weeks after the last dose of rituximab) for the experimental arm. Treatment period 3 is 44 weeks in duration. In treatment period 3, both control and experimental arm subjects received rituximab monotherapy.

5.1.2 Study dates

- First / Last Date of randomization
- Last Visit Last Patient
- Study Duration

5.2 Study patients

5.2.1 Disposition of patients

Subject disposition will be based on the ITT population (cf §4.1.1) and tabulated for subjects who prematurely discontinued from treatment and subjects who prematurely discontinued from the study.

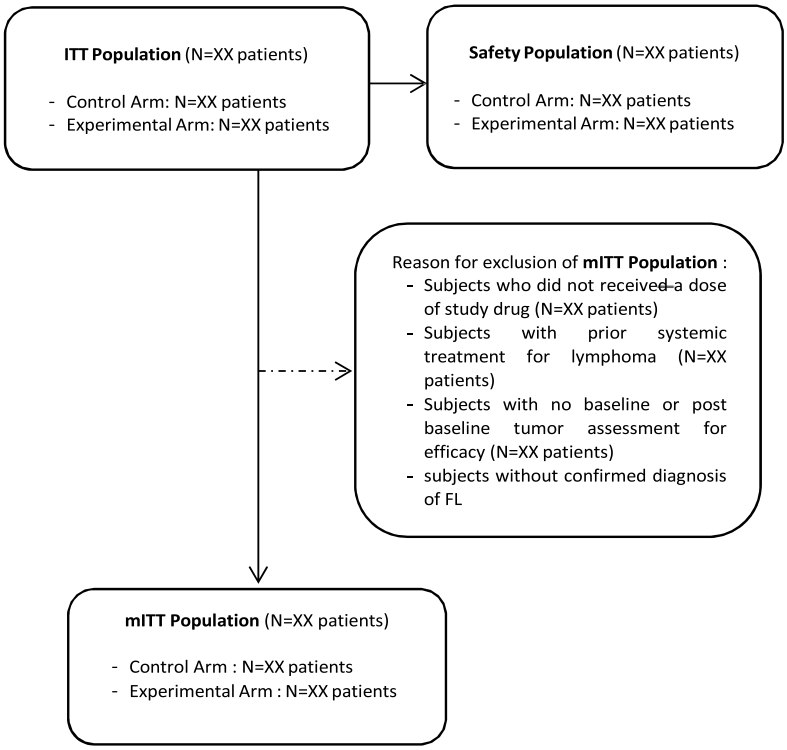
In addition, the following listings will be displayed:

- Listing of subjects who prematurely discontinued treatment due to major protocol violation(s)
- Listing of subjects who prematurely discontinued treatment due to other reason
- Listing of subjects who prematurely discontinued treatment due to death

5.2.2 Analysis Sets

- Number of subjects in each population described in the Section §4.1 will be displayed by treatment arm and in total
- Listing of subjects excluded from each population will be displayed

Figure 2: Analysis Sets



5.3 Protocol deviations and protocol violations

Protocol deviations and protocol violations will be reviewed during blinded review meetings and the list of protocol deviations and violations will be defined during these meetings which occur before each planned analysis where the protocol deviations/violations are to be reported.

Protocol deviations/violations occurring before drug administration will be separated from those occurring after drug administration.

A data review plan which describes the criteria that need to be checked will be performed. The detailed description of the decision taken during this blinded review meeting will be described in a blinded review report.

Description of the protocol deviations/violations will be performed on the ITT population (cf §4.1.1).

5.4 Demographic and other baseline characteristics

The following items will be described on ITT population (cf §4.1.1) according to treatment arm.

- Demography,
- Prior venous thromboembolic event
- Medical history
- Concomitant treatment
- Pathological diagnosis
- Clinical examination at screening :
    - Nodal involvement
    - Extra-nodal involvement
    - Bone Marrow Biopsy
    - PET Scan
    - Number of sites used for response evaluation
    - Methods of measurement
- Staging and physical examination
    - Performance Status (ECOG scale)
    - Ann Arbor stage (I, II, III, IV and I-II vs III-IV)
    - Number of extral-nodal sites (≤1, >1)
    - Number of peripheral Lymph nodes (≤4, >4)
    - Nodal Mass (>6 cm, ≤6 cm)
    - Nodal or extra-nodal Mass (>7 cm, ≤7 cm)
    - FLIPI (0,1,2,3,4,5 and 0-1 vs 2 vs 3-5)
    - FLIPI2 (0,1,2,3,4,5 and 0-1 vs 2 vs 3-5)
- Females of Chilbearing Potential
- Pregnancy tests

Baseline is defined as the latest value collected during screening or on the date of the first dose of study treatment. For subjects who were not treated, the baseline value will be defined as the latest value collected on Day 1 of the Cycle 1 visit if available; otherwise, the latest value on or prior to the randomization date will be used.

5.5 Clinical Examination

The following items will be described on ITT population (cf §4.1.1) according to treatment arm for each cycle of treatment period 1:

- Clinical examination
- Performance status

5.6 Response assessment during the study

The following items will be described on ITT population (cf §4.1.1) according to treatment arm.

- Response assessment at 12 weeks according to investigator assessment
    - Number of sites used
    - Methods of measurement
    - Sum of the products of the diameters (SPD) Reduction

for each evaluation timepoint (W24 – W36 – W52 – W76 – W100 - W120):

- Response assessment
    - Clinical examination
    - Performance status
    - B Symptoms
    - Lactic dehydrogenase (LDH) elevated
    - Bone Marrow Biopsy
    - PET Scan
    - Number of sites used

- Methods of measurement
- Response

5.7 Efficacy Analysis

5.7.1 Primary efficacy analyses

The co-primary endpoints are the CR/CRu rate at 120 weeks and the PFS as assessed by IRC. The analyses of the co-primary efficacy endpoints will be based on the ITT population (cf §4.1.1). Analysis based on investigator assessments and the mITT population (cf §4.1.2) will be considered as supportive.

5.7.1.1 Complete Response Rate

The number and percent of subjects with CR/CRu at 120 weeks will be presented according to treatment arm.

The primary analysis of the complete response will be performed using a stratified Cochran-Mantel- Haenszel (CMH) test to adjust for possible confounding effects of the stratification factors per CRF:

- FLIPI score (0-1 vs 2 vs 3-5),
- Age (> 60 vs ≤ 60),
- Longest diameter of the largest node (> 6 vs ≤ 6 cm).

The experimental arm will be declared superior if the two-sided p-value from a chi-square test is ≤ 0.05 in favor of the experimental arm.

5.7.1.2 Progression Free Survival

PFS will be compared between the two treatment arms at three timepoints: (i) at the time when the co-primary endpoint CR/CRu rate at 120 weeks is reported, ie, when all randomized patients have their response assessment at 120 weeks, or have had disease progression or died prior to the 120 week assessment (ie, ~0.50 information), (ii) at the time when 342 PFS events (or ~0.75 information) are observed and recorded in the clinical database, and (iii) at the time when the required 456 progression/relapse/death events have occurred among all randomized patients.

The Kaplan-Meier estimates of PFS function will be provided.

If a patient has a missing or incomplete CT scan, all other available CT scans or MRIs of the patient will still be used for the analysis.

PFS evaluation will be done using a stratified log rank test. The stratification factors per CRF will be those used for the randomization:

- FLIPI score (0-1 vs 2 vs 3-5),
- Age (> 60 vs ≤ 60),
- Longest diameter of the largest node (> 6 vs ≤ 6 cm).

The experimental arm will be declared superior if the two-sided p-value from a stratified log-rank test is ≤ 0.011 at the first interim PFS analysis, or ≤ 0.019 at the second interim PFS analysis, or ≤ 0.039 at the final PFS analysis in favor of the experimental arm.

Conventionally, a HR with two-sided 95% CI will be estimated using the Cox proportional hazards model. But the treatment effect will be determined by the log-rank test p-value, not by this 95% CI.

The following sensitive analysis will be performed:

- PFS assessed by the investigator (concordance between IRC assessment and investigator assessment will also be evaluated)

In order to evaluate the robustness of the PFS analysis, sensitivity analysis will be performed based on censoring rules per European Medicines Agency (EMA) guideline. For CSR submission, the PFS analysis based on FDA censoring rules will serve as the primary analysis.

At the primary analysis, the assumption of proportional hazard (PH) will be tested by a time-dependent Cox model including an interaction term of treatment and time. A significant interaction of treatment and time indicates the violation of PH assumption. A figure of smoothed hazard function over time provides visual display of hazard trend over the course of the study. When there is modest deviation from the assumption, inferences in PH models are generally fairly robust. If there is a serious non-
-proportional hazard (non-PH),, restricted mean survival time will be generated and compared between the two arms. Piece-wise Cox regression will be used to provide hazard estimates at 6 -month-intervals. Generalized Wilcoxon test will also be used in addition to log-rank test. Exploratory analyses will be conducted to better understand the possible cause of non-PH.

Censoring rules used for PFS analysis per FDA and EMA Guidelines:

Situation	Main analysis (FDA)		Sensitivity analysis (EMA)	
	Date of Event or Censoring	Outcome	Date of Event or Censoring	Outcome
Progression or death without two or more prior consecutive missed assessments	Date of first assessment which revealed the progression* Or date of death	Not censored	Date of first assessment which revealed the progression* Or date of death	Not censored
Progression after treatment discontinuation (without receiving new-anti-lymphoma therapy)	Date of first assessment which revealed the progression*	Not censored	Date of first assessment which revealed the progression*	Not censored
Progression or death with two or more prior consecutive missed assessments (followed by death or not)	Date of last adequate assessment with evidence of no progression prior to missing assessments*	Censored	Date of first assessment which revealed the progression or date of death regardless of missing assessments	Not censored
Progression after start of new anti-lymphoma therapy (followed by death or not)	Date of last adequate assessment with evidence of no progression prior to new therapy	Censored	Date of first assessment which revealed the progression	Not censored
Death after start of a new anti-lymphoma therapy	Date of last adequate assessment with evidence of no progression prior to new therapy	Censored	Date of death	Not censored
No baseline tumor assessment	Randomization	Censored	Randomization	Censored
No progression, nor death	Date of last assessment with evidence of no progression*	Censored	Date of last assessment with evidence of no progression*	Censored
Lost to Follow-up without progression	Date of last assessment with evidence of no progression*	Censored	Date of last assessment with evidence of no progression*	Censored

*:according to IRC

Note for FDA rules: if progression/death occurs the same day as start of a new antilymphoma therapy, event is considered for PFS analysis

5.7.2 Secondary efficacy analyses

5.7.2.1 Complete Response Rate (CR)

The analysis of the complete response (CR) rate at 120 weeks will be performed on ITT population (cf §4.1.1).

The number and percent of subjects with complete response (CR) at 120 weeks will be presented according to treatment arm.

The primary analysis of the complete response will be performed using a stratified CMH test to adjust for possible confounding effects of the stratification factors:

- FLIPI score (0-1 vs 2 vs 3-5),
- Age (> 60 vs ≤ 60),
- Longest diameter of the largest node (> 6 vs ≤ 6 cm).

5.7.2.2 Event Free Survival (EFS)

Event-free survival analysis will be performed on ITT population (cf §4.1.1) according to statistical methods defined in section §4.6. Relapse/progression assessed by investigator using the IWG (Cheson, 1999) criteria will be taken into account.

Censoring rules used for the EFS analysis per FDA guidance:

Situation	Date of Event or Censoring	Outcome
Death without progression	Date of death	Not Censored
Progression without two or more prior consecutive missed assessments	Date of first assessment which revealed the progression*	Not Censored
Progression after treatment discontinuation (without receiving new anti-lymphoma therapy)	Date of first assessment which revealed the progression*	Not censored
Progression with two or more prior consecutive missed assessments (followed by death or not)	Date of last adequate assessment with evidence of no progression prior to missing assessments*	Censored
Start of a new anti-lymphoma therapy	Date of start of new therapy	Not Censored
No baseline tumor assessment	Randomization	Censored
No progression, nor death, nor new anti-lymphoma treatment started	Date of last adequate assessment with evidence of no progression*	Censored
Lost to Follow-up without progression or start of new anti-lymphoma treatment	Date of last adequate assessment with evidence of no progression*	Censored

*: according to investigator assessment

5.7.2.3 Time to Next Anti-Lymphoma Treatment (TTNLT)

TTNLT analysis will be performed on ITT population (cf §4.1.1) according to statistical methods defined in section §4.6.

Censoring rules used for the TTNLT analysis:

Situation	Date of Event or Censoring	Outcome
Death without start of new anti-lymphoma treatment	Date of death	Censored
Start of new anti-lymphoma treatment	Date of start of therapy	Not Censored
Lost to Follow up without start of new anti-lymphoma treatment	Date of last vist	Censored
No Death nor new administration of any new anti-lymphoma treatment	Date of last visit	Censored

5.7.2.4 Overall Survival (OS)

OS analysis will be performed on ITT population (cf §4.1.1) according to statistical methods defined in section §4.6.

Censoring rules used for the OS analysis:

Situation	Date of Event or Censoring	Outcome
Death for any cause	Date of death	Not Censored
Lost to Follow up	Date of last visit or contact	Censored
Patients alive	Date of last contact	Censored

5.7.2.5 Subgroup Analysis

Appropriate subgroup analyses will also be performed for the primary endpoint. These analyses may include the following subgroups:

- Age (≤60 vs. >60)
- ECOG (0 vs 1 or 2)
- Baseline FLIPI (0-1, 2, 3-5)
- Baseline nodal mass (>6 cm, ≤6 cm)
- Sex (Male, Female)
- Region (US, Non-US)
- Ann Arbor Stage (1-2, 3-4)

Subgroup analyses may not be performed when there is insufficient number of subjects in certain subgroups.

5.7.3 Exploratory analyses

5.7.3.1 Histological transformation rate at first progression

Histological transformation rate at first progression will be summarized by treatment for subjects who have experienced first disease progression.

5.7.3.2 CR/CRu Rate at 24 weeks (Cheson, 1999).

The number and percent of subjects with complete response (CR) or complete response unconfirmed (CRu) at 24 weeks will be presented according to treatment arm.
The same analysis as performed for the primary efficacy analysis (§5.7.1.1) will be performed on CR/CRu according to IWG 1999 criteria by IRC and by investigator's assessment.

5.7.3.3 Overall Response Rate at 24 weeks (Cheson, 1999).

ORR at 24 weeks will be considered as CR or CRu or PR patients. The same analysis as performed for the primary efficacy analysis (§5.7.1.1) will be performed on ORR according to IWG 1999 criteria by IRC and by investigator's assessment.

5.7.4 Progression / Relapse

The following items will be described on ITT population (cf §4.1.1) according to treatment arm.

- Patients presenting with progression/relapse according to investigator assessment
- Progression/relapse involvement
- Progression/relapse documentation
- Examination used to evaluate progression/relapse
- Progression/relapse - FLIPI
- Progression/relapse - Treatments
- Progression/relapse - Response after additional treatments for the progression
- Progression/relapse – Subsequent Treatment after progression
- Progression/relapse – Response after additional subsequent treatment after progression

5.8 Safety analysis

Safety analysis will be performed on the Safety population (cf §4.1.3) according to the statistical methods defined in the section §4.5. No statistical tests will be performed.

All descriptive tables will be performed according to treatment arm, with separate output for three different treatment periods, and overall study.

5.8.1 Number of cycles received

- Cycles received during each treatment period
- Treatment duration (months) for different treatment period and overall.

Treatment duration of lenalidomide, CVP, CHOP, Benda and rituximab for treatment period 1 is defined as follows:

Treatment Arm	Treatment Duration Calculation	Condition
Experimental Arm	Earliest date of (Date of death, C8D1 -1 day – C1D1 + 1	If the subject completed rituximab and all 4 weeks lenalidomide in Cycle 7.
	Earliest date of (Date of death, Date of last cycle in treatment period 1 + 27 days) – C1D1 + 1	If the subject prematurely discontinued study treatment during or prior to Cycle 7.
R-CHOP/R-CVP	Earliest date of (Date of death, Visit 1/C9D1 - 1 day) – C1D1 + 1	If the subject completed 6 cycles R-CHOP plus Cycle 7 and Cycle 8 rituximab in R-CHOP arm; If the subject completed 8 cycles R-CVP in R-CVP arm.
	Earliest date of (Date of death, Date of last cycle (between C1 and C7) in treatment period 1 + 20 days) – C1D1 + 1	If patient prematurely discontinued study treatment prior to or during Cycle 7.
	Earliest date of (Date of death, C8D1 + 48 days) – C1D1 + 1	If patient prematurely discontinued study treatment during cycle 8

R-Benda	Earliest date of (Date of death, Visit 1/C9D1 - 1 day) – C1D1 + 1	If the subject completed 6 cycles R-Benda.
	Earliest date of (Date of death, Date of last cycle (between C1 and C5) in treatment period 1 + 27 days) – C1D1 + 1	If the subject prematurely discontinued study treatment prior to or during Cycle 5.
	Earliest date of (Date of death, C6D1 + 55 days) – C1D1 + 1	If patient prematurely discontinued study treatment during cycle 6

Treatment Duration of lenalidomide and rituximab for the treatment periods 2 is defined only for subjects who entered the treatment period 2 as follows:

Treatment Arm	Treatment Duration Calculation	Condition
Experimental Arm	Earliest date of (Date of death, C19D1 -1day) – C8D1 + 1	If the subject completed R^2 at Cycle 18 .
	Earliest date of (Date of death, Date of last cycle (between C8 and C17) in treatment period 2 + 27 days)– C8D1 + 1	If the subject prematurely discontinued study treatment prior to or during cycle 17.
	Earliest date of (Date of death, C18D1 + 55 days) – C8D1 + 1	If the subject prematurely discontinued study treatment during Cycle 18
Control Arm	Earliest date of (Date of death, Visit 7/C15D1 -1 day) – Visit 1/C9D1 + 1	If subject completed all rituximab treatment through Visit 6/Cycle 14.
	Earliest date of (Date of death, Date of last	If subject prematurely
	cycle of rituximab + 55 days in treatment period 2) – Visit 1/C9D1 + 1	discontinued rituximab prior to or during Visit 6/Cycle 14.

Treatment duration of rituximab for the treatment periods 3 is defined only for subjects who entered the treatment period 3 as follows:

Treatment Arm	Treatment Duration Calculation	Condition
Experimental Arm	Earliest date of (Date of death, C24D1 + 27 days) – C19D1 + 1	If the subject completed R^2 at Cycle 24 or prematurely discontinued treatment during cycle 24.
	Earliest date of (Date of death, Date of last cycle (between C19 and C23) in treatment period 3 + 55 days) – C19D1 + 1	If the subject prematurely discontinued study treatment prior to or during cycle 23.
Control Arm	Earliest date of (Date of death, Visit 12/C20D1 + 27 days) – Visit 7/C15D1 + 1	If subject completed all rituximab treatment through Visit 12/Cycle 20 or prematurely discontinued study treatment during Visit12/Cycle 20.
	Earliest date of (Date of death, Date of last cycle of rituximab (between Visit 7/C15 and Visit 11/C19) in treatment period 3 + 55 days in treatment period 2) – Visit 7/ C15D1 + 1	If subject prematurely discontinued rituximab prior to or during Visit 11/Cycle 19.

Treatment duration of rituximab for the Entire Study is defined as follows:

Treatment Arm	Treatment Duration Calculation	Condition
Experimental Arm	Earliest date of (Date of death, C24D1 + 27 days) – C1D1 + 1	If the subject entered treatment period 3 and completed all subsequent rituximab through cycle 24 or prematurely discontinued study treatment during cycle 24.
	Earliest date of (Date of death, Date of last cycle (between C1 and C17) + 27 days) – C1D1 + 1	If the subject prematurely discontinued study treatment prior to or during cycle 17 .
	Earliest date of (Date of death, Date of last cycle + 55 days) – C1D1 + 1	If the subject prematurely discontinued study treatment between cycle 18 and cycle 23.
Control Arm	Earliest date of (Date of death, Visit 12/C20D1 + 27 days) – C1D1 + 1	If the subject entered treatment period 2 and completed all subsequent rituximab through V12/C20 or prematurely discontinued study treatment during V12/C20.
	Earliest date of (Date of death, Date of last cycle of Rituximab + 55 days in treatment period 2/3) – C1D1 + 1	If the subject entered treatment period 2 but prematurely discontinued rituximab prior to V12/C20.
	Same as treatment duration in treatment period 1	If the subject did not enter the treatment period 2.

5.8.2 Time between cycles

- Time between cycles by treatment arm.

5.8.3 Extent of exposure to trial medication

5.8.3.1 Experimental Arm

5.8.3.1.1 Lenalidomide administration

- Duration between first and last intake in total
- Duration by cycle will be calculated between first intake from cycle 'N' to first intake from Cycle 'N+1' taking into account the week off period
- Dose of lenalidomide received
    - Total dose by cycle
    - Average dose by cycle :
        - Total dose administered during the cycle divided by the treatment duration of the cycle
- Average relative dose intensity (ARDI) of lenalidomide in total and by cycle :
    - The ARDI of lenalidomide will be calculated by expressing the average delivered dose of lenalidomide per unit time (day) as a percentage of the target dose.

5.8.3.1.2 Rituximab administration

- For each treatment period
    - Total dose administration in total and by cycle
    - Relative Total Dose Intensity (RTDI) in total and by cycle
        - The RTDI of rituximab will be calculated by expressing the total delivered dose of rituximab as a percentage of the target dose.

5.8.3.2 Control Arm

5.8.3.2.1 Treatment period 1

- Administration of rituximab will be described for control arm patients on the following items
    - Total dose administration in total and by cycle
    - Relative total dose intensity (RTDI) in total and by cycle
        - The RTDI of each agent will be calculated by expressing the total delivered dose of agent as a percentage of the target dose.

- Administration of each component of treatment period 1 (CHOP, Bendamustin, and CVP) will be described for control arm patients on the following items :
    - Total dose administration by cycle
    - RTDI by cycle
        - The RTDI of each agent will be calculated by expressing the total delivered dose of agent as a percentage of the target dose.

5.8.3.2.2 Treatment period 2 and 3

- Administration of rituximab will be described for control arm subjects on the following items:
    - Total dose administration by cycle
    - RTDI by cycle
        - The RTDI of each agent was calculated by expressing the total delivered dose of agent as a percentage of the target dose.

5.8.4 Total Dose Taken

5.8.4.1 Experimental Arm

- Total administration of rituximab and lenalidome during the study will be described for each treatment period on the following items:
    - Total dose administration by treatment period

5.8.4.2 Control Arm

- Total administration of each component of treatment (CHOP, Bendamustin, and CVP) during the study will be described for control arm subjects on the following items :
    - Total dose administration
- Total administration of rituximab during the study will be described at each treatment period for control arm subjects on the following items:
    - Total dose administration by treatment period

5.8.5 Dose reduction of Lenalidomide

- Patients with at least one dose reduction of study treatment by cycle

5.8.6 Adverse Events

- At least one AE
- Number of AE by subject
- At least one AE leading to dose reduction
- At least one AE leading to dose interruption
- At least one AE leading to treatment discontinuation
- At least one AE related to study drugs
- At least one NCI CTCAE Grade 5 AE
- At least one NCI CTCAE Grade 5 AE related to study drugs
- Subjects with at least one AE by study period
- Characteristics of AEs
- Grades increase/decrease
- AE by system organ class (SOC) and preferred term (PT) for all AEs and for:
    - AE related to lenalidomide
    - AE related to rituximab
    - AE related to chemotherapy during treatment period 1
    - AE that lead to treatment discontinuation
    - AE of NCI CTCAE Grade 3/ or 4 only
    - NCI CTCAE Grade 5 AE

Listing of AEs will be provided in descending order by SOC and then within each SOC, descending order by PT.

5.8.7 Treatment-Emergent Adverse Events (TEAEs)

TEAEs are defined as any AEs that occured or worsened or became serious after the first study drug intake (included) and up to 28 days after the last study drug intake. The analysis of TEAEs will be reported in the CSR.

All the TEAEs will be summarized for the different treatment periods, and overall treatment. Any TEAE that occurred between the 1st dose of treatment period 1 and before the 1st dose of treatment period 2 will be counted in treatment period 1. Any TEAE that occurred on or after the 1st dose of treatment

period 2 and before the first dose of treatment period 3 will be counted in treatment period 2. Any TEAE that occurred on or after the 1st dose of treatment period 3 and to the end of period 3 plus 28 days will be counted in treatment period 3.

TEAEs will be described on the following items:

- At least one TEAE
- At least one TEAE related to study treatment
- At least one NCI CTCAE Grade 3/ or 4 TEAE
- At least one NCI CTCAE Grade 3/ or 4 TEAE related to study treatment
- At least one TEAE leading to early discontinuation of treatment
- At least one TEAE leading to dose reduction
- At least one TEAE leading to dose interruption
- At least one TEAE leading to dose reduction or interruption
- At least one NCI CTCAE Grade 5 TEAE
- At least one NCI CTCAE Grade 5 TEAE related to study treatment
- Number of TEAEs by patient
- Patients with at least one TEAE by study period
- Characteristic of TEAEs

The following TEAEs will be summarized by SOC, PT, and treatment arm:

- NCI CTCAE Grade 5 TEAE
- TEAEs by worst grade
- Subgroup analysis of TEAEs by Age (<65 vs. >=65), by Sex (male vs. female), region (Asian Pacific, North America and EU), Ann Arbor stage (I-II vs III-IV), and by baseline creatinine clearance (<60 mL/min vs ≥60 mL/min)
- TEAEs by cycle of onset
- Non-serious common TEAEs (≥ 10% in any treatment arm)

Listing of AEs will be provided in descending order by SOC and then within each SOC, descending order by PT.

The categories of selected TEAEs, or sometimes called AE of Special Interest (AESI) will be presented based on the current MedDRA version. AESIs will be defined using either standardized MedDRA queries (SMQs), SOCs, HLGTs, HLTs, ad hoc PT lists, or a combination of them. The AESI will be based on the important identified and potential risks in the Lenalidomide Risk Management Plan (RMP) and the internal expertise on the drug and the disease. AESIs will be summarized by category and by the SOC and the AE preferred term.

Second Primary Malignancy (SPM) will be reported after 1st dose and up through the follow-up period of 10 years. The SPM analysis will be described in a separate section.

5.8.8 Serious Adverse Event (SAEs)

- At least one SAE
- Number of SAEs by patient
- Characteristics of SAEs
- SAEs by SOC and PT for all SAEs and for:
    - SAE related to lenalidomide
    - SAE related to rituximab
    - SAE related to chemotherapy

Listing of SAEs will be provided in descending order by SOC and then within each SOC, descending order by PT.

5.8.9 Serious Treatment-Emergent Adverse Events (Serious TEAEs)

- At least one Serious TEAE
- At least one Serious TEAE related to study treatment
- Number of serious TEAEs by patient
- Characteristics of Serious TEAE
- Serious TEAEs by SOC and PT for all SAEs and for:
    - Serious TEAE related to lenalidomide
    - Serious TEAE related to rituximab
    - Serious TEAE related to chemotherapy

Listing of Serious TEAEs will be provided in descending order by SOC and then within each SOC, descending order by PT.

5.8.10 Deaths

- Number of subjects who died
- Primary cause of death
- Disease status at death
- Listing of subjects who died

Death events will be summarized separately as during the treatment period, in the follow-up period, and in the overall study period.

5.8.11 Clinical Laboratory / Serologies / Vital signs

Clinical laboratory measurements, serologies and vital signs will be described on the safety population (cf §4.1.3) in total and according to statistical method defined in section §4.5 by treatment arm.
Clinical laboratory of interest will also be described by grade according to NCI CTCAE classification.

5.8.12 SPM

SPM will be described on the safety population for patients who were diagnosed to have SPM after first dose through the follow-up period of 10 years.

Research analysis will be based on information coming from the safety database whereas the CSR analysis will be based on the clinical database. Potentially, differences between the two sets of outputs might appear.

The following analyses will be performed on the safety population by treatment arm and overall:

- Second Primary Malignancies by patient
- Description of Second Primary Malignancies by SPM categories and preferred term.

Note: All summary tables for patients with SPMs will be summarized overall for the entire study, including the post-treatment follow-up phase as defined in the protocol.

Following analyses will be performed for CSR only:

- The frequency of patients who are diagnosed with SPM during maintenance and through post-treatment follow-up as defined in the protocol will be summarized by SPM category/PT. Categories of SPM include hematologic malignancies, solid tumors, invasive SPMs, non-melanoma skin cancers, and total SPMs. The hematologic malignancy category includes the subcategories:ALL, AML, MDS, MDS to AML, B-cell malignancies, and other hematologic cancers.
- The number and percentage of subjects will be provided by SPM category/PT for subjects who died and remain alive separately.
- Follow up time of SPM will be summarized for all surviving subjects in the safety population.
- Incidence rates in person-years will be calculated and summarized by SPM category.
- Listings for subjects with SPMs and subjects excluded from the SPM analyses including reason for exclusion will be provided.
- Time to onset of SPM will be presented in scatter plots for hematologic malignancies, solid tumors and invasive SPMs.

In addition, prior cancer history will be described in data listings for subjects who experienced SPM after first dose through the follow-up period of 10 years.

- Subject with a prior cancer history
- Type of cancer
- Assessment of prior cancer history
- Prior cancer exams
- Prior cancer history – Risk factors
- Type of cancer of blood relatives
- Prior procedures for cancer not under study
- Prior radiation treatments for cancer not under study
- Prior regimen treatments for cancer not under study

6 REFERENCE LIST

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Summary of Changes from Original SAP to Final SAP

- Addition of a new secondary endpoint “CR rate at 120 weeks by IWG 1999” (following protocol amendment 2)
- Addition of histological transformation to be consistent with protocol
- Modification of statistical approaches for control alpha following the addition of the new secondary endpoint and the PFS interim analysis
- Addition of the PFS interim analysis when the co-primary endpoint CR/CRu rate at 120 weeks is reported
- Update of the simulation for the analysis of the second futility co-primary endpoint CR/CRu rate at 120 weeks
- Addition of imputation rules for the secondary efficacy endpoint (CR at 120 weeks)
- Addition of censoring rules for PFS (per FDA and EMA Guidance)
- Modification of censoring rules for EFS according to FDA guidance
- Definition of the treatment period
- Modification of imputation rules for CR/CRu status and ORR status
- Addition of imputation rules for adverse event / prior or concomitant medication start/stop dates
- Deletion of Per protocol population
- Addition of a new exploratory endpoint “CR/CRu rate at 24 weeks” by IRC and investigator’s assessment
- Addition of a new exploratory endpoint “ORR rate at 24 weeks” by IRC and investigator’s assessment

A PHASE 3 OPEN-LABEL RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE (CC-5013) VERSUS RITUXIMAB PLUS CHEMOTHERAPY FOLLOWED BY RITUXIMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA

The "RELEVANCE" trial
(Rituximab Lenalidomide Versus ANy ChEmotherapy)

INVESTIGATIONAL PRODUCT (IP):	Lenalidomide
PROTOCOL NUMBER:	RV-FOL-GELARC-0683C
DATE FINAL:	July 7, 2011
EudraCT NUMBER:	2011-002792-42
IND NUMBER:	60100

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1. STUDY OBJECTIVES

1.1. Primary Objective

The primary objective of the study is to compare the efficacy of rituximab plus lenalidomide to rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma. Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the Independent Review Committee (IRC) using the IWG (Cheson, 1999) criteria The primary analysis of complete response (CR/CRu) rate at 120 weeks will be conditional upon statistical validation that this endpoint accurately predicts PFS and the study will continue to final PFS analysis.

1.2. Secondary objectives

The secondary objectives of the study are:

- To compare the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab using other parameters of efficacy:
    - Time to Treatment Failure (TTF), Event Free Survival (EFS), Time to Next Anti-Lymphoma Treatment (TTNLT), Time to Next Chemotherapy Treatment (TTNCT), Overall Survival (OS) and ORR rate at 120 weeks by IWG 1999 criteria.
    - Health related quality of life as measured by the EORTC QLQ-C3
- To compare the safety of rituximab plus lenalidomide versus rituximab plus chemotherapy

2. OVERALL STUDY DESIGN

2.1. Study Design Rational

Follicular lymphoma (FL) is a distinct histologic type within B-cell NHL further divided by the WHO classification (2007) into three different grades. Within grade 3, grade 3a is differentiated histopathologically from 3b. FL grade 3b is treated in a manner similar to DLBCL. Thus, FL grade 3b is excluded from this study.

Rituximab has become the backbone of first line treatment for follicular lymphoma patients who are in need of therapy. Recent studies have established several standard-of-care immuno-chemotherapy regimens in previously untreated FL. In most phase 3 studies in front line FL, it has not been possible to demonstrate OS benefit, and PFS has been used to assess efficacy. These studies showed that the addition of rituximab to multi-agent chemotherapy regimens led to significantly longer PFS and sometimes longer OS. These regimens are R-CVP, R-CHOP and R-bendamustine. Which of these regimens are considered standard of care varies depending on the geographic location and physician preference. Furthermore, rituximab-maintenance studies have shown improved PFS, and European and US regulatory agencies recently approved rituximab as a first-line maintenance treatment for patients with follicular lymphoma whose disease has responded to initial induction therapy based upon the results of the PRIMA study (Salles 2011).

The current study is designed to investigate the efficacy and safety of lenalidomide therapy in patients with previously untreated FL. The multicenter nature of the study provides assurance that the results are likely to have general applicability. The inclusion of a control arm, and the fact that the Investigator must select the Investigator's choice option of a standard-of-care for the subject before randomization, is intended to provide a realistic comparison to current standard-of-care in this patient population. Subject eligibility criteria are consistent with those used in other studies of this population.

Patients are required to have measurable disease to facilitate the accurate assessment of CR/CRu, which is a direct measure of the co-primary efficacy endpoint CR/CRu rate at 120 weeks. The International Working Group (IWG) response criteria were selected to provide an international standard for the assessment of lymphoma (Cheson 1999). The use of this tool will ensure that data across centers are evaluated consistently and also allow for direct comparison to historical data. Safety will be assessed by evaluating AEs and laboratory data. AE and abnormal laboratory value severity will be graded using version 4.03 of the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE).

Known toxicities of lenalidomide, given alone or in combination with rituximab have been reported. In addition, in the clinical database and safety database of the sponsor, tumor flare, tumor lysis and venous thromboembolus have been reported.

Monitoring for tumor flare and venous thromboembolic events (VTE – including pulmonary embolism and deep vein thrombosis) will be performed along with safety measures that are routinely assessed in investigational studies of hematologic malignancies. VTE prophylaxis is recommended for patients in the lenalidomide arm who are at high risk for a thromboembolic event. VTE, TFR and TLS will be recorded as AEs.

2.2. Study Design

This multi-center, open-label study is designed to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab. The overall study

design is described in Figure 1. The study is divided into the Screening Period, Treatment Period, and Follow-up Period.

Once a subject gives written consent, the subject may enter the Screening Period, which is permitted to last up to 4 weeks. During the Screening Period, the investigator will choose one standard-of-care regimen ("investigator's choice") for the subject from a list of permitted choices of rituximab-containing chemotherapy regimens. In addition, during the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either experimental arm (rituximab plus lenalidomide) versus control arm ("investigator's choice" of rituximab-chemotherapy).

It is noted that subject eligibility will be based on investigator assessment. However, subject's disease will be assessed by central pathology review to confirm the FL diagnosis using formalin-fixed paraffin embedded (FFPE) tumor or lymph node tissue submitted in the Screening Phase or obtained from the Screening biopsy.

The subject will enter the Treatment Period once the subject has fulfilled the required assessment in the Screening Period and has been randomized. The treatments will be given as described in detail in Section 4. The patients will receive protocol-specified treatments, until :

(1) Inability to achieve a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment),

(2) Inability to achieve a response by 24 weeks (second CT assessment),

(3) Relapse or progression of disease,

(4) Withdrawal of consent or

(5) Unacceptable toxicity.

All randomized patients are followed for progression free survival and overall survival. This includes patients who discontinue the study early for any reason without documented evidence of disease progression.

Upon completion of the required treatments, the subject will enter the Follow-Up Period. In the follow-up period, the patients will be followed for disease progression, next lymphoma treatment (including next chemotherapy) and overall survival.

All protocol defined efficacy assessments will be conducted by Central Review including central radiology and clinical review by an Independent Review Committee (IRC). However, a subject's withdrawal from the study for disease progression or failure to achieve threshold clinical activity at the 12 and 24 week assessments [see points (1) and (2) above] will be based upon investigator assessment.

Since the study endpoint is PFS based on computed axial tomography (CT) as determined by IRC, progression will be based on CT scans.

For suspected progression based on clinical evaluation, a CT scan must be available demonstrating unequivocal progression.

For equivocal progression based on CT findings, the site Investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases of equivocal progression, immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if the PD is not confirmed by central radiology review, the patient should continue treatment as per protocol.

In limited instances where progression is evident only by assessments other than CT, CT scans must still be obtained along with the non-CT documentation of progression.

The same methodology will be performed for equivocal cases of threshold clinical activity at the 12 and 24 week assessments. That is, in equivocal cases of threshold clinical activity, the site investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if threshold clinical activity is confirmed by central radiological review, the patient should continue treatment as per protocol.

DSMC will conduct two early futility analyses, the first, 6 months after the 200th subject has been randomized and the second, 120 weeks after the 200th subject has been randomized. The first futility analysis is to evaluate the complete response (CR/CRu) rate at 6 months of treatment for the first 200 patients. The second futility analysis is to evaluate the complete response (CR/CRu) rate at 120 weeks for the first 200 patients.

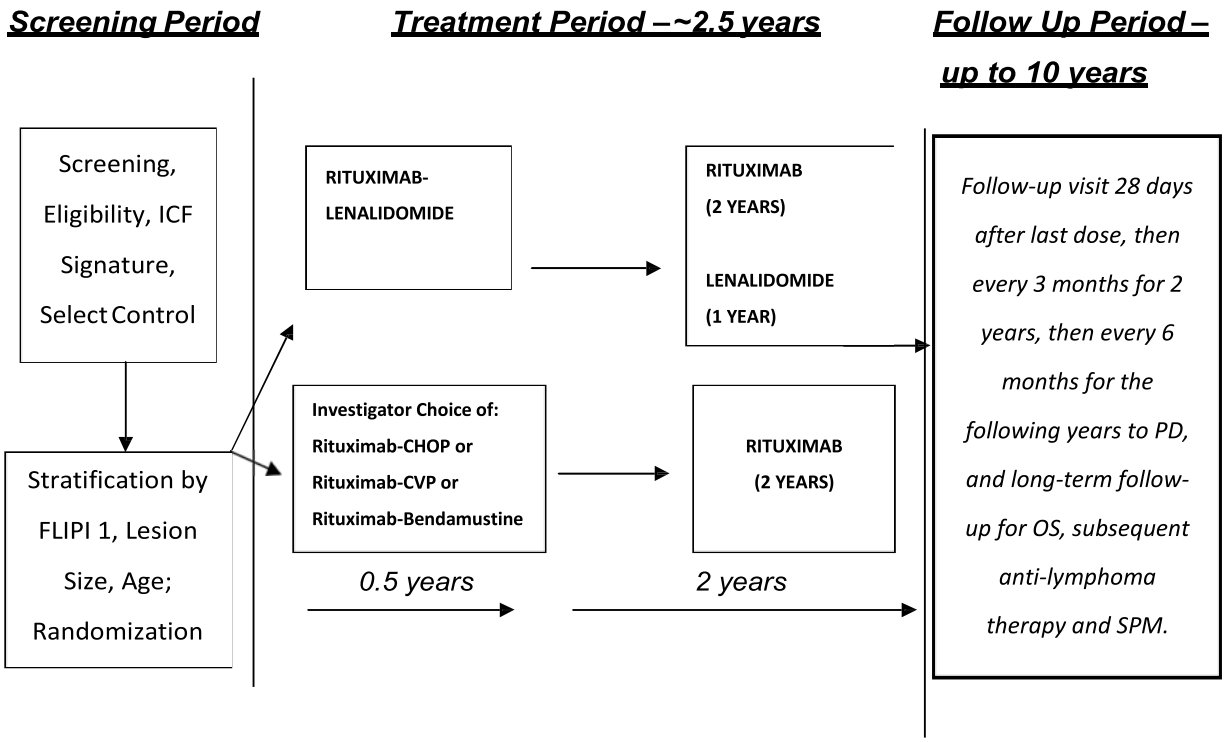
Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG (Cheson 1999) criteria. Because all protocol specified analyses including early futility analyses are based on IRC review, all CT scans must be sent for central review as soon as possible.

See Section 8 for a detailed description of Statistical Analyses.

The study will be conducted in compliance with Good Clinical Practices (GCPs).

Lenalidomide concentrations will be determined in patients who consent to this analysis in selected countries and sites.

Figure 1: Overall Study Design



All randomized patients are followed for progression free survival and overall survival. This includes patients who discontinue the study early for any reason without documented evidence of disease progression.

The duration of the entire study will be approximately 12-13 years. Patients receive two-four weeks of screening, approximately 2.5 years of treatment and up to 10 years of follow-up.

The expected accrual duration is 40 months. Patients will be stratified by FLIPI score (0-1 v 2 v 3-5), age (>60 v $\leq$ 60) and longest diameter of the largest node (> 6 v $\leq$ 6 cm) and randomized to receive either rituximab-lenalidomide or Investigators Choice of R-CHOP, R- CVP, or R-B.

Randomized patients will receive therapy for approximately 2.5 years and followed until relapse or progression. After relapse or progression, OS, anti-lymphoma therapy and second primary malignancy (SPM) data will continue to be collected.

3. STUDY POPULATION

Patients must have an investigator-assessed diagnosis of Stage II-IV follicular lymphoma, grade 1-3a, have not been previously treated for their lymphoma other than local radiation for localized disease, have signs or symptoms of lymphoma requiring treatment, and have adequate bone marrow function, liver function and renal function.

3.1. Inclusion criteria

Patients must satisfy all the following criteria to be enrolled in the study:

1. Histologically confirmed CD20+ follicular lymphoma grade 1, 2 or 3a as assessed by the investigators:
   - a formalin fixed paraffin embedded specimen taken within 18 months before signing informed consent must be available for central review, and
   - a formalin fixed paraffin embedded bone marrow biopsy taken within 18 months before subject signing informed consent must be available for central review.

2. Have no prior systemic treatment for lymphoma.

3. Must be in need of treatment as evidenced by at least one of the following criteria:
   - Bulky disease defined as:
     - a nodal or extranodal (except spleen) mass >7cm in its greater diameter or,
     - involvement of at least 3 nodal or extranodal sites (each with a diameter greater than ≥3 cm)
   - Presence of at least one of the following B symptoms:
     - fever (>38C) of unclear etiology
     - night sweats
     - weight loss greater than 10% within the prior 6 months
   - Symptomatic splenomegaly
   - Compression syndrome (ureteral, orbital, gastrointestinal)
   - Any one of the following cytopenias due to lymphoma:
     - hemoglobin < 10g/dL (6.25 mmol/L)
     - platelets <100 x 10^9/L , or
     - absolute neutrophil count (ANC) < 1.5 x 10^9 /L
   - Pleural or peritoneal serous effusion or (irrespective of cell content)

4. Bi-dimensionally measurable disease with at least one mass lesion > 2 cm that was not previously irradiated.

5. Stage II, III or IV disease.

6. Must be ≥ 18 years and sign an informed consent.

7. Performance status ≤ 2 on the ECOG scale

8. Adequate hematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) within 28 days prior to signing informed consent, including:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 /L
    - Platelet count ≥ 75 x 10^9 /L
    - Hemoglobin ≥ 8.0 g/dl (5 mmol/L)
9. Must be able to adhere to the study visit schedule and other protocol requirements.
10. Females of childbearing potential (FCBP) receiving lenalidomide must:

    Have two negative pregnancy tests as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices complete abstinence from heterosexual contact.

    Either commit to complete abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.
11. Male patients receiving lenalidomide must:

    Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

    Agree to not donate semen during study drug therapy and for 28 days after discontinuation of study drug therapy.
12. All patients receiving lenalidomide must:

    Have an understanding that the study drug could have a potential teratogenic risk.

    Agree to abstain from donating blood while taking study drug therapy and for 28 days after discontinuation of study drug therapy.

    Agree not to share study medication with another person.

    Agree to be counseled about pregnancy precautions and risk of fetal exposure

    Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.
13. For all patients receiving Rituximab:

    Women must not breast feed and must use effective contraception must not be pregnant and agree not to become pregnant during participation in the trial and

during the 6 months thereafter. Men must agree not to father a child during participation in the trial and during the 6 months thereafter.

3.2. Exclusion criteria

The presence of any of the following will exclude a subject from enrollment:

1. Clinical evidence of transformed lymphoma by investigator assessment.
2. Grade 3b follicular lymphoma.
3. Patients taking corticosteroids during the last 4 weeks, unless administered at a dose equivalent to ≤ 10 mg/day prednisone (over these 4 weeks).
4. Major surgery (excluding lymph node biopsy) within 28 days prior to signing informed consent.
5. Seropositive for or active viral infection with hepatitis B virus (HBV):
   - HBsAg positive
   - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA

   Note:
   - Patients who are HBsAg negative and viral DNA negative are eligible
   - Patients who are seropositive due to a history of hepatitis B vaccine are eligible.
6. Known seropositive for, or active infection with hepatitis C virus (HCV).
7. Known seropositive for, or active viral infection with human immunodeficiency virus (HIV).
8. Life expectancy < 6 months.
9. Known sensitivity or allergy to murine products.
10. Prior history of malignancies, other than follicular lymphoma, unless the subject has been free of the disease for ≥ 10 years. Exceptions include a history of previously ***treated***:
    - Localized non-melanoma skin cancer
    - Carcinoma in situ of the cervix
11. Prior use of lenalidomide.
12. Neuropathy > Grade 1.
13. Presence or history of CNS involvement by lymphoma.
14. Patients who are at a high risk for a thromboembolic event and are not willing to take venous thromboembolic (VTE) prophylaxis.
15. Any of the following laboratory abnormalities:

    -serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) > 3x upper limit of normal (ULN), except in patients with documented liver involvement by lymphoma

-total bilirubin > 2.0 mg/dl (34 µmol/L) except in cases of Gilberts Syndrome and documented liver or pancreatic involvement by lymphoma

- creatinine clearance of < 30 mL/min

16. Uncontrolled intercurrent illness.
17. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
18. Pregnant or lactating females.
19. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study, or which confounds the ability to interpret data from the study.

4. STUDY TREATMENTS

4.1. Drugs description

Lenalidomide will be supplied as 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg capsules for oral administration and labeled as IP.

Commercially available IV formulation of Rituximab background therapy and standard of care therapy, i.e. cyclophosphamide, doxorubicin, vincristine and bendamustine will be used.

Commercially available prednisone will also be used as oral formulation. Standard of care chemotherapy must be available by prescription, generally reimbursed by the health system and used routinely in previously untreated FL patients at the center.

4.2. Treatment schedule and design

4.2.1. Experimental Arm : Rituximab - Lenalidomide

Patients randomized to receive rituximab-lenalidomide will receive six cycles of lenalidomide 20 mg daily on days 2-22 every 28 days. Patients exhibiting a CR/CRu after six cycles then receive 12 cycles of 10 mg lenalidomide daily on days 2-22 every 28 days for a total of 18 cycles. Patients exhibiting a PR after six cycles receive an additional 3 to a maximum of 6 cycles of the 20 mg lenalidomide dose until they achieve a CR/CRu at which time they receive the 10 mg lenalidomide dosing for 9 or 6 cycles respectively for a total of 18 cycles. Patients who remain in PR after the additional 6 cycles will receive 10 mg lenalidomide dosing for a total of 18 cycles.

All patients randomized to receive rituximab-lenalidomide receive rituximab, 375 mg/m^2 on days 1, 8, 15 and 22 of cycle 1, day 1 of cycles 2 to 6; 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Lenalidomide treatment is continued for 18 cycles or until disease progression, unacceptable toxicity, or voluntary withdrawal. In addition, patients who do not achieve a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment), and patients who do not achieve a response by 24 weeks (second CT assessment) will be withdrawn from treatment and followed for survival and PFS using the same schedule of assessments as patients continuing treatment.

Lenalidomide dosing will be based on patients creatinine clearance calculated using the Cockcroft-Gault formula. Creatinine clearance should be calculated using ideal body weight or actual, whichever is less.

Patients who have a creatinine clearance ≥ 60 mL/min will receive oral lenalidomide that is initiated on Day [D] 2 of Cycle 1 at a dose of 20 mg [p.o.] once daily for 21 days (D2 – D22) in each 28 day cycle.

Patients who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min] will receive a lower starting dose of lenalidomide of 10 mg once daily for 21 days (D2 – D22) in Cycle 1 and Cycle 2.

After completion of Cycle 2, if the subject remains free of Grade 3 or Grade 4 toxicity, the dose may be increased to a maximum of 15 mg once daily for 21 days (D2 – D22) starting on day 2 of cycle 3.

Lenalidomide should be taken at approximately the same time every day. There is no requirement for taking lenalidomide with or without food, or with or without certain types of foods or liquids. If a subject misses a dose of lenalidomide and it is within 12 hours of their normal dosing time, the subject should be instructed to make up the missed dose, and to then take their

next dose according to their regular schedule. Lenalidomide concentration is low at 12 hours post dose, therefore making up a missed dose and then resuming regular dosing with a greater than or equal to (≥) 12 hour interval between the two doses will not cause considerable drug accumulation.

4.2.2. Standard Arm : Investigators Choice

Patients randomized to receive investigators choice will receive ONE of the following

Rituximab-CHOP: with six cycles of R-CHOP in 21 day cycles followed by two 21 day cycles of 375 mg/m^2 rituximab and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles,

OR

Rituximab-CVP: with eight cycles of R-CVP in 21 day cycles; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles,

OR

Rituximab-Bendamustine: with rituximab 375 mg/m^2 (day 1) plus bendamustine 90 mg/m^2 (days 1 + 2) every 28 days for six cycles; and 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles.

Patients who do not achieve the threshold clinical activity of 1) 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment) or 2) a response by 24 weeks (second CT assessment) will be withdrawn from treatment and followed for survival and PFS using the same schedule of assessments as patients continuing treatment.

4.2.3. Rituximab background therapy

The planned dose of rituximab is 375 mg/m^2 in all regimens. Schedule is as described for individual regimens. Premedication should be administered.

All dosage calculations for rituximab and chemotherapies will be based on the subject‘s body surface area (BSA), using actual weight for calculations. This will be determined on the first day of study drug administration of Cycle 1. For rituximab, no dosage adjustments should be performed.

For large changes in body weight compared to baseline (≥ 10%), the dose of chemotherapy may be modified accordingly. However, the same dose of rituximab should be infused regardless of any fluctuations in body weight.

4.2.4. R-CHOP regimen

Standard CHOP chemotherapy consists of cyclophosphamide, doxorubicin, vincristine and prednisone.

The doses of CHOP components are:

Cyclophosphamide, 750 mg/m2 IV on day 1

Doxorubicin, 50 mg/m2 IV on day 1

Vincristine, 1.4 mg/m2 (2 mg cap) IV on day 1

Prednisone, 100 mg/day PO on days 1-5

CHOP will be administered according to the standard preparation and infusion procedures of each investigational site.

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For subject ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Rituximab is administered on day 1 for six cycles with CHOP in 21 day cycles followed by two 21 day cycles of 375 mg/m^2 rituximab; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert).

4.2.5. R-CVP regimen

Standard CVP chemotherapy consists of cyclophosphamide IV push, vincristine IV bolus and prednisone PO. The doses of CVP components are:

Cyclophosphamide 750 mg/m^2 day 1

Vincristine 1.4 mg/m^2 (2 mg cap) day 1,

Prednisone 40 mg/m^2 (5 days 1-5)

CVP will be administered according to the standard preparation and infusion procedures of each investigational site.

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For subject ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be adjusted in case of are large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Rituximab is administered on day 1 for eight cycles with CVP in 21 day cycles: and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert).

4.2.6. R-Bendamustine regimen

Bendamustine is administered at 90 mg/m^2 on days 1 + 2 every 28 days for six cycles.

Bendamustine will be administered according to the standard preparation and infusion procedures of each investigational site. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Rituximab is administered on day 1 for six cycles with bendamustine in 28 day cycles and 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert)

4.3. Dose Modifications

4.3.1. Lenalidomide Dose Modifications

The lenalidomide dose for each subject will be interrupted and modified following toxicity as described in Table 1 and Table 2. If a dose is reduced, re-escalation is not permitted.

If dose modifications are required during a cycle then the subject will be given a new medication bottle, and will start the new dose of lenalidomide immediately. Patients should take study drug

from the new bottle for the remainder of that cycle only and then receive a new bottle for the next cycle.

The next cycle of treatment may begin on the next scheduled Day 1 if:

- The ANC is ≥ 1,000 cells/mm³ (1.0 X 10^9/L);
- The platelet count is ≥ 50,000 cells/mm³ (50 X 10^9/L);
- Lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity;
- Any other lenalidomide-related AE not requiring discontinuation has resolved to ≤ Grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated once every seven days and a new cycle of treatment with lenalidomide will not be initiated until the toxicity has resolved as described above. If a new cycle is delayed for more than 28 days, the Medical Monitor must be notified.

Table 1: Lenalidomide Dose Modification Rules

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Grade 3 neutropenia (one time reading)	Follow CBC at least every seven days.
Neutropenia Sustained (≥ 7 days) Grade 3 OR ≥ Grade 3 associated with fever (temperature ≥ 38.5º C) OR Grade 4	• Hold (interrupt dose) • Follow CBC every seven days • If neutropenia has resolved to ≤ Grade 2 restart at next lower dose level • Use of growth factors (G-CSF, GM-CSF) is permitted at the discretion of the Investigator as per ASCO and ESMO guidelines
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000 cells/mm³ [50x109/L])	• Hold (interrupt dose) • Follow CBC weekly every seven days • If thrombocytopenia resolves to ≤ Grade 2 restart at next lower dose level
Rash Desquamating (blistering) ≥Grade 3 OR Non-desquamating Grade 4	Permanently discontinue lenalidomide study drug
Allergic reaction or hypersensitivity Grade 2 Grade 3-4	• Hold (interrupt dose). Follow at least every seven days • When the toxicity resolves to ≤ Grade 1 restart at next lower dose level • Permanently discontinue lenalidomide study drug
Constipation Grade 1-2 ≥ Grade 3	• Initiate bowel regimen and maintain dose level • Hold (interrupt dose). Follow at least every seven days • When the toxicity resolves to ≤ Grade 2 restart at next lower dose level
Venous thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at Investigator's discretion (maintain dose level)
Peripheral neuropathy Newly developed ≥ Grade 3 **(applies only to those neuropathies which begin or worsen while on study)**	• Hold (interrupt dose) • When the toxicity resolves to ≤ Grade 1 or to baseline, restart at the next lower dose level

Tumor Flare Reaction (TFR)*	☐ Continue lenalidomide, maintain dose level
Grade 1-2	☐ At the investigator's discretion may initiate therapy with NSAIDs, limited duration corticosteroids, and/or narcotics
Grade 3-4	☐ Hold (interrupt) dose. Initiate therapy with NSAIDs, corticosteroids, and/or narcotics ☐ When symptoms resolve ≤Grade 1, restart at next lower dose level
Tumor Lysis Syndrome (TLS)**	• Continue lenalidomide (maintain dose), or at the investigator's discretion, continue lenalidomide and reduce dose by one level
Laboratory TLS or Grade 1 TLS	• Provide vigorous intravenous hydration and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy is appropriate (if approved by the local Health Authority) as needed to reduce hyperuricemia • Hospitalization will be at investigator's discretion
Grade 2-4	• Hold (interrupt dose) • When symptoms resolve to Grade 0, restart at next lower dose level • If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following re-initiation of lenalidomide
Other lenalidomide related non-hematologic AEs ≥ Grade 3	• Hold (interrupt dose) • When the AE resolves to ≤ Grade 2, restart at the same or next lower dose level per the investigator's discretion

*AEs are graded using the NCI CTCAE v 4.03; however TFR will be graded using NCI CTCAE v 3.0 as subsequent versions do not contain a provision for TFR.

** AEs are graded using the Cairo-Bishop toxicity grade

Please note that leucopenia and Lymphopenia are not part of the dose modification rules, only Neutropenia grade 3 or 4 requires dose modification.

Table 2: Lenalidomide Dose Modification Rules For Abnormal Liver Function*

AST or ALT > 3 x ULN	Hold lenalidomide dosing; re-test at least weekly until AST or ALT ≤ 2.5 x ULN or return to baseline	• Resume the same dose of lenalidomide if the event is considered NOT related to study drug treatment • Restart lenalidomide treatment at next lower dose level if the event is considered as related to drug treatment
Bilirubin ≥ 3 x ULN	Hold lenalidomide dosing; re-test at least weekly until bilirubin ≤ 1.5 x ULN	• Resume the same dose of lenalidomide if the event is considered NOT related to study drug treatment • Restart lenalidomide treatment at next lower dose level if the event is considered as related to drug treatment

*For patients with Gilberts Syndrome or liver involvement by lymphoma, dose reductions should be made in consultation with the medical monitor.

4.3.2. Lenalidomide Dose Reductions Levels

The daily dose of lenalidomide may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction per cycle. Once a subject's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase. Refer to Table 3 for patients starting at the 20 mg dose, and to Table 4 for patients starting at the 10 mg dose.

Table 3: Dose Reduction Levels from 20 mg Start Dose

Starting Dose	20 mg daily on Days 2-22, every 28 days
Level –1 Dose	15 mg daily on Days 2-22, every 28 days
Level –2 Dose	10 mg daily on Days 2-22, every 28 days
Level –3 Dose	5 mg daily on Days 2-22, every 28 days
Level –4 Dose	2.5 mg daily on Days 2-22, every 28 days

Table 4: Dose Reduction Levels from 10 (or 15) mg Start Dose

Starting Dose	10 mg daily on Days 2-22, every 28 days
Level A Dose*	15 mg daily on Days 2-22, every 28 days
Level –1 Dose	5 mg daily on Days 2-22, every 28 days
Level –2 Dose	2.5 mg daily on Days 2-22, every 28 days

*After completion of Cycle 2, if the patient remains free of Grade 3 or Grade 4 toxicity, the dose may be increased to a maximum of 15 mg once daily for 21 days (D2 – D22) starting on day 2 of cycle 3. The same dose reduction rules as in Table 3 would then apply.

Table 5: Dose Reduction Levels from the Cycle 13 - 10 mg Dose*

Starting Dose	10 mg daily on Days 2-22, every 28 days
Level –1 Dose	5 mg daily on Days 2-22, every 28 days
Level –2 Dose	2.5 mg daily on Days 2-22, every 28 days

*All patients receive the 10 mg lenalidomide dose from cycle 13 through cycle 18. Patients exhibiting CR/CRu after 6 and before 12 cycles begin the 10 mg lenalidomide at the next cycle.

Patients with no dose reduction or dose reduction to 15 mg or 10 mg during cycles 1-12 continue with 10 mg. Patients who dose reduced to 5 mg or 2.5 mg during cycles 1-12 continue with 5 mg and 2.5 mg respectively.

4.3.3. Dose Adjustment for Patients in the Control Arm

Patients will be evaluated for adverse events at each visit with the NCI CTCAE v 4.03 used as a guide for the grading of severity. The dose of Investigator's Choice for each subject will be interrupted and modified according to the clinical practice of the Investigator's institution, and in line with the approved prescribing information including administration, warnings, precautions, contraindications, and adverse reactions, as applicable.

4.4. Method of Treatment Assignment

The treatment assignment will occur in the screening period, once all the required screening procedures have been completed, and all required data have been submitted to the IVRS/IWRS system.

Investigators will select one protocol specified standard of care chemotherapy (i.e., bendamustine, CHOP or CVP) for their subject during screening and enter this data into IVRS/IWRS. Standard of care chemotherapy must be available by prescription, generally reimbursed by the health system and used routinely in previously untreated FL patients at the center.

Patients will be stratified by FLIPI score (0-1 v 2 v 3-5), age (>60 v $\leq$ 60) and longest diameter of the largest node (> 6 v $\leq$ 6 cm) and randomized to receive either rituximab-lenalidomide or Investigators Choice of R-CHOP, R-CVP, or R-B.

4.5. Drug Dispensation and accountability

4.5.1. Packaging and labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

4.5.2. Accountability and destruction

The sponsor will instruct the Investigator on the return, disposal and/or destruction of investigational product if applicable.

4.5.3. Compliance

For the oral medications of lenalidomide, study personnel will review the dosing instructions with the patient prior to dispensing the study drug. The subject will be instructed to return the study drug bottle, including any unused study drug, to the site at the next visit. Subject compliance will be noted on the appropriate CRFs and source records based on a capsule count. To monitor treatment compliance, reconciliation of capsules will be done at each scheduled study visit.

5. STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS

5.1. Study flow chart

See Figure 1.

5.2. Screening Examination and Procedures

Patients will be screened for protocol eligibility during a period of no more than 4 weeks prior to randomization as outlined in the Schedule of Study Assessments.

Screening assessments and recording of AEs/SAEs will begin once the subject has signed the informed consent form.

The subject's eligibility (inclusion and exclusion criteria) has to be evaluated during the screening period prior to randomization.

5.2.1. Demographic Information

- Written Informed Consent
- Complete medical history (including previous cancer)
- Physical examination performed within 2 weeks prior to the first day of treatment
- Age, gender
- Weight, height and BSA
- Vital signs (including Blood Pressure, pulse and temperature)

5.2.2. Histological diagnosis

FFPE tumor block of diagnostic tumor tissue taken within the 18 months before signing the informed consent must be confirmed to be available at the time of randomization and must be submitted to central pathology within 12 weeks after randomization.

If block cannot be sent, an H&E slide and 10 unstained slides will be acceptable.

Pathology reports associated with these tissues are also required and will be sent to the central pathology laboratory with the tissue and/or slides. The sponsor will provide detailed instructions and materials for sample handling and shipping. *Note that diagnosis based on fine needle aspirations is not considered acceptable pathologic data for entry into this study.*

Eligibility will be based on local pathology review; confirmation of diagnosis by central pathology laboratory is not required for entry or initiation of treatment. If tumor tissue was not collected within 18 months prior to the subject signing the informed consent, a newly obtained tumor biopsy (excisional or core) is required.

5.2.3. Tumor and disease staging

- CT/MRI of neck, chest, abdomen and pelvis is required to locally confirm measurable disease of at least 2 cm. CT is to be performed with contrast unless it is medically contraindicated. This scan may be used as the baseline CT scan if it is obtained within 4 weeks of cycle 1 day 1.
- Evaluation of all involved nodal and extra-nodal sites of lymphoma.
- Assessment of spleen and liver enlargement based on CT scan or physical examination.

- FDG-PET scan (optional). FDG-PET is to be submitted in addition to CT/MRI data, not in lieu of it.
- Patients with a presence of CNS lymphoma involvement are excluded from the study. Patients with suspicion of CNS involvement must undergo neurologic evaluation and CT/MRI of head and lumbar puncture to exclude CNS disease.
- Paraffin fixed bone marrow biopsy taken within 18 months of subject signing the informed consent or if bone marrow block are not available 5 representative, unstained slides must be submitted to central pathology within 12 weeks after randomization.

  The pathology reports must also be submitted. Although receipt of the blocks or slides by central pathology is required, the outcome of the central review of the slides is not part of the eligibility requirements.

  If bone marrow biopsy was not collected within 18 months of signing the informed consent, a newly obtained bone marrow biopsy is required.
- B-symptoms
- FLIPI and FLIPI 2
- Ann Arbor staging
- ECOG performance status

5.2.4. Laboratory assessments

- Compete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, MCV, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.
- sodium, potassium, calcium,
- phosphorous,
- glucose,
- uric acid,
- alkaline phosphatase, AST, ALT, total protein, albumin, total bilirubin,
- chloride,
- blood urea nitrogen,
- lactate dehydrogenase (LDH), β2-microglobulin
- creatinine (clearance calculated by the Cockcroft-Gault formula)

Cockcroft-Gault estimation of creatinine clearance (CrCl):

Serum creatinine units mg/dL => for females, the formula is multiplied by 0.85.

CrCl (mL/min) = [(**140** – **age** (years)) x (**weight** [kg])] / [**72** x (**serum creatinine** [mg/dL])];

Serum creatinine units µmol/L => A = 1.23 for men and A = 1.04 for females.

CrCl (mL/min) = [(**140** – **age** (years)) x (**weight** [kg]) x **A**] / (**serum creatinine** [µmol/L]);

Creatinine clearance should be determined utilizing actual body weight or ideal body weight, whichever is less (**Cockcroft 1976**, **Luke 1990**).

Eligibility for the study is based on the local laboratory results.

Laboratories used for hematological and biochemical tests and assays including ongoing pregnancy tests during the study are individual centre laboratories. All the laboratories must provide their normal values and an updated accreditation for quality control.

However, if Screening labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.

5.2.5. Cardiac function evaluation

- 12-Lead ECG is performed at Screening and as clinically indicated thereafter.
- Left VEF (measured by Ultrasound echocardiography or scintigraphy) according to physician decision (if patient planned to receive anthracycline).

5.2.6. Serologies and specific laboratory assessments

- Two pregnancy tests for females of childbearing potential (FCBP)

Please note that following laboratory assessments will be performed only by selected sites and countries.

- FcgR polymorphism is measured in peripheral blood cells once during screening.
- Blood MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation in peripheral blood or other MRD assays.
- Bone marrow MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation or other MR.
- Serum immunoglobulin levels
- Total T cells and B cells, as well as CD4/CD8 and NK cells
- Tetanus (T-cell dependent) and pneumococcal (Pure B cell) response specific serum IgG

5.2.7. Quality of life assessments

- EORTC QLQ-C30
- EQ-5D

5.2.8. Selection of Standard-of-Care regimen (Investigator's Choice)

The intent of this study is to compare the rituximab plus lenalidomide regimen to standard-of-care rituximab-chemotherapy regimens in use in a particular country, geographic region or institution.

Therefore, during the Screening Phase, prior to randomization, Investigators will select one regimen from a choice of protocol specified choices of standard-of-care chemotherapy regimens from the choices described in Section 8.2 for their subject during screening and enter this choice into IVRS/IWRS.

Standard of care chemotherapy regimen must be available by prescription, generally reimbursed by the health system and used routinely to treat previously untreated FL patients at the center.

After randomization, study drug is dispensed on Day 1 for lenalidomide patients or Investigator's Choice patients assigned to oral prednisone (R-CHOP or R-CVP). For Cycle 1 only, a 7 day window between randomization and Cycle1 Day 1 is allowed; however, the Screening period must remain within 28 days of Cycle 1 Day 1 dosing.

5.3. Evaluation during treatment and follow-up

Serial assessments of safety and efficacy will be performed as outlined in the Schedule of Study Assessments.Patients in both arms will follow comparable assessment schedules.
Note that for the first year of maintenance rituximab cycles are administered every 56 days and lenalidomide cycles every 28 days. To balance subject contacts during this time, subjects in the rituximab arm will call the site/or call center for a phone call interview every 28 days after each rituximab treatment (for months without rituximab administration) during the first year of maintenance. Laboratories used for hematological and biochemical tests and assays including ongoing pregnancy tests during the study are individual centre laboratories.

5.3.1. Evaluation during each cycle of treatment

- Physical examination (including weight, vital signs and ECOG PS) at day 1 of every treatment cycle
- Serum chemistry laboratory evaluations (sodium, potassium, chloride, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, ALP, total bilirubin, AST/SGOT, ALT/SGPT, LDH and uric acid) within 48 hours of Day 1 of every treatment cycle

Note that the Cycle 1 Day 2, 4, 8 and 15, and Cycle 2-4 Day 15 chemistry labs are required only for patients in the experimental arm and suggested for patients in the control arm to monitor for tumor lysis.

- Hematology laboratory evaluations (RBC count, hemoglobin, hematocrit, WBC count and differential, ANC, and platelet count) within 48 hours of Day 1 of every treatment Cycle

Note that the Cycle 1 Day 2, 4, 8 and 15 and Cycle 2-4 Day 15 hematology labs are required only for patients in the experimental arm and suggested for patients in the control arm to monitor for cytopenias.

However, if Screening labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1

5.3.2. Pharmacokinetic assessments (experimental arm)

Pharmacokinetic assessments will be performed in patients who provide additional consent at select centers. All patients participating in the sparse PK assessment will be instructed to take the oral dose of lenalidomide in the morning at approximately the same time each day. For each PK sample, approximately 3 mL blood will be drawn and plasma will be prepared by centrifugation as described in the study manual.

Sparse PK sampling

Sparse PK sampling will be performed in selected countries and at select centers in patients (up to 200 patients) who are randomized to the rituximab plus lenalidomide arm and sign the PK ICF. A single PK blood sample will be collected between 1 to 10 hours after the morning lenalidomide dose at each of the following visits:

- Cycle 1 Days 2, 4, 8, 15
- Cycle 4 Day 15

Patients should visit the study site at a post dosing time that is at least one hour different from the prior PK visit(s).

5.3.3. Evaluation of response

- All response assessesments will be determined from first dose date and will follow the counting of calendar days and not the dosing cycles.
- Patients with positive bone marrow at screening will have a repeat unilateral bone marrow biopsy if a) they otherwise achieve CR and the repeat biopsy will be taken within 28 days after first achieving CR, or b) they are in PR at 120 weeks.
- CT scans using contrast media are the preferred radiology method (MRI is allowed in case of contraindications to the use of CT scans):

  - 12 weeks after the first dose date (± 1 week),
  - 24 weeks after the first dose date (± 2 weeks),
  - 36 weeks after the first dose date (± 2 weeks),
  - 52 weeks after the first dose date (± 2 weeks),
  - 76 weeks after the first dose date (± 3 weeks),
  - 100 weeks after the first dose date (± 3 weeks),
  - 120 weeks after the first dose date (± 4 weeks)
  - and then every 6 months (± 4 weeks) for 5 years and then every year (± 4 weeks) until disease progression or relapse.

- FDG-PET scan (will be optional). FDG-PET is to be submitted in addition to CT/MRI data, not in lieu of it :

  - 24 weeks after the first dose date (± 2 weeks),
  - 76 weeks after the first dose date (± 3 weeks)
  - 120 weeks after the first dose date (± 4 weeks).

Since the study endpoint is PFS based on CT, FDG PET scan is not the basis for disease progression. For suspected progression based on FDG-PET, a CT scan must be available demonstrating unequivocal progression.

All protocol defined efficacy assessments will be conducted by Central Review including central radiology and clinical review by an IRC. Since the study endpoint is PFS based on CT as determined by IRC, progression will be based on CT scans.

For suspected progression based on clinical evaluation, a CT scan must be available demonstrating unequivocal progression.

For equivocal progression based on CT findings, the site Investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases of equivocal progression, immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if the PD is not confirmed by central radiology review, the patient should continue treatment as per protocol.

In limited instances where progression is evident only by assessments other than CT, CT scans will still be provided along with the non-CT documentation of progression.

The same methodology will be performed for equivocal cases of threshold clinical activity at the 12 and 24 week assessments. That is, in equivocal cases of threshold clinical activity, the site investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases immediate central reading of the CT scan in question

may be requested prior to removing the patient from the study. In such cases, if threshold clinical activity is confirmed by central radiological review, the patient should continue treatment as per protocol.

5.3.4. Quality of Life Assessments

- ☐ EORTC QLQ-C30: Follow the same schedule as described for CT scans.

- EQ-5D: Follow the same schedule as described for CT scans with the exception that EQ-5D assessments continue beyond disease progression/relapse until the end of follow-up period.

5.3.5. Specific laboratory assessments

- Blood MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation in peripheral blood or other MRD assays at the following time points : 24 weeks (± 1 week), 76 weeks (± 2 weeks), 120 weeks (± 4 weeks).
- Bone marrow MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation or other MRD assays at the following time points : 24 weeks (± 1 week), and only for patients with bone marrow involved by lymphoma at screening.
- Serum immunoglobulin levels are measured at the following time points: 24 weeks (± 1 week), 52 weeks (± 1 week), 76 weeks (± 2 weeks), 100 weeks (± 2 weeks), 120 weeks (± 4 weeks).
- Total T cells and B cells, as well as CD4/CD8 and NK cells are at the following time points: 24 weeks (± 1 week), 76 weeks (± 2 weeks), 120 weeks (± 4 weeks).
- ☐ Tetanus (T-cell dependent) and pneumococcal (Pure B cell) response specific serum IgG is measured at 24 weeks (± 2 weeks) and 120 weeks (± 4 weeks) after the first dose date in patients with documentation of prior vaccination who consent to this additional assessment.

5.3.6. Assessments for Veinous Thromboembolitic events (VTE)

VTE including Deep vein thrombosis and pulmonary embolism will be assessed

Deep vein thrombosis in Non-Hodgkin's Lymphoma

Ottinger et al (1995) analyzed incidence, risk factors, causes and prognostic significance of venous thromboembolism (VTE) in high-grade non-Hodgkin's lymphoma (HG-NHL) in a prospective clinical trial. In 593 patients, they reported a 6.6% incidence of VTE, with 77% of all cases occurring before or within the first 3 months of chemotherapy. Vessel compression by HG-NHL was identified as the leading cause of VTE.

In lymphoma patients receiving lenalidomide, DVT and PE were reported in 7 (3.2%) and 6 (2.8%) of 266 patients with relapsed or refractory aggressive NHL receiving lenalidomide in clinical studies NHL-002 and NHL-003 (Wiernik 2006, Witzig 2011). DVT and PE were reported in 0 (0%) and 1 (2.3%) of 43 patients with indolent relapsed refractory NHL (Witzig 2009). Anti-thrombotic prophylaxis was not suggested in NHL-001 or NHL-002 but required for patients considered to be high risk of developing DVT in NHL-003.

Unlike the increased risk of DVT reported when adding lenalidomide to dexamethasone in multiple myeloma patients, there is no evidence to suggest an increased risk of DVT in lymphoma patients receiving lenalidomide as single agent.

Nonetheless, in the current study, it is recommended that patients randomized to the rituximab-lenalidomide who are considered to be at high risk for DVT receive anti-thrombotic prophylaxis (see Section 9.1.2) and all patients will be closely monitored for VTE including Deep vein thrombosis and pulmonary embolism.

5.4. Follow-up assessments

Follow-up period will start at the end of treatment (120 weeks) or at treatment discontinuation (if applicable).

Patient will be followed every 3 months (12 weeks) for the first two years and every 6 months (24 weeks) up to end of follow-up period.

Follow-up assessments include :

- Physical examination including ECOG PS
- Hematology laboratory evaluations (RBC count, hemoglobin, hematocrit, WBC count and differential, ANC, and platelet count)
- CT scans every 6 months (24 weeks) for 5 years and then every year until disease progression/relapse or end of follow-up period.
- Serum immunoglobulin levels every 6 months/24 weeks (± 4 weeks) for 1 year of follow-up.

5.5. Progression/relapse

Relapse/progression will be determined as per Cheson 1999 criteria (Progressive disease should be based on CT scan.

A pathological confirmation by biopsy of the lesion should be done if possible.

6. STUDY PROCEDURES

6.1. Informed consent

Written informed consent written and approved in compliance with local regulatory authority will be obtained from each patient prior to being randomized in the trial. Specific informed consent should be signed for biological studies and genetic analysis. The informed consent for biological studies and genetics analysis should be signed before sampling.

The patient and the investigator will date and sign the informed consent form.

The investigator shall provide a copy of the signed consent to the study patient; the original shall be maintained in the investigator's study file.

6.2. Pathological diagnosis

Histopathology central review process has become in the last years a common and prerequisite procedure for clinical trials in the field of lymphomas. It requires both a histopathological and immunohistochemical approach using an appropriate panel of antibodies according to the morphological pattern and, in some instances, further molecular or genetic analysis. A mandatory pathological review will be organized for all patients included in the trial. The goal of this central review will be to confirm the diagnosis and to classify precisely the malignancy according to the WHO classification 2008.

Therefore for each patient, the investigator will be requested to submit a registration form along with a copy of the histopathological report where the name and address of the pathologist having diagnosed the lymphoma will be easily identified as well as a copy of the bone marrow report.

All the requested tumor paraffin embedded blocks from the formalin fixed sample (that was used for diagnosis), or 10 unstained slides, and bone marrow biopsy (or 5 unstained slides with H&E) will be collected

At reception, routinely stained sections will be assessed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a pathological review will be organized, and a consensus diagnosis will be entered on review form. This review form will then be sent to the clinical coordinator and to the pathologist coordinator.

Initial tumor block will also be used to make tissue microarray (TMA) and tissue core for DNA extraction; both will be used to study the expression of markers known to influence the prognosis of follicular lymphoma.

When the review process is completed, tissue array and tissue core analysis are completed, a pathological report will be sent to the initial pathologist as well as the investigator at the enrolling centre and the remaining pathologic material will be sent back to the initial pathologist.

6.3. CT scan Review

A central review of CT scan is mandatory and organized. For each patient, when applicable, data and images of CT scan performed at following timepoints will be reviewed by a panel of CT experts:

- screening,
- 12 weeks after the first dose date (± 1 week),

- 24 weeks after the first dose date (± 2 weeks),
- 36 weeks after the first dose date (± 2 weeks),
- 52 weeks after the first dose date (± 2 weeks),
- 76 weeks after the first dose date (± 3 weeks),
- 100 weeks after the first dose date (± 3 weeks),
- 120 weeks after the first dose date (± 4 weeks)
- Every 6 months (± 4 weeks) for 5 years and then every year (± 4 weeks) until disease progression or relapse
- to document progression/relapse

The central analysis of the imaging should be done according to IWG response criteria (Cheson 1999) for the NHL.

For CTs, the reviewer panel is composed by 3 CT experts for review of the CTs according to the following rules:

- 2 reviewers will analyze the CT scans independently.
- In case of disagreement between the 2 reviewers, the 3rd reviewer will analyze the CT exams independently.

6.4. PET scan Review

A central review of the PET scan is organized. For each patient when applicable, the data and images of Pet scan performed at following time points will be reviewed by a panel of PET experts:

- screening
- 24 weeks after the first dose date (± 2 weeks),
- 76 weeks after the first dose date (± 3 weeks)
- 120 weeks after the first dose date (± 4 weeks).

For PETs, The reviewer panel is composed by 3 nuclear physicians for review of the PETs according to the following rules:

- 2 reviewers will analyze the PET scans independently.
- In case of disagreement between the 2 reviewers, the 3rd reviewer will analyze the PET exams independently.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

7. CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

7.1. Premature withdrawal from trial intervention

Circumstances that lead to premature withdrawal of a patient from the trial must be reported by the investigator on the appropriate CRF page.

Criteria for subject withdrawal include (but are not limited to) :

- Death,

- Toxicity (adverse event),

- Disease progression/relapse,

- Concomitant disease,

- Non compliance (including loss of subject to follow-up),

- Voluntary withdrawal,

- Major protocol violation, including initiation of alternate anti-neoplasic therapy.

Patients should however remain in the trial for the purposes of follow-up and data analysis.

7.2. Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states their wish not to contribute further data to the study, the relevant sponsor contact should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. However, data up to the time of consent withdrawal will be included in the data reported for the study.

7.3. Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained by investigator since one year and at least three unsuccessful documented attempts of contact are available in source documentation.

8. ADVERSE EVENTS

8.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of study drug(s). AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported immediately (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

8.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

8.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

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

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

SPM will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in (see Section 7.5). This includes any SPM, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the ICD up to and including the follow-up period of up to 10 years. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- A procedure or hospitalization for progression/relapse investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling).
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen 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 study drug(s), action taken regarding study drug(s), and outcome.

8.2.2. Severity

For both AEs and SAEs, the Investigator must assess the severity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the NCI CTCAE should be evaluated for severity/intensity according to the following scale:

Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5 = Death - the event results in death]

Specific NCI Working Group or other criteria pertinent to the indication may also be used as applicable.

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as “serious” which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

8.2.3. Causality

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

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

If an event is assessed as suspected of being related to a comparator, ancillary or additional study drug(s) that has not been manufactured or provided by Sponsor, please provide the name of the manufacturer when reporting the event.

8.2.4. Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

8.2.5. Action Taken

The Investigator will report the action taken with study drug(s) as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

8.2.6. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

8.3. Abnormal laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of study drug(s) dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

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

8.4. Pregnancy

8.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the patient is on IP, or within 28 days of the patient's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form. The exposure of any pregnant female (e.g., caregiver or pharmacist) to lenalidomide is also an immediately reportable event.

The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female patient until completion of the pregnancy, and must notify immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is

related to the in utero exposure to the IP should also be reported immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

8.4.2. Male Patients

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

8.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page of the CRF. All SAEs must be reported (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

SPM will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the patient is in. This includes any SPM, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the ICD up to and including the follow-up period of 10 years. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and patient's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study drug(s)) that occur during the study (from the time the patient signs informed consent to 28 days after the last dose of study drug (s), and those made known to the Investigator at anytime thereafter that are suspected of being related to study drug(s). SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with the IRB/EC.

Safety Queries

Queries pertaining to SAEs will be communicated to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g., missing causality assessment) may be handled by phone.

8.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Drug Safety of the sponsor or its authorized representative will determine the expectedness of events suspected of being related to lenalidomide based on the Investigator Brochure.

Adverse events such as disease progression, death related to disease progression (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the sponsor to regulatory authorities.

the sponsor or its authorized representative shall notify the Investigator of the following information

- Any AE associated with the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to patients.

The Investigator must keep copies of all pertinent safety information on file.

8.7. Follow up of Serious Adverse events

Any SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported as soon as information becomes available.

9. STATISTICAL CONSIDERATIONS

This phase 3 study (RV-FOL_Gelarc-0683C) is a companion to the RV-FOL-Gelarc-0683 study with a combined enrollment target of 1000 patients and will enroll 250 patients. The data from both studies will be collected into one database and the statistical analyses as described in this Section will be performed on the combined total of patients enrolled into both studies. A single data safety monitoring committee (DSMC), central pathology, and Central Independent Review committee (IRC) will be utilized for these two studies.

9.1. Overview

The objective of this statistical analysis is to investigate efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma.

Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG (Cheson 1999) criteria.

All statistical analyses specified in this protocol will be conducted using *SAS*® version 9.1.3 or higher.

9.2. Study Population Definitions

For this study, the following three populations will be defined and used in the analysis and presentation of the data.

Intent-to-treat (ITT) population: The ITT population is defined as all patients who are randomized into the trial, regardless of whether they received study treatment or not.

The ITT population will be used for the primary efficacy analysis. Patients will be analyzed according to the treatment arm to which they are initially assigned.

Modified ITT (mITT) population: The mITT population is defined as all randomized patients who have received at least one dose of study drug, have confirmed diagnosis of follicular lymphoma with no prior systemic treatment for lymphoma, have baseline and at least one post-baseline tumor assessment for efficacy.

The efficacy analysis will also be performed on the mITT population as supportive evidence and/or sensitivity analysis. Patients will be analyzed according to the treatment arm to which they are initially assigned.

Safety population: The safety population is defined as all patients who have received at least one dose of study drug. The safety population will be used for all safety analysis. Patients will be analyzed according to the treatment which they actually received.

9.3. Sample Size and Power Considerations

Sample size calculation is based on providing adequate power to evaluate treatment effect on the co-primary efficacy endpoints.

The co-primary efficacy endpoints are complete response (CR/CRu) rate at 120 weeks and PFS.

It is hypothesized that the complete response (CR/CRu) rate at 120 weeks is 60% in the control arm and 72% in the experimental arm. For 90% power to detect this difference with two-sided $\alpha = 0.05$, a total of 644 patients (322 in each arm) will be required.

It is hypothesized that the median PFS is 83 months in the control arm, and there is a 30% increase in the median PFS in the experimental arm (corresponding hazard ratio of 0.7692). For 80% power to detect this difference with two-sided = 0.05, a total of 456 progression/relapse/death events will be required.

Therefore, for an enrollment rate of 10 patients per month in the first six months, 25 patients per month in the next 11 months, and 30 patients per months thereafter with 6% dropout rate per year, a total of 1000 patients in 1:1 ratio to the two treatment arms (500 in each arms) will be needed, with a 40-month accrual period and up to 10 years follow-up. The analysis of PFS will occur in about 142 months when the required 456 progression/relapse/death events are expected to be observed.

The assumptions used in sample size calculations are derived from available literature, especially from the published results of PRIMA and STiL studies. For the proposed sample size, it should be noted that any reasonable deviations from these assumptions have limited impact on the power of the test. For example, if the complete response (CR/CRu) rate at 120 weeks is down to 50% in the control arm instead of 60%, the proposed sample size of 644 patients still have more than 85% power to detect a 12% rate difference. If the median PFS reduces to 70 months in the control arm instead of 83 months, it still requires a total of 456 events to detect a 30% increase in the median PFS, and the only impact is that the study duration will be reduced to 113 months if 1000 patients are to be randomized.

9.4. Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum), while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

Subject's demographics and baseline characteristics will be summarized for the ITT population.

Subject disposition (analysis population allocation, randomized, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment arms. Protocol deviations will be summarized using frequency tabulations.

9.5. Efficacy Analysis

9.5.1. Co-Primary Efficacy Endpoints

Complete Response (CR/CRu) Rate at 120 weeks

The tumor response data will be assessed by the IRC using the IWG (Cheson 1999) criteria.

Progression Free Survival (PFS)

PFS is an accepted endpoint of clinical benefit for previously untreated FL patient and was the basis for the recent approval of rituximab maintenance in this population (Salles 2011). The disease progression status will be assessed by IRC using the IWG (Cheson 1999) criteria. PFS is defined as the time from randomization into the study to the first observation of documented disease progression or death due to any cause. If a subject has not progressed or died, PFS will be censored at the time of last visit with adequate assessment. If a subject received other anti-cancer treatment for follicular lymphoma before progression, the CT/MRI assessments should

continue as scheduled until disease progression or death which will be counted as events.

Various censoring rules will be considered in sensitivity analyses. Detailed censoring rules for PFS will be provided in the Statistical Analysis Plan based on "Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics" (see reference http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf) and "Methodological Considerations For Using Progression-Free Survival As Primary Endpoint In Confirmatory Trials For Registration" (http://www.emea.europa.eu/pdfs/human/ewp/26757506en.pdf).

9.5.2. Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed using appropriate statistical methods.

- Time to Treatment Failure (TTF),
- Event Free Survival (EFS),
- Time to Next Anti-Lymphoma Treatment (TTNLT),
- Time to Next Chemotherapy Treatment (TTNCT),
- Overall Survival (OS)
- ORR rate at 120 weeks by IWG 1999 criteria and
- Health related quality of life as measured by the EORTC QLQ-C30

TTF will be measured from the date of randomization to the date of first documented treatment discontinuation for any reason, including disease progression, treatment toxicity, and deaths.

EFS will be measured from the date of randomization to the date of first documented progression, relapse, and initiation of a new anti-lymphoma treatment or death by any cause. Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

TTNLT will be measured from the date of randomization to the date of first documented administration of any new anti-lymphoma treatment (chemotherapy, radiotherapy, radio-immunotherapy, immunotherapy). Patients continuing in response or who are lost to follow-up will be censored on their last visit date. Patients who died (due to any cause) before having received a new anti-lymphoma treatment will be included in the statistical analysis with death being counted as an event.

TTNCT will be measured from the date of randomization to the date of first documented administration of new chemotherapy or new cytotoxic agent. For any given patient, the TTNCT may be the same as TTNLT. Patients continuing in response or who are lost to follow-up will be censored on their last visit date. Patients who died (due to any cause) before having received a new chemotherapy treatment will be included in the statistical analysis with death being counted as an event.

9.5.3. Analysis Method

The primary efficacy analysis will be based on the ITT population. Analysis based on the mITT population is supportive.

The number and percent of patients with complete response (CR/CRu) at 120 weeks will be tabulated by treatment arm. The experimental arm will be declared superior if the two-sided p-value from a chi-square test is ≤ 0.05 in favor of the experimental arm. If the experimental arm is declared superior than the control arm on this endpoint, the study will still continue to collect data for the PFS analysis. The primary analysis will be performed using a stratified Cochran-Mantel-Haenszel (CMH) test to adjust for possible confounding effects of the stratification factors: FLIPI

score (0-1 vs 2 vs 3-5), Age (>60 vs ≤ 60), longest diameter of the largest node (> 6 v ≤ 6 cm). The un-stratified test will be a supportive analysis.

PFS will be compared between the two treatment arms when the required 456 progress/relapse/death events are observed. The Kaplan-Meier estimates of PFS function will be provided. If a subject has a missing or incomplete CT scan, all other available CT scans or MRIs of the subject will still be used for the analysis. The experimental arm will be declared superior if the two-sided p-value from a stratified log-rank test is ≤ 0.05 in favor of the experimental arm. Conventionally, hazard ratio with two-sided 95% confidence interval (CI) will be estimated using the Cox proportional hazards model. But the treatment effect will be determined by the p-value, not by this 95% CI. The un-stratified log-rank test will be a supportive analysis. Subgroup analysis for PFS will be performed as appropriate.

The analyses of secondary and exploratory efficacy endpoints will be conducted at the same time when analyses of the primary and co-primary efficacy endpoints are performed. Overall survival (OS) comparison will also be performed at the end of study.

9.6. Safety Analysis

Safety analysis will include all patients in the Safety population.

Study medication exposure will be summarized for each treatment arm including duration of study medication, total dose taken, and dose reductions.

Adverse events, vital sign measurements, clinical laboratory measurements, and concomitant medications will be summarized by treatment arm.

AEs will be coded according to medical dictionary for drug regulatory activities (MedDRA) and classified using the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE). The incidence rates of AEs will be tabulated by system organ class and preferred term. Subsets of AEs to be summarized include serious AEs (SAEs), AEs of interest including SPM, events of all CTCAE grade severities, suspected treatment-related AEs, and events that resulted in withdrawal of study medication. The most severe grade of each preferred term for a subject will be utilized for summaries of adverse events by NCI CTCAE grade. All AEs with corresponding attributes will be displayed in a by-subject listing. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, suspected treatment-related events, and serious adverse events will also be displayed in separate by-subject listings.

Laboratory data will be summarized according to the NCI CTC severity grade.

9.7. Interim Analysis

For the co-primary endpoint of the complete response (CR/CRu) rate at 120 weeks, one interim analysis and one primary analysis is pre-planned. The interim analysis will be performed for the first 200 patients, and the primary analysis for the co-primary endpoint of complete response (CR/CRu) will be performed for the total of 644 patients. The purpose of the interim analysis is to check for futility to see if the trial needs to stop early.

Moreover, a first futility analysis will be done to evaluate the complete response (CR/CRu) rate as determined by IRC at 6 months of treatment for the first 200 patients.

Appropriate futility boundaries will be described in detail in a separate Statistical Analysis Plan (SAP).

10. STUDY COMMITTEES

10.1. Independent Data Safety Monitoring Committee (DSMC)

An independent external Data Safety Monitoring Committee (DSMC) will periodically review ongoing safety data throughout the study and make recommendations to the sponsor for any safety concerns.

In addition, the DSMC will also review efficacy data for futility. In particular, DSMC will conduct two early futility analyses. The first futility analysis is to evaluate the complete response (CR/CRu) rate as determined by IRC at 6 months of treatment for the first 200 patients. The DSMC will also review the results of the pre-planned interim analysis described above.

10.2. Independent Review Committee (IRC)

For complete response rate assessment an independent review of all CT scans according to an independent review charter.

Bone Marrow examination will be reviewed by GELA-P in patients with positive bone marrow at screening if a) they otherwise achieve CR and the repeat biopsy will be taken within 28 days after first achieving CR or b) they are in PR at 120 weeks.

11. REFERENCES

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RELEVANCE

Rituximab Lenalidomide Versus ANy ChEmotherapy

A PHASE 3 OPEN-LABEL RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE (CC-5013) VERSUS RITUXIMAB PLUS CHEMOTHERAPY FOLLOWED BY RITUXIMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA

GELARC

GELARC : **G**roupe d'**E**tude des **L**ymphomes de l'**A**dulte - **R**echerche **C**linique

: Centre Hospitalier Lyon Sud - Secteur Sainte Eugénie - Bâtiment 6D - Chemin du Grand Revoyet - 69495 Pierre Bénite Cedex - France

PROGRAM COORDINATION CENTER:	**GELARC**

Version and date of Protocol: Protocol v2.0 - 17 October 2011

EudraCT Number: 2011-002792-42

Authorized by:

Coordinating Investigator	Date and signature:
Co-Coordinating Investigator	Date and signature:

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STUDY OBJECTIVES

1.1 Primary Objective

The primary objective of the study is to compare the efficacy of rituximab plus lenalidomide to rituximab plus chemotherapy followed by Rituximab in patients with previously untreated follicular lymphoma. Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the Independent Review Committee (IRC) using the IWG (Cheson, 1999) criteria

1.2 Secondary objectives

The secondary objectives of the study are:

- To compare the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab using other parameters of efficacy:
    - Time to Treatment Failure (TTF), Event Free Survival (EFS), Time to Next Anti-Lymphoma Treatment (TTNLT), Time to Next Chemotherapy Treatment (TTNCT), Overall Survival (OS) and ORR rate at 120 weeks by IWG 1999 criteria.
    - Health related quality of life as measured by the EORTC QLQ-C30 (Appendix C)
- To compare the safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab.

2 OVERALL STUDY DESIGN

2.1 Study Design Rational

Follicular lymphoma (FL) is a distinct histologic type within B-cell NHL further divided by the WHO classification (2007) into three different grades. Within grade 3, grade 3a is differentiated histopathologically from 3b. FL grade is treated in a manner similar to DLBCL. Thus, FL grade 3b is excluded from this study.

Rituximab has become the backbone of first line treatment for follicular lymphoma patients who are in need of therapy. Recent studies have established several standard-of-care immuno-chemotherapy regimens in previously untreated FL. In most phase 3 studies in front line FL, it has not been possible to demonstrate OS benefit, and PFS has been used to assess efficacy. These studies showed that the addition of rituximab to multi-agent chemotherapy regimens led to significantly longer PFS and sometimes longer OS. These regimens are R-CVP, R-CHOP and R-bendamustine. Which of these regimens are considered standard of care varies depending on the geographic location and physician preference. Furthermore, rituximab-maintenance studies have shown improved PFS, and European and US regulatory agencies recently approved rituximab as a first-line maintenance treatment for patients with follicular lymphoma whose disease has responded to initial induction therapy based upon the results of the PRIMA study (Salles 2011).

The current study is designed to investigate the efficacy and safety of lenalidomide therapy in patients with previously untreated FL. The multicenter nature of the study provides assurance that

the results are likely to have general applicability. The inclusion of a control arm, and the fact that the Investigator must select the Investigator's choice option of a standard-of-care for the subject before randomization, is intended to provide a realistic comparison to current standard-of-care in this patient population. Subject eligibility criteria are consistent with those used in other studies of this population.

Patients are required to have measurable disease to facilitate the accurate assessment of CR/CRu, which is a direct measure of the co-primary efficacy endpoint CR/CRu rate at 120 weeks. The International Working Group (IWG) response criteria were selected to provide an international standard for the assessment of lymphoma (Cheson 1999). The use of this tool will ensure that data across centers are evaluated consistently and also allow for direct comparison to historical data.

Safety will be assessed by evaluating AEs and laboratory data. AE and abnormal laboratory value severity will be graded using version 4.03 of the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE).

Known toxicities of lenalidomide, given alone or in combination with rituximab have been reported. In addition, in the clinical database and safety database of the sponsor, tumor flare, tumor lysis and venous thromboembolus have been reported.

Monitoring for tumor flare and venous thromboembolic events (VTE – including pulmonary embolism and deep vein thrombosis) will be performed along with safety measures that are routinely assessed in investigational studies of hematologic malignancies. VTE prophylaxis is recommended for patients in the lenalidomide arm who are at high risk for a thromboembolic event. VTE, TFR and TLS will be recorded as AEs.

2.2 Study Design

This multi-center, open-label study is designed to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab. The overall study design is described in Figure 2. The study is divided into the Screening Period, Treatment Period, and Follow-up Period.

Once a subject gives written consent, the subject may enter the Screening Period, which is permitted to last up to 4 weeks. During the Screening Period, the investigator will choose one standard-of-care regimen ("investigator's choice") for the subject from a list of permitted choices of rituximab-containing chemotherapy regimens. In addition, during the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either experimental arm (rituximab plus lenalidomide) versus control arm ("investigator's choice" of rituximab-chemotherapy).

It is noted that subject eligibility will be based on investigator assessment. However, subject's disease will be assessed by central pathology review to confirm the FL diagnosis using formalin-fixed paraffin embedded (FFPE) tumor or lymph node tissue submitted in the Screening Phase or obtained from the Screening biopsy.

The subject will enter the Treatment Period once the subject has fulfilled the required assessment in the Screening Period and has been randomized. The treatments will be given as described in detail in Section 4. The patients will receive protocol-specified treatments, until :

(1) Inability to achieve a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment),

(2) Inability to achieve a response by 24 weeks (second CT assessment),

(3) Relapse or progression of disease,

(4) Withdrawal of consent or

(5) Unacceptable toxicity.

All randomized patients are followed for progression free survival and overall survival. This includes patients who discontinue the study early for any reason without documented evidence of disease progression.

Upon completion of the required treatments, the subject will enter the Follow-Up Period. In the follow-up period, the patients will be followed for disease progression, next lymphoma treatment (including next chemotherapy) and overall survival.

All protocol defined efficacy assessments will be conducted by Central Review including central radiology and clinical review by an Independent Review Committee (IRC). However, a subject's withdrawal from the study for disease progression or failure to achieve threshold clinical activity at the 12 and 24 week assessments [see points (1) and (2) above] will be based upon investigator assessment.

Since the study endpoint is PFS based on computed axial tomography (CT) as determined by IRC, progression will be based on CT scans.

For suspected progression based on clinical evaluation, a CT scan must be available demonstrating unequivocal progression.

For equivocal progression based on CT findings, the site Investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases of equivocal progression, immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if the PD is not confirmed by central radiology review, the patient should continue treatment as per protocol.

In limited instances where progression is evident only by assessments other than CT, CT scans must still be obtained along with the non-CT documentation of progression.

The same methodology will be performed for equivocal cases of threshold clinical activity at the 12 and 24 week assessments. That is, in equivocal cases of threshold clinical activity, the site investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if threshold clinical activity is confirmed by central radiological review, the patient should continue treatment as per protocol.

DSMC will conduct two early futility analyses, the first, 6 months after the 200th subject has been randomized and the second, 120 weeks after the 200th subject has been randomized. The first futility analysis is to evaluate the complete response (CR/CRu) rate at 6 months of treatment for the first 200 patients. The second futility analysis is to evaluate the complete response (CR/CRu) rate at 120 weeks for the first 200 patients.

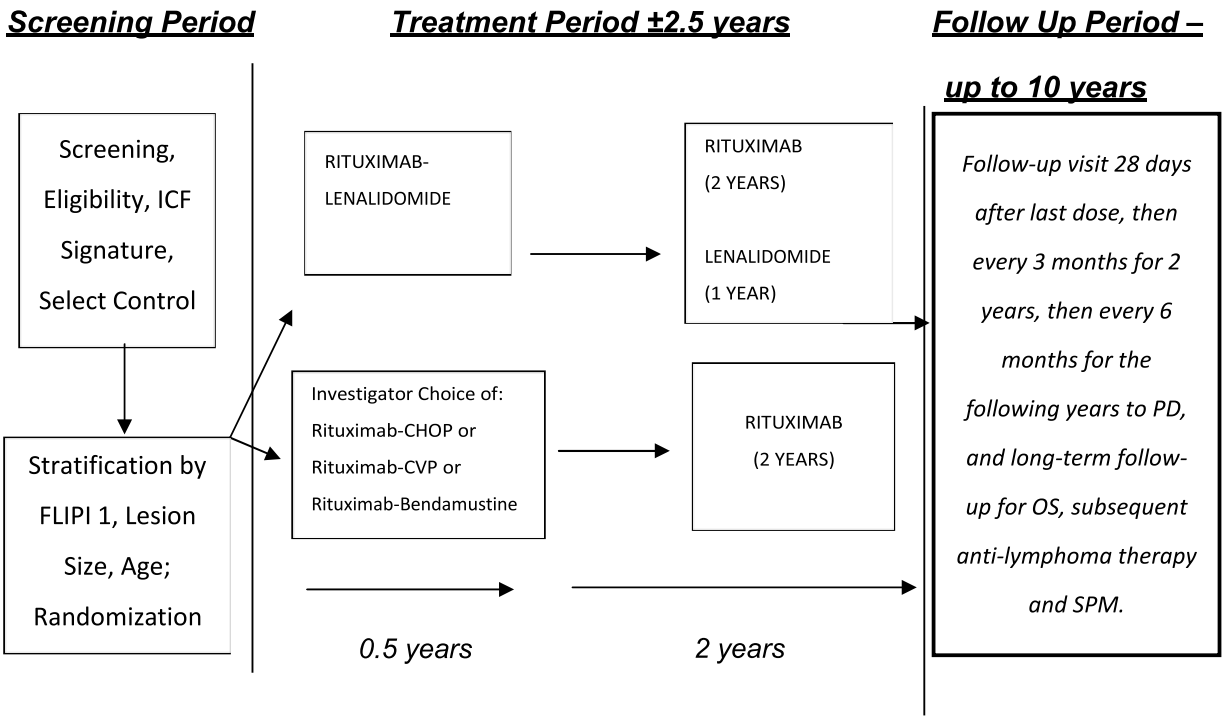
Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG (Cheson 1999) criteria. Because all protocol specified analyses including early futility analyses are based on IRC review, all CT scans must be sent for central review as soon as possible.

See Section 8 for a detailed description of Statistical Analyses.

The study will be conducted in compliance with Good Clinical Practices (GCPs).

Lenalidomide concentrations will be determined in patients who consent to this analysis in selected countries and sites.

Figure 2: Overall Study Design



All randomized patients are followed for progression free survival and overall survival. Schedule of Assessments. This includes patients who discontinue the study early for any reason without documented evidence of disease progression.

2.3 Study Duration

The duration of the entire study will be approximately 12-13 years. Patients receive two-four weeks of screening, approximately 2.5 years of treatment and up to 10 years of follow-up.

The expected accrual duration is 40 months. Patients will be stratified by FLIPI score (0-1 v 2 v 3-5), age (>60 v ≤ 60) and longest diameter of the largest node (> 6 v ≤ 6 cm) and randomized to receive either rituximab-lenalidomide or Investigators Choice of R-CHOP, R-CVP, or R-B.

Randomized patients will receive therapy for approximately 2.5 years and followed until relapse or progression. After relapse or progression, OS, anti-lymphoma therapy and second primary malignancy (SPM) data will continue to be collected.

3 STUDY POPULATION

Patients must have an investigator-assessed diagnosis of Stage II-IV follicular lymphoma, grade 1-3a, have not been previously treated for their lymphoma other than local radiation for localized disease, have signs or symptoms of lymphoma requiring treatment, and have

adequate bone marrow function, liver function and renal function.

3.1 Inclusion criteria

Patients must satisfy all the following criteria to be enrolled in the study:

1. Histologically confirmed CD20+ follicular lymphoma grade 1, 2 or 3a as assessed by the investigators:

   - a formalin fixed paraffin embedded specimen taken within 18 months before signing informed consent must be available for central review, and

   - a formalin fixed paraffin embedded bone marrow biopsy taken within 18 months before subject signing informed consent must be available for central review.

2. Have no prior systemic treatment for lymphoma.

3. Must be in need of treatment as evidenced by at least one of the following criteria:

   - Bulky disease defined as:
     - a nodal or extranodal (except spleen) mass >7cm in its greater diameter or,
     - involvement of at least 3 nodal or extranodal sites (each with a diameter greater than ≥3 cm)

   - Presence of at least one of the following B symptoms:
     - fever (>38C) of unclear etiology
     - night sweats
     - weight loss greater than 10% within the prior 6 months

   - Symptomatic splenomegaly

   - Compression syndrome (ureteral, orbital, gastrointestinal)

   - Any one of the following cytopenias due to lymphoma:
     - hemoglobin < 10g/dL (6.25 mmol/L)
     - platelets $<100 \times 10^9$/L , or
     - absolute neutrophil count (ANC) $< 1.5 \times 10^9$/L

   - Pleural or peritoneal serous effusion or (irrespective of cell content)

4. Bi-dimensionally measurable disease with at least one mass lesion > 2 cm that was not previously irradiated.

5. Stage II, III or IV disease.

6. Must be ≥ 18 years and sign an informed consent.

7. Performance status ≤ 2 on the ECOG scale.

8. Adequate hematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) within 28 days prior to signing informed consent, including:
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   - Platelet count $\geq 75 \times 10^9$/L
   - Hemoglobin ≥ 8.0 g/dl (5 mmol/L)

9. Must be able to adhere to the study visit schedule and other protocol requirements.

10. Females of childbearing potential (FCBP) receiving lenalidomide must:

    Have two negative pregnancy tests as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices complete abstinence from heterosexual contact.

    Either commit to complete abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.

11. Male patients receiving lenalidomide must:

    Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

    Agree to not donate semen during study drug therapy and for 28 days after discontinuation of study drug therapy.

12. All patients receiving lenalidomide must:

    Have an understanding that the study drug could have a potential teratogenic risk.

    Agree to abstain from donating blood while taking study drug therapy and for 28 days after discontinuation of study drug therapy.

    Agree not to share study medication with another person.

    Agree to be counseled about pregnancy precautions and risk of fetal exposure

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

13. For all patients receiving Rituximab:

    Women must not breast feed and must use effective contraception must not be pregnant and agree not to become pregnant during participation in the trial and during the 6 months thereafter. Men must agree not to father a child during participation in the trial and during the 6 months thereafter.

3.2 Exclusion criteria

The presence of any of the following will exclude a subject from enrollment:

1. Clinical evidence of transformed lymphoma by investigator assessment.

2. Grade 3b follicular lymphoma.

3. Patients taking corticosteroids during the last 4 weeks, unless administered at a dose equivalent to ≤ 10 mg/day prednisone (over these 4 weeks).

4. Major surgery (excluding lymph node biopsy) within 28 days prior to signing informed consent.

5. Seropositive for or active viral infection with hepatitis B virus (HBV):

   - HBsAg positive

   - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA

   Note:
   - Patients who are HBsAg negative and viral DNA negative are eligible
   - Patients who are seropositive due to a history of hepatitis B vaccine are eligible.

6. Known seropositive for, or active infection with hepatitis C virus (HCV).

7. Known seropositive for, or active viral infection with human immunodeficiency virus (HIV).

8. Life expectancy < 6 months.

9. Known sensitivity or allergy to murine products.

10. Prior history of malignancies, other than follicular lymphoma, unless the subject has been free of the disease for ≥ 10 years. Exceptions include a history of previously ***treated***:

    - Localized non-melanoma skin cancer

    - Carcinoma in situ of the cervix

11. Prior use of lenalidomide.

12. Neuropathy > Grade 1.

13. Presence or history of CNS involvement by lymphoma.

14. Patients who are at a high risk for a thromboembolic event and are not willing to take venous thromboembolic (VTE) prophylaxis.

15. Any of the following laboratory abnormalities:

    -serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) > 3x upper limit of normal (ULN), except in patients with documented liver or pancreatic involvement by lymphoma

    -total bilirubin > 2.0 mg/dl (34 µmol/L) except in cases of Gilberts Syndrome and documented liver involvement by lymphoma

- creatinine clearance of < 30 mL/min

16. Uncontrolled intercurrent illness.

17. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

18. Pregnant or lactating females.

19. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study, or which confounds the ability to interpret data from the study.

4 STUDY TREATMENTS

4.1 Drugs description

Lenalidomide will be supplied as 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg capsules for oral administration and labeled as IP.

Commercially available IV formulation of Rituximab background therapy and standard of care therapy, i.e. cyclophosphamide, doxorubicin, vincristine and bendamustine will be used

Commercially available prednisone will also be used as oral formulation. Standard of care chemotherapy must be available by prescription, generally reimbursed by the health system and used routinely in previously untreated FL patients at the center.

4.2 Treatment schedule and design

4.2.1 Experimental Arm : Rituximab - Lenalidomide

Patients randomized to receive rituximab-lenalidomide will receive six cycles of lenalidomide 20 mg daily on days 2-22 every 28 days. Patients exhibiting a CR/CRu after six cycles then receive 12 cycles of 10 mg lenalidomide daily on days 2-22 every 28 days for a total of 18 cycles. Patients exhibiting a PR after six cycles receive an additional 3 to a maximum of 6 cycles of the 20 mg lenalidomide dose until they achieve a CR/CRu at which time they receive the 10 mg lenalidomide dosing for 9 or 6 cycles respectively for a total of 18 cycles.

Patients who remain in PR after the additional 6 cycles will receive 10 mg lenalidomide dosing for a total of 18 cycles.

All patients randomized to receive rituximab-lenalidomide receive rituximab, 375 mg/m^2 on days 1, 8, 15 and 22 of cycle 1, day 1 of cycles 2 to 6; 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12. Lenalidomide treatment is continued for 18 cycles or until disease progression, unacceptable toxicity, or voluntary withdrawal. In addition, patients who do not achieve a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment), and patients who do not achieve a response by 24 weeks (second CT assessment) will be withdrawn from treatment and followed for survival and PFS using the same schedule of assessments as patients continuing treatment.

Lenalidomide dosing will be based on patients creatinine clearance calculated using the Cockcroft-

Gault or MDRD formula. Creatinine clearance should be calculated using ideal body weight or actual, whichever is less.

Patients who have a creatinine clearance ≥ 60 mL/min will receive oral lenalidomide that is initiated on Day [D] 2 of Cycle 1 at a dose of 20 mg [p.o.] once daily for 21 days (D2 – D22) in each 28 day cycle

Patients who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min] will receive a lower starting dose of lenalidomide of 10 mg once daily for 21 days (D2 – D22) in Cycle 1 and Cycle 2.

After completion of Cycle 2, if the subject remains free of Grade 3 or Grade 4 toxicity, the dose may be increased to a maximum of 15 mg once daily for 21 days (D2 – D22) starting on day 2 of cycle 3.

Lenalidomide should be taken at approximately the same time every day. There is no requirement for taking lenalidomide with or without food, or with or without certain types of foods or liquids. If a subject misses a dose of lenalidomide and it is within 12 hours of their normal dosing time, the subject should be instructed to make up the missed dose, and to then take their next dose according to their regular schedule. Lenalidomide concentration is low at 12 hours post dose, therefore making up a missed dose and then resuming regular dosing with a greater than or equal to (≥) 12 hour interval between the two doses will not cause considerable drug accumulation.

4.2.2 Standard Arm : Investigators Choice

Patients randomized to receive investigators choice will receive ONE of the following

Rituximab-CHOP: with six cycles of R-CHOP in 21 day cycles followed by two 21 day cycles of 375 mg/m^2 rituximab; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles,

OR

Rituximab-CVP: with eight cycles of R-CVP in 21 day cycles; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles,

OR

Rituximab-Bendamustine: with rituximab 375 mg/m^2 (day 1) plus bendamustine 90 mg/m^2 (days 1 + 2) every 28 days for six cycles; and 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles.

Patients who do not achieve the threshold clinical activity of 1) 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment) or 2) a response by 24 weeks (second CT assessment) will be withdrawn from treatment and followed for survival and PFS using the same schedule of assessments as patients continuing treatment.

4.2.3 Rituximab background therapy

The planned dose of rituximab is 375 mg/m^2 in all regimens. Schedule is as described for individual regimens. Premedication should be administered (see package insert).

All dosage calculations for rituximab and chemotherapies will be based on the subject‘s body surface area (BSA), using actual weight for calculations. This will be determined on the

first day of study drug administration of Cycle 1. For rituximab, no dosage adjustments should be performed.

For large changes in body weight compared to baseline (≥ 10%), the dose of chemotherapy may be modified accordingly. However, the same dose of rituximab should be infused regardless of any fluctuations in body weight.

4.2.4 R-CHOP regimen

Standard CHOP chemotherapy consists of cyclophosphamide, doxorubicin, vincristine and prednisone.

The doses of CHOP components are:

Cyclophosphamide, 750 mg/m2 IV on day 1

Doxorubicin, 50 mg/m2 IV on day 1

Vincristine, 1.4 mg/m2 (2 mg cap) IV on day 1

Prednisone, 100 mg/day PO on days 1-5

CHOP will be administered according to the standard preparation and infusion procedures of each investigational site.

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For subject ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Rituximab is administered on day 1 for six cycles with CHOP in 21 day cycles followed by two 21 day cycles of 375 mg/m^2 rituximab; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert).

4.2.5 R-CVP regimen

Standard CVP chemotherapy consists of cyclophosphamide IV push, vincristine IV bolus and prednisone PO. The doses of CVP components are:

Cyclophosphamide 750 mg/m^2 day 1

Vincristine 1.4 mg/m^2 (2 mg cap) day 1,

Prednisone 40 mg/m^2 (5 days 1-5)

CVP will be administered according to the standard preparation and infusion procedures of each investigational site.

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For subject ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Rituximab is administered on day 1 for eight cycles with CVP in 21 day cycles and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert).

4.2.6 R-Bendamustine regimen

Bendamustine is administered at 90 mg/m^2 on days 1 + 2 every 28 days for six cycles.

Bendamustine will be administered according to the standard preparation and infusion procedures of each investigational site. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Rituximab is administered on day 1 for six cycles with bendamustine in 28 day cycles; and 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert)

4.3 Dose Modifications

4.3.1 Lenalidomide Dose Modifications

The lenalidomide dose for each subject will be interrupted and/or modified by following the toxicity rules as described in table 1 and table 2.

Basically, if a significant toxicity, defined as dose-limiting toxicity in Table 2, occurs on or after day 15 of the cycle, treatment will be held (interrupted) until the end of the cycle and the dose will then be reduced by a step (dose level -1) in the subsequent cycle.

If toxicity occurs before day 15 of the cycle, treatment will be held until recovery and restarted without dose reduction for the rest of the cycle (continue until day 21; missed doses will not be made up).

The next cycle will resume at reduced dose (dose level -1) in subsequent cycles. In those instances where in the opinion of the investigator re-challenge at the same dose level poses an unacceptable risk to the patient, treatment will be held (interrupted) until the end of the cycle and the dose will be reduced by a step in the subsequent cycle

In case of recurrence of an event during the same cycle, lenalidomide will be held until the next cycle.

Doses that were missed, due to toxicity or any other reasons, will not be rescheduled. If a dose is reduced, re-escalation is not permitted.

There will be no dose adjustment for rituximab. In case of cycle delay due to lenalidomide induced toxicity, rituximab of the next cycle will also be postponed until AE has resolved and recycling is allowed.

Resumption of dosing (if dose interrupted prior to day 15 and day 1 of next cycle) may begin if:

- The ANC is ≥ 1,000 cells/mm³ (1.0 X 10^9/L);
- The platelet count is ≥ 50,000 cells/mm³ (50 X 10^9/L);
- Lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity;

- Any other lenalidomide-related AE not requiring discontinuation has resolved to ≤ Grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated once every seven days and a new cycle of treatment with lenalidomide will not be initiated until the toxicity has resolved as described above. If a new cycle is delayed for more than 28 days, the Medical Monitor must be notified.

Table 1: Lenalidomide Dose Modification Rules

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Grade 3 neutropenia (one time reading)	Follow CBC at least every seven days.
Neutropenia Sustained (≥ 7 days) Grade 3 OR ≥ Grade 3 associated with fever (temperature ≥ 38.5º C) OR Grade 4	• If neutropenia has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow CBC every seven days • If neutropenia has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • Use of G-CSF is permitted if the ANC is below 500 during a cycle at the discretion of the Investigator as per ASCO and ESMO guidelines. Treatment with G-CSF up to 3 days is allowed to reach ANC required to give the next cycle • In both cases, restart subsequent cycle at next lower dose
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000 cells/mm³ [50x109/L])	• If thrombocytopenia has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow CBC every seven days • If thrombocytopenia has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Rash Grade 2 or grade 3 without desquamating Desquamating (blistering) ≥Grade 3 or Non-desquamating Grade 4	• Hold (interrupt dose). Administer antihistamines or a short course of steroids at the discretion of the investigator. When resolved (grade ≤1), restart at the same dose level. • Permanently discontinue lenalidomide study drug

Allergic reaction or hypersensitivity Grade 2	• If allergic reaction has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If allergic reaction has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Grade 3-4	• Permanently discontinue lenalidomide study drug
Constipation Grade 1-2	• Initiate bowel regimen and maintain dose level
≥ Grade 3	• If constipation has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If constipation has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Venous thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at Investigator's discretion (maintain dose level)
Peripheral neuropathy Newly developed ≥ Grade 3 **(applies only to those neuropathies which begin or worsen while on study)**	• If neuropathy has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If neuropathy has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Tumor Flare Reaction (TFR)* Grade 1-2	☐ Continue lenalidomide, maintain dose level • At the investigator's discretion may initiate therapy with NSAIDs, limited duration corticosteroids, and/or narcotics
Grade 3-4	☐ Initiate therapy with NSAIDs, corticosteroids, and/or narcotics ☐ If TFR has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle, and follow at least every seven days • If TFR has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle ☐ In both cases, restart subsequent cycle at next lower dose

Tumor Lysis Syndrome (TLS)**	• Continue lenalidomide (maintain dose), or at the investigator's discretion, continue lenalidomide and reduce dose by one level
Laboratory TLS or Grade 1 TLS	• Provide vigorous intravenous hydration and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy is appropriate (if approved by the local Health Authority) as needed to reduce hyperuricemia • Hospitalization will be at investigator's discretion
Grade 2-4	• If TLS has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If TLS has occurred before day 15 and resolved to ≤ Grade 0 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose • If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following re-initiation of lenalidomide
Other lenalidomide related non-hematologic AEs ≥ Grade 3	• If AE has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If AE has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose

*AEs are graded using the NCI CTCAE v 4.0; however TFR will be graded using NCI CTCAE v 3.0 as subsequent versions do not contain a provision for TFR.

** AEs are graded using the Cairo-Bishop toxicity grade

Please note that leucopenia and lymphopenia are not part of dose modification rules, only neutropenia grade 3 or 4 requires dose modification.

Table 2: Lenalidomide Dose Modification Rules For Abnormal Liver Function*

AST or ALT > 3 x ULN	• If AE has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle; re-test at least weekly until AST and ALT ≤ 2.5 x ULN or return to baseline • If AE has occurred before day 15 and resolved as described, restart at same dose level for the rest of the cycle	Restart subsequent cycle at the same dose of lenalidomide if the event is considered NOT related to study drug treatment.
Bilirubin ≥ 3 x ULN	• If AE has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle; re-test at least weekly until bilirubin ≤ 1.5 x ULN • If AE has occurred before day 15 and resolved as described, restart at same dose level for the rest of the cycle	Restart subsequent cycle at next lower dose if the event is considered as related to drug treatment.

*For patients with Gilberts Syndrome or liver involvement by lymphoma, dose reductions should be made in consultation with the medical monitor.

4.3.2 Lenalidomide Dose Reductions Levels

The daily dose of lenalidomide may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction per cycle. Once a subject's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase. Refer to Table 4 for patients starting at the 20 mg dose, and to Table 5 for patients starting at the 10 mg dose.

Table 3: Dose Reduction Levels from 20 mg Start Dose

Starting Dose	20 mg daily on Days 2-22, every 28 days
Level –1 Dose	15 mg daily on Days 2-22, every 28 days
Level –2 Dose	10 mg daily on Days 2-22, every 28 days
Level –3 Dose	5 mg daily on Days 2-22, every 28 days
Level –4 Dose	2.5 mg daily on Days 2-22, every 28 days

Table 4: Dose Reduction Levels from 10 (or 15) mg Start Dose

Starting Dose	10 mg daily on Days 2-22, every 28 days
Level A Dose*	15 mg daily on Days 2-22, every 28 days
Level –1 Dose	5 mg daily on Days 2-22, every 28 days
Level –2 Dose	2.5 mg daily on Days 2-22, every 28 days

*After completion of Cycle 2, if the patient remains free of Grade 3 or Grade 4 toxicity, the dose may be increased to a maximum of 15 mg once daily for 21 days (D2 – D22) starting on day 2 of cycle 3. The same dose reduction rules as in Table 3 would then apply.

Table 5: Dose Reduction Levels from the Cycle 13 - 10 mg Dose*

Starting Dose	10 mg daily on Days 2-22, every 28 days
Level –1 Dose	5 mg daily on Days 2-22, every 28 days
Level –2 Dose	2.5 mg daily on Days 2-22, every 28 days

*All patients receive the 10 mg lenalidomide dose from cycle 13 through cycle 18. Patients exhibiting CR/CRu after 6 and before 12 cycles begin the 10 mg lenalidomide at the next cycle.

Patients with no dose reduction or dose reduction to 15 mg or 10 mg during cycles 1-12 continue with 10 mg. Patients who dose reduced to 5 mg or 2.5 mg during cycles 1-12 continue with 5 mg and 2.5 mg respectively.

4.3.3 Dose Adjustment for Patients in the Control Arm

Patients will be evaluated for adverse events at each visit with the NCI CTCAE v 4.03 used as a guide for the grading of severity. The dose of Investigator's Choice for each subject will be interrupted and modified according to the clinical practice of the Investigator's institution, and in line with the approved prescribing information including administration, warnings, precautions, contraindications, and adverse reactions, as applicable.

4.4 Method of Treatment Assignment

The treatment assignment will occur in the screening period, once all the required screening procedures have been completed, and all required data have been submitted to the IVRS/IWRS system.

Investigators will select one protocol specified standard of care chemotherapy (i.e., bendamustine, CHOP or CVP) for their subject during screening and enter this data into IVRS/IWRS. Standard of care chemotherapy must be available by prescription, generally reimbursed by the health system and used routinely in previously untreated FL patients at the center.

Patients will be stratified by FLIPI score (0-1 v 2 v 3-5), age (>60 v $\leq$ 60) and longest diameter of the largest node (> 6 v $\leq$ 6 cm) and randomized to receive either rituximab-lenalidomide or Investigators Choice of R-CHOP, R-CVP, or R-B.

4.5 Drug Dispensation and accountability

4.5.1 Packaging and labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

4.5.2 Accountability and destruction

The sponsor will instruct the Investigator on the return, disposal and/or destruction of investigational product if applicable.

4.5.3 Compliance

For the oral medications of lenalidomide, study personnel will review the dosing instructions with the patient prior to dispensing the study drug. The subject will be instructed to return the study drug bottle, including any unused study drug, to the site at the next visit. Subject compliance will be noted on the appropriate CRFs and source records based on a capsule count. To monitor treatment compliance, reconciliation of capsules will be done at each scheduled study visit.

5 STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS

5.1 Study flow chart

See Figure 1.

5.2 Screening Examination and Procedures

See Table 1 – Schedule of Assessments.

Patients will be screened for protocol eligibility during a period of no more than 4 weeks prior to randomization as outlined in the Schedule of Study Assessments.

Screening assessments and recording of AEs/SAEs will begin once the subject has signed the informed consent form.

The subject's eligibility (inclusion and exclusion criteria) has to be evaluated during the screening period prior to randomization.

5.2.1 Demographic Information

- Written Informed Consent
- Complete medical history (including previous cancer)
- Physical examination performed within 2 weeks prior to the first day of treatment
- Age, gender
- Weight, height and BSA
- Vital signs (including Blood Pressure, pulse and temperature)

5.2.2 Histological diagnosis

FFPE tumor block of diagnostic tumor tissue taken within the 18 months before signing the informed consent must be confirmed to be available at the time of randomization and must be submitted to central pathology within 12 weeks after randomization.

If block cannot be sent, an H&E slide and 10 unstained slides will be acceptable.

Pathology reports associated with these tissues are also required and will be sent to the central pathology laboratory with the tissue and/or slides. The sponsor will provide detailed instructions and materials for sample handling and shipping. *Note that diagnosis based on fine needle aspirations is not considered acceptable pathologic data for entry into this study.*

Eligibility will be based on local pathology review; confirmation of diagnosis by central pathology laboratory is not required for entry or initiation of treatment. If tumor tissue was not collected within 18 months prior to the subject signing the informed consent, a newly obtained tumor biopsy (excisional or core) is required.

5.2.3 Tumor and disease staging

- CT/MRI of neck, chest, abdomen and pelvis is required to locally confirm measurable disease of at least 2 cm. CT is to be performed with contrast unless it is medically

contraindicated. This scan may be used as the baseline CT scan if it is obtained within 4 weeks of cycle 1 day 1.

- Evaluation of all involved nodal and extra-nodal sites of lymphoma.
- Assessment of spleen and liver enlargement based on CT scan or physical examination.
- FDG-PET scan (optional). FDG-PET is to be submitted in addition to CT/MRI data, not in lieu of it.
- Patients with a presence of CNS lymphoma involvement are excluded from the study. Patients with suspicion of CNS involvement must undergo neurologic evaluation and CT/MRI of head and lumbar puncture to exclude CNS disease.
- Paraffin fixed bone marrow biopsy taken within 18 months of subject signing the informed consent or if bone marrow block are not available 5 representatives, unstained slides must be submitted to central pathology within 12 weeks after randomization.

The pathology reports must also be submitted. Although receipt of the blocks or slides by central pathology is required, the outcome of the central review of the slides is not part of the eligibility requirements.

If bone marrow biopsy was not collected within 18 months of signing the informed consent, a newly obtained bone marrow biopsy is required.

- B-symptoms
- FLIPI and FLIPI 2 (See Appendix E)
- Ann Arbor staging (See Appendix F)
- ECOG performance status (See Appendix G)

5.2.4 Laboratory assessments

- Compete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, MCV, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.
- sodium, potassium, calcium,
- phosphorous,
- glucose,
- uric acid,
- alkaline phosphatase, AST, ALT, total protein, albumin, total bilirubin,
- chloride,
- blood urea nitrogen,
- lactate dehydrogenase (LDH), β2-microglobulin
- creatinine (clearance calculated by the Cockcroft-Gault formula or MDRD formula)

Cockcroft-Gault estimation of creatinine clearance (CrCl):

Serum creatinine units mg/dL => for females, the formula is multiplied by 0.85.

CrCl (mL/min) = [(**140** – **age** (years)) x (**weight** [kg])] / [**72** x (**serum creatinine** [mg/dL])];

Serum creatinine units µmol/L => A = 1.23 for men and A = 1.04 for females.

CrCl (mL/min) = [(**140** – **age** (years)) x (**weight** [kg]) x **A**] / (**serum creatinine** [µmol/L]);

Creatinine clearance should be determined utilizing actual body weight or ideal body weight, whichever is less (**Cockcroft 1976**, **Luke 1990**).

MDRD estimation of creatinine clearance (CrCl) :

Serum creatinine units mg/dL

CrCl (mL/min) = 175 x [**Serum creatinine**$^{-1.154}$ x **age**$^{-0.203}$ x 0.742 (if female) x 1.212 (if black)

Serum creatinine units µmol/L

CrCl (mL/min) = 30849 x [**Serum creatinine**$^{-1.154}$ x **age**$^{-0.203}$ x 0.742 (if female) x 1.212 (if black)

Eligibility for the study is based on the local laboratory results.

Laboratories used for hematological and biochemical tests and assays including ongoing pregnancy tests during the study are individual centre laboratories. All the laboratories must provide their normal values and an updated accreditation for quality control.

However, if Screening labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.

5.2.5 Cardiac function evaluation

- 12-Lead ECG is performed at Screening and as clinically indicated thereafter.
- Left VEF (measured by Ultrasound echocardiography or scintigraphy) according to physician decision (if patient planned to receive anthracycline).

5.2.6 Serologies and specific laboratory assessments

- Hepatitis B screening is required in all patients and includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs).
- Two pregnancy tests for females of childbearing potential (FCBP)

Please note that following laboratory assessments will be performed only by selected sites and countries.

- FcgR polymorphism is measured in peripheral blood cells once during screening.
- Blood MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation in peripheral blood or other MRD assays.
- Bone marrow MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation or other MR.
- Serum immunoglobulin levels
- Total T cells and B cells, as well as CD4/CD8 and NK cells
- Tetanus (T-cell dependent) and pneumococcal (Pure B cell) response specific serum IgG

5.2.7 Quality of life assessments

- EORTC QLQ-C30 (Appendix C)
- EQ-5D (Appendix D)

5.2.8 Selection of Standard-of-care regimen (Investigator's choice)

The intent of this study is to compare the rituximab plus lenalidomide regimen to standard-of-care rituximab-chemotherapy regimens in use in a particular country, geographic region or institution.

Therefore, during the Screening Phase, prior to randomization, Investigators will select one regimen from a choice of protocol specified choices of standard-of-care chemotherapy regimens from the choices described in Section 8.2 for their subject during screening and enter this choice into IVRS/IWRS.

Standard of care chemotherapy regimen must be available by prescription, generally reimbursed by the health system and used routinely to treat previously untreated FL patients at the center.

After randomization, study drug is dispensed on Day 1 for lenalidomide patients or Investigator's Choice patients assigned to oral prednisone (R-CHOP or R-CVP). For Cycle 1 only, a 7 day window between randomization and Cycle1 Day 1 is allowed; however, the Screening period must remain within 28 days of Cycle 1 Day 1 dosing.

5.3 Evaluation during treatment and follow-up

Serial assessments of safety and efficacy will be performed as outlined in the Schedule of Study Assessments (Table 1). Patients in both arms will follow comparable assessment schedules. Note that for the first year of maintenance rituximab cycles are administered every 56 days and lenalidomide cycles every 28 days. To balance subject contacts during this time, subjects in the rituximab arm will call the site/or call center for a phone call interview every 28 days after each rituximab treatment (for months without rituximab administration) during the first year of maintenance.

Laboratories used for hematological and biochemical tests and assays including ongoing pregnancy tests during the study are individual centre laboratories.

5.3.1 Evaluation during each cycle of treatment

- Physical examination (including weight, vital signs and ECOG PS) at day 1 of every treatment cycle
- Serum chemistry laboratory evaluations (sodium, potassium, chloride, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, ALP, total bilirubin, AST/SGOT, ALT/SGPT, LDH and uric acid) within 48 hours of Day 1 of every treatment cycle

Note that the Cycle 1 Day 2, 4, 8 and 15 and Cycle 2-4 Day 15 chemistry labs are required only for patients in the experimental arm and suggested for patients in the control arm to monitor for tumor lysis.

- Hematology laboratory evaluations (RBC count, hemoglobin, hematocrit, WBC count and

differential, ANC, and platelet count) within 48 hours of Day 1 of every treatment Cycle

Note that the Cycle 1 Day 2, 4, 8 and 15 and Cycle 2-4 Day 15 hematology labs are required only for patients in the experimental arm and suggested for patients in the control arm to monitor for cytopenias.

However, if Screening labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1

5.3.2 Pharmacokinetic assessments (experimental arm)

Pharmacokinetic assessments will be performed in patients who provide additional consent at select centers. All patients participating in the sparse PK assessment will be instructed to take the oral dose of lenalidomide in the morning at approximately the same time each day. For each PK sample, approximately 3 mL blood will be drawn and plasma will be prepared by centrifugation as described in the study manual.

Sparse PK sampling

Sparse PK sampling will be performed in selected countries and at select centers in patients (up to 200 patients) who are randomized to the rituximab plus lenalidomide arm and sign the PK ICF. A single PK blood sample will be collected between 1 to 10 hours after the morning lenalidomide dose at each of the following visits:

- Cycle 1 Days 2, 4, 8, 15
- Cycle 4 Day 15

Patients should visit the study site at a post dosing time that is at least one hour different from the prior PK visit(s).

5.3.3 Evaluation of response

- Patients with positive bone marrow at screening will have a repeat unilateral bone marrow biopsy if a) they otherwise achieve CR and the repeat biopsy will be taken within 28 days after first achieving CR, or b) they are in PR at 120 weeks. .
- CT scans using contrast media are the preferred radiology method (MRI is allowed in case of contraindications to the use of CT scans):

  - 12 weeks after the first dose date (± 1 week),
  - 24 weeks after the first dose date (± 2 weeks),
  - 36 weeks after the first dose date (± 2 weeks),
  - 52 weeks after the first dose date (± 2 weeks),
  - 76 weeks after the first dose date (± 3 weeks),
  - 100 weeks after the first dose date (± 3 weeks),
  - 120 weeks after the first dose date (± 4 weeks)

  and then every 6 months (± 4 weeks) for 5 years and then every year (± 4 weeks) until disease progression or relapse.

- FDG-PET scan (will be optional). FDG-PET is to be submitted in addition to CT/MRI data, not in lieu of it :

  - 24 weeks after the first dose date (± 2 weeks),
  - 76 weeks after the first dose date (± 3 weeks)
  - 120 weeks after the first dose date (± 4 weeks).

Since the study endpoint is PFS based on CT, FDG PET scan is not the basis for disease progression. For suspected progression based on FDG-PET, a CT scan must be available demonstrating unequivocal progression.

All protocol defined efficacy assessments will be conducted by Central Review including central radiology and clinical review by an IRC. Since the study endpoint is PFS based on CT as determined by IRC, progression will be based on CT scans.

For suspected progression based on clinical evaluation, a CT scan must be available demonstrating unequivocal progression.

For equivocal progression based on CT findings, the site Investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases of equivocal progression, immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if the PD is not confirmed by central radiology review, the patient should continue treatment as per protocol.

In limited instances where progression is evident only by assessments other than CT, CT scans will still be provided along with the non-CT documentation of progression.

The same methodology will be performed for equivocal cases of threshold clinical activity at the 12 and 24 week assessments. That is, in equivocal cases of threshold clinical activity, the site investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if threshold clinical activity is confirmed by central radiological review, the patient should continue treatment as per protocol.

5.3.4 Quality of Life Assessments

- EORTC QLQ-C30: Follow the same schedule as described for CT scans in Section 10.3.3. .

- EQ-5D : Follow the same schedule as described for CT scans in Section 10.3.3 with the exception that EQ-5D assessments continue beyond disease progression/relapse until the end of follow-up period.

5.3.5 Specific laboratory assessments

- Blood MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation in peripheral blood or other MRD assays at the following time points : 24 weeks (± 1 week), 76 weeks (± 2 weeks), 120 weeks (±4 weeks).

- Bone marrow MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation or other MRD assays at the following time points : 24 weeks (± 1 week), and only for patients with bone marrow involved by lymphoma at

screening.

- Serum immunoglobulin levels are measured at the following time points: 24 weeks (± 1 week), 52 weeks (± 1 week), 76 weeks (± 2 weeks), 100 weeks (± 2 weeks), 120 weeks (± 4 weeks).

- Total T cells and B cells, as well as CD4/CD8 and NK cells are at the following time points : 24 weeks (± 1 week), 76 weeks (± 2 weeks), 120 weeks (± 4 weeks).

- Tetanus (T-cell dependent) and pneumococcal (Pure B cell) response specific serum IgG is measured at 24 weeks (± 2 weeks) and 120 weeks (± 4 weeks) after the first dose date in patients with documentation of prior vaccination who consent to this additional assessment.

5.3.6 Assessments for Veinous Thromboembolitic events (VTE)

VTE including Deep vein thrombosis and pulmonary embolism will be assessed

Deep vein thrombosis in Non-Hodgkin's Lymphoma

Ottinger et al (1995) analyzed incidence, risk factors, causes and prognostic significance of venous thromboembolism (VTE) in high-grade non-Hodgkin's lymphoma (HG-NHL) in a prospective clinical trial. In 593 patients, they reported a 6.6% incidence of VTE, with 77% of all cases occurring before or within the first 3 months of chemotherapy. Vessel compression by HG-NHL was identified as the leading cause of VTE.

In lymphoma patients receiving lenalidomide, DVT and PE were reported in 7 (3.2%) and 6 (2.8%) of 266 patients with relapsed or refractory aggressive NHL receiving lenalidomide in clinical studies NHL-002 and NHL-003 (Wiernik 2006, Witzig 2011). DVT and PE were reported in 0 (0%) and 1 (2.3%) of 43 patients with indolent relapsed refractory NHL (Witzig 2009). Anti-thrombotic prophylaxis was not suggested in NHL-001 or NHL-002 but required for patients considered to be high risk of developing DVT in NHL-003.

Unlike the increased risk of DVT reported when adding lenalidomide to dexamethasone in multiple myeloma patients, there is no evidence to suggest an increased risk of DVT in lymphoma patients receiving lenalidomide as single agent.

Nonetheless, in the current study, it is recommended that patients randomized to the rituximab-lenalidomide who are considered to be at high risk for DVT receive anti-thrombotic prophylaxis (see Section 9.1.2) and all patients will be closely monitored for VTE including Deep vein thrombosis and pulmonary embolism.

5.4 Follow-up assessments

Follow-up period will start at the end of treatment (120 weeks) or at treatment discontinuation (if applicable).

Patient will be followed every 3 months (12 weeks) for the first two years and every 6 months (24 weeks) up to end of follow-up period.

Follow-up assessments include :

- Physical examination including ECOG PS
- Hematology laboratory evaluations (RBC count, hemoglobin, hematocrit, WBC count and differential, ANC, and platelet count)
- CT scans every 6 months (24 weeks) for 5 years and then every year until disease progression/relapse or end of follow-up period.
- Serum immunoglobulin levels every 6 months/24 weeks (± 4 weeks) for 1 year of follow-up.

5.5 Progression/relapse

Relapse/progression will be determined as per Cheson 1999 criteria (see Appendix A).

Progressive disease should be based on CT scan.

A pathological confirmation by biopsy of the lesion should be done if possible.

6 STUDY PROCEDURES

6.1 Informed consent

Written informed consent written and approved in compliance with local regulatory authority will be obtained from each patient prior to being randomized in the trial. Specific informed consent should be signed for biological studies and genetics analysis. The informed consent for biological studies and genetic analysis should be signed before sampling.

The patient and the investigator will date and sign the informed consent form.

The investigator shall provide a copy of the signed consent to the study patient; the original shall be maintained in the investigator's study file.

6.2 Pathological diagnosis

Histopathology central review process has become in the last years a common and prerequisite procedure for clinical trials in the field of lymphomas. It requires both a histopathological and immunohistochemical approach using an appropriate panel of antibodies according to the morphological pattern and, in some instances, further molecular or genetic analysis. A

mandatory pathological review will be organized for all patients included in the trial at diagnosis. The goal of this central review will be to confirm the diagnosis and to classify precisely the malignancy its classification according to the WHO classification 2008.

Therefore for each patient, the investigator will be requested to submit a registration form along with a copy of the histopathological report where the name and address of the pathologist having diagnosed the lymphoma will be easily identified as well as a copy of the bone marrow report.

All the requested tumor paraffin embedded blocks from the formalin fixed sample (that was used for diagnosis), or 10 unstained slides, and bone marrow biopsy (or 5 unstained slides with H&E) will be collected.

At reception, routinely stained sections will be assessed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a pathological review will be organized, and a consensus diagnosis will be established and entered on the review form. This review form will then be sent to the clinical coordinator and to the pathologist coordinator.

Initial tumor block will also be used to make tissue microarray (TMA) and tissue core for DNA extraction; both will be used to study the expression of markers known to influence the prognosis of follicular lymphoma

When the review process is completed, tissue array and tissue core analysis are completed, a pathological report will be sent to the initial pathologist as well as the investigator of the inclusion at the enrolling centre and the remaining pathologic material will be sent back to the initial pathologist.

At the end of the inclusion, frozen tumor tissue will be requested for all French and Belgium randomized patients. The collection of the frozen tumor specimen will be organized and centralized at the GELA-P. On frozen tissue, gene and protein expression analysis will be performed to assess the level of expression of genes/proteins known to influence the outcome of follicular lymphoma patients.

6.3 CT scan Review

A central review of CT scan is mandatory and organized. For each patient, when applicable, data and images of CT scan performed at following time points will be reviewed by a panel of CT experts:

- screening,
- 12 weeks after the first dose date (± 1 week),
- 24 weeks after the first dose date (± 2 weeks),
- 36 weeks after the first dose date (± 2 weeks),
- 52 weeks after the first dose date (± 2 weeks),
- 76 weeks after the first dose date (± 3 weeks),
- 100 weeks after the first dose date (± 3 weeks),
- 120 weeks after the first dose date (± 4 weeks)

- every 6 months (24 weeks) for 5 years and then every year until disease progression/relapse .

- to document progression/relapse

The central analysis of the imaging should be done according to IWG response criteria (Cheson 1999) for the NHL.

For CTs, the reviewer panel is composed by 3 CT experts for review of the CTs according to the following rules :

- 2 reviewers will analyze the CT scans independently.

- In case of disagreement between the 2 reviewers, the 3rd reviewer will analyze the CT exams independently.

6.4 PET scan Review

A central review of the PET scan is organized. For each patient when applicable, the data and images of Pet scan performed at following time points will be reviewed by a panel of PET experts:

- screening

- 24 weeks after the first dose date (± 2 weeks),

- 76 weeks after the first dose date (± 3 weeks)

- 120 weeks after the first dose date (± 4 weeks).

For PETs, The reviewer panel is composed by 3 nuclear physicians for review of the PETs according to the following rules:

- 2 reviewers will analyze the PET scans independently.

- In case of disagreement between the 2 reviewers, the 3rd reviewer will analyze the PET exams independently.

7 CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

7.1 Premature withdrawal from trial intervention

Circumstances that lead to premature withdrawal of a patient from the trial must be reported by the investigator on the appropriate CRF page.

Criteria for subject withdrawal include (but are not limited to) :

- Death,

- Toxicity (adverse event),

- Disease progression/relapse,

- Concomitant disease,

- Non compliance (including loss of subject to follow-up),

- Voluntary withdrawal,

- Major protocol violation, including initiation of alternate anti-neoplasic therapy.

Patients should however remain in the trial for the purposes of follow-up and data analysis.

7.2 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states their wish not to contribute further data to the study, the relevant sponsor contact should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. However, data up to the time of consent withdrawal will be included in the data reported for the study.

7.3 Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained by investigator since one year and at least three unsuccessful documented attempts of contact are available in source documentation.

8 ADVERSE EVENTS

8.1 Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of study drug(s). AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported immediately (i.e., within 24 hours of the Investigator's

knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

8.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

8.2.1 Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

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

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

SPM will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in (see Section 7.5). This includes any SPM, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the ICD up to and including the follow-up period of up to 10 years. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of

such transfusion remains a reportable SAE.

- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.

- A procedure or hospitalization for progression/relapse investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling).

- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of a pre-existing condition unrelated to the studied indication.

- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen 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 study drug(s), action taken regarding study drug(s), and outcome.

8.2.2 Severity

For both AEs and SAEs, the Investigator must assess the severity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the NCI CTCAE should be evaluated for severity/intensity according to the following scale:

Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5 = Death - the event results in death]

Specific NCI Working Group or other criteria pertinent to the indication may also be used as applicable.

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as “serious” which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

8.2.3 Causality

The Investigator must determine the relationship between the administration of study drugs and the occurrence of an AE/SAE as Not related or related as defined below:

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

If an event is assessed as suspected of being related to a comparator, ancillary or additional study drugs that has not been manufactured or provided by Sponsor, please provide the name of the manufacturer when reporting the event.

8.2.4 Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event

8.2.5 Action Taken

The Investigator will report the action taken with study drug(s) as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

8.2.6 Outcome

All SAEs that have not resolved upon discontinuation of the subject’s participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

8.3 Abnormal laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;

- requires treatment, modification/ interruption of study drug(s)dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

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

8.4 Pregnancy

8.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on IP, or within 28 days of the patient's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form. The exposure of any pregnant female (e.g., caregiver or pharmacist) to lenalidomide is also an immediately reportable event.

The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female patient until completion of the pregnancy, and must notify immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

8.4.2 Male Patients

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

8.5 Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page of the CRF. All SAEs must be reported (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

SPM will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. This includes any SPM, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the ICD up to and including the follow-up period of 10 years. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and patient's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study drugs) that occur during the study (from the time the patient signs informed consent to 28 days after the last dose of study drug(s)) , and those made known to the Investigator at anytime thereafter that are suspected of being related to study drugs. SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to GELARC Pharmacovigilance Department as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with the IRB/EC.

Safety Queries

Queries pertaining to SAEs will be communicated to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g., missing causality assessment) may be handled by phone.

8.6 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Drug Safety of the sponsor or its authorized representative will determine the expectedness of events suspected of being related to lenalidomide based on the Investigator Brochure.

For countries within the European Economic Area (EEA), the sponsor or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with

Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, the sponsor or its authorized representative will determine the expectedness of events suspected of being related to the other IPs that is, rituximab, cyclophosphamide, doxorubicin, prednisone/prednisolone, vincristine, and bendamustine based on the appropriate Prescribing Information (PI) or Summary of Product Characteristics (SmPC)].

Adverse events such as disease progression, death related to disease progression (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the sponsor to regulatory authorities.

the sponsor or its authorized representative shall notify the Investigator of the following information

- Any AE associated with the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to patients.

The Investigator must keep copies of all pertinent safety information on file.

8.7 Follow up of Serious Adverse events

Any SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported as soon as information becomes available.

9 STATISTICAL CONSIDERATIONS

A phase 3 study (RV-FOL_Gelarc-0683C) will be conducted as a companion to the RV-FOL-Gelarc-0683 study with a combined enrollment target of 1000 patients and will enroll 250 patients. The data from both studies will be collected into one database and the statistical analyses as described in Section 14 will be performed on the combined total of patients enrolled into both studies. A single data safety monitoring committee (DSMC), central pathology and central Independent Review Committee (IRC) will be utilized for these two studies.

9.1 Overview

The objective of this statistical analysis is to investigate efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma.

Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the Independent Review Committee (IRC) using the IWG (Cheson 1999) criteria..

All statistical analyses specified in this protocol will be conducted using *SAS*® version 9.1.3 or higher.

9.2 Study Population Definitions

For this study, the following three populations will be defined and used in the analysis and presentation of the data.

Intent-to-treat (ITT) population: The ITT population is defined as all patients who are randomized into the trial, regardless of whether they received study treatment or not.

The ITT population will be used for the primary efficacy analysis. Patients will be analyzed according to the treatment arm to which they are initially assigned.

Modified ITT (mITT) population: The mITT population is defined as all randomized patients who have received at least one dose of study drug, have confirmed diagnosis of follicular lymphoma with no prior systemic treatment for lymphoma, have baseline and at least one post-baseline tumor assessment for efficacy.

The efficacy analysis will also be performed on the mITT population as supportive evidence and/or sensitivity analysis. Patients will be analyzed according to the treatment arm to which they are initially assigned.

Safety population: The safety population is defined as all patients who have received at least one dose of study drug. The safety population will be used for all safety analysis. Patients will be analyzed according to the treatment which they actually received.

9.3 Sample Size and Power Considerations

Sample size calculation is based on providing adequate power to evaluate treatment effect on the co-primary efficacy endpoints.

The co-primary efficacy endpoints are complete response (CR/CRu) rate at 120 weeks and PFS.

It is hypothesized that the complete response (CR/CRu) rate at 120 weeks is 60% in the control arm and 72% in the experimental arm. For 90% power to detect this difference with two-sided α = 0.05, a total of 644 patients (322 in each arm) will be required.

It is hypothesized that the median PFS is 83 months in the control arm, and there is a 30% increase in the median PFS in the experimental arm (corresponding hazard ratio of 0.7692). For 80% power

to detect this difference with two-sided $\alpha = 0.05$, a total of 456 progression/relapse/death events will be required.

Therefore, for an enrollment rate of 10 patients per month in the first six months, 25 patients per month in the next 11 months, and 30 patients per months thereafter with 6% dropout rate per year, a total of 1000 patients in 1:1 ratio to the two treatment arms (500 in each arms) will be needed, with a 40-month accrual period and up to 10 years follow-up. The analysis of PFS will occur in about 142 months when the required 456 progression/relapse/death events are expected to be observed.

The assumptions used in sample size calculations are derived from available literature, especially from the published results of PRIMA and STiL studies. For the proposed sample size, it should be noted that any reasonable deviations from these assumptions have limited impact on the power of the test. For example, if the complete response (CR/CRu) rate at 120 weeks is down to 50% in the control arm instead of 60%, the proposed sample size of 644 patients still have more than 85% power to detect a 12% rate difference. If the median PFS reduces to 70 months in the control arm instead of 83 months, it still requires a total of 456 events to detect a 30% increase in the median PFS, and the only impact is that the study duration will be reduced to 113 months if 1000 patients are to be randomized.

9.4 Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum), while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

Subject's demographics and baseline characteristics will be summarized for the ITT population.

Subject disposition (analysis population allocation, randomized, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment arms. Protocol deviations will be summarized using frequency tabulations.

9.5 Efficacy Analysis

9.5.1 Co-Primary Efficacy Endpoints

Complete Response (CR/CRu) Rate at 120 weeks

The tumor response data will be assessed by the IRC using the IWG (Cheson 1999) criteria.

Progression Free Survival (PFS)

PFS is an accepted endpoint of clinical benefit for previously untreated FL patient and was the basis for the recent approval of rituximab maintenance in this population (Salles 2011). The disease progression status will be assessed by IRC using the IWG (Cheson 1999) criteria. PFS is defined as the time from randomization into the study to the first observation of documented disease progression or death due to any cause. If a subject has not progressed or died, PFS will be censored at the time of last visit with adequate assessment. If a subject received other anti-cancer treatment for follicular lymphoma before progression, the CT/MRI assessments should continue as scheduled until disease progression or death which will be counted as events.

Various censoring rules will be considered in sensitivity analyses. Detailed censoring rules for PFS will be provided in the Statistical Analysis Plan based on “Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics” (see reference http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf) and “Methodological Considerations For Using Progression-Free Survival As Primary Endpoint In Confirmatory Trials For Registration” (http://www.emea.europa.eu/pdfs/human/ewp/26757506en.pdf).

9.5.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed using appropriate statistical methods.

- Time to Treatment Failure (TTF),

TTF will be measured from the date of randomization to the date of first documented treatment discontinuation for any reason, including disease progression, treatment toxicity, and deaths.

- Event Free Survival (EFS),

EFS will be measured from the date of randomization to the date of first documented progression, relapse, and initiation of a new anti-lymphoma treatment or death by any cause. Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

- Time to Next Anti-Lymphoma Treatment (TTNLT),

TTNLT will be measured from the date of randomization to the date of first documented administration of any new anti-lymphoma treatment (chemotherapy, radiotherapy, radio-immunotherapy, immunotherapy). Patients continuing in response or who are lost to follow-up will be censored on their last visit date. Patients who died (due to any cause) before having received a new anti-lymphoma treatment will be included in the statistical analysis with death being counted as an event.

- Time to Next Chemotherapy Treatment (TTNCT),

TTNCT will be measured from the date of randomization to the date of first documented administration of new chemotherapy or new cytotoxic agent. For any given patient, the TTNCT may be the same as TTNLT. Patients continuing in response or who are lost to follow-up will be censored on their last visit date. Patients who died (due to any cause) before having received a new chemotherapy treatment will be included in the statistical analysis with death being counted as an event.

- Overall Survival (OS)

- ORR rate at 120 weeks by IWG 1999 criteria and
- Health related quality of life as measured by the EORTC QLQ-C30

9.5.3 Analysis Method

The primary efficacy analysis will be based on the ITT population. Analysis based on the mITT population is supportive.

The number and percent of patients with complete response (CR/CRu) at 120 weeks will be tabulated by treatment arm. The experimental arm will be declared superior if the two-sided p-value from a chi-square test is ≤ 0.05 in favor of the experimental arm. If the experimental arm is declared superior than the control arm on this endpoint, the study will still continue to collect data for the PFS analysis. The primary analysis will be performed using a stratified Cochran-Mantel-Haenszel (CMH) test to adjust for possible confounding effects of the stratification factors: FLIPI score (0-1 vs 2 vs 3-5), Age (> 60 vs ≤ 60), longest diameter of the largest node (> 6 v ≤ 6 cm). The un-stratified test will be a supportive analysis.

PFS will be compared between the two treatment arms when the required 456 progress/relapse/death events are observed. The Kaplan-Meier estimates of PFS function will be provided. If a subject has a missing or incomplete CT scan, all other available CT scans or MRIs of the subject will still be used for the analysis. The experimental arm will be declared superior if the two-sided p-value from a stratified log-rank test is ≤ 0.05 in favor of the experimental arm.

Conventionally, hazard ratio with two-sided 95% confidence interval (CI) will be estimated using the Cox proportional hazards model. But the treatment effect will be determined by the p-value, not by this 95% CI. The un-stratified log-rank test will be a supportive analysis. Subgroup analysis for PFS will be performed as appropriate.

The analyses of secondary and exploratory efficacy endpoints will be conducted at the same time when analyses of the primary and co-primary efficacy endpoints are performed. Overall survival (OS) comparison will also be performed at the end of study.

9.6 Safety Analysis

Safety analysis will include all patients in the Safety population.

Study medication exposure will be summarized for each treatment arm including duration of study medication, total dose taken, and dose reductions.

Adverse events, vital sign measurements, clinical laboratory measurements, and concomitant medications will be summarized by treatment arm.

AEs will be coded according to medical dictionary for drug regulatory activities (MedDRA) and classified using the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE). The incidence rates of AEs will be tabulated by system organ class and preferred term. Subsets of AEs to be summarized include serious AEs (SAEs), AEs of interest including SPM, events of all CTCAE grade severities, suspected treatment-related AEs, and events that resulted in withdrawal of study medication. The most severe grade of each preferred term for a subject will be utilized for summaries of adverse events by NCI CTCAE grade. All AEs with corresponding attributes will be displayed in a by-subject listing. Adverse events leading to death or to

discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, suspected treatment-related events, and serious adverse events will also be displayed in separate by-subject listings.

Laboratory data will be summarized according to the NCI CTC severity grade.

9.7 Interim Analysis

For the co-primary endpoint of the complete response (CR/CRu) rate at 120 weeks, one interim analysis and one primary analysis is pre-planned. The interim analysis will be performed for the first 200 patients, and the primary analysis for co-primary endpoint of complete response (CR/CRu) will be performed for the total of 644 patients. The purpose of the interim analysis is to check for futility to see if the trial needs to stop early.

Moreover, a first futility analysis will be done to evaluate the complete response (CR/CRu) rate as determined by IRC at 6 months of treatment for the first 200 patients.

As similarly defined for the primary efficacy endpoint, based on the CT/MRI schedule, any assessments in a time window of 24 weeks ± 2 weeks are qualified as the 6 months assessments. If two or more assessments are performed in this time window, the assessment with the least favorable response will be used.

If a subject discontinues the treatment prior to this time window due to disease progression, that subject is classified as a non-responder at 6 months. If a subject discontinues the treatment prior to this time window due to any other reasons, the CT/MRI assessments should continue as scheduled until disease progression. If a subject whose disease was not progressed prior to this time window does not have any tumor assessments in this time window, that subject is also considered as a non-responder for this endpoint.

Appropriate futility boundaries will be described in detail in a separate Statistical Analysis Plan (SAP).

10 STUDY COMMITTEES

10.1 Independent Data Safety Monitoring Committee (DSMC)

An independent external Data Safety Monitoring Committee (DSMC) will periodically review ongoing safety data throughout the study and make recommendations to the sponsor for any safety concerns.

In addition, the DSMC will also review efficacy data for futility. In particular, DSMC will conduct two early futility analyses. The first futility analysis is to evaluate the complete response (CR/CRu) rate as determined by IRC at 6 months of treatment for the first 200 patients. The DSMC will also review the results of the pre-planned interim analysis described above.

10.2 Independent Review Committee (IRC)

For complete response rate assessment an independent review of all CT scans according to an independent review charter.

Bone Marrow examination will be reviewed by GELA-P in patients with positive bone marrow at

screening if a) they otherwise achieve CR and the repeat biopsy will be taken within 28 days after first achieving CR or b) they are in PR at 120 weeks.

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A PHASE 3 OPEN-LABEL RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE (CC-5013) VERSUS RITUXIMAB PLUS CHEMOTHERAPY FOLLOWED BY RITUXIMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA

The "RELEVANCE" trial
(Rituximab Lenalidomide Versus ANy ChEmotherapy)

INVESTIGATIONAL PRODUCT (IP):		Lenalidomide
PROTOCOL NUMBER:		RV-FOL-GELARC-0683C
DATE FINAL:		July 7, 2011
AMENDMENT 1		June 8, 2012
AMENDMENT 2		February 8, 2016
AMENDMENT 3		April 21, 2016
EudraCT NUMBER:		2011-002792-42
IND NUMBER:		60100

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1. STUDY OBJECTIVES

1.1. Primary Objective

The primary objective of the study is to compare the efficacy of rituximab plus lenalidomide to rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma. Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the Independent Review Committee (IRC) using the IWG (Cheson, 1999) criteria.

1.2. Secondary objectives

The secondary objectives of the study are:

- To compare the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab using other parameters of efficacy:
  - Complete Response (CR) at 120 weeks by IWG 1999, Event Free Survival (EFS) by IWG 1999, Time to Next Anti-Lymphoma Treatment (TTNLT), and Overall Survival (OS).
- To compare the safety of rituximab plus lenalidomide versus rituximab plus chemotherapy

2. OVERALL STUDY DESIGN

2.1. Study Design Rationale

Follicular lymphoma (FL) is a distinct histologic type within B-cell NHL further divided by the WHO classification (2007) into three different grades. Within grade 3, grade 3a is differentiated histopathologically from 3b. FL grade 3b is treated in a manner similar to DLBCL. Thus, FL grade 3b is excluded from this study.

Rituximab has become the backbone of first line treatment for follicular lymphoma patients who are in need of therapy. Recent studies have established several standard-of-care immuno-chemotherapy regimens in previously untreated FL. In most phase 3 studies in front line FL, it has not been possible to demonstrate OS benefit, and PFS has been used to assess efficacy. These studies showed that the addition of rituximab to multi-agent chemotherapy regimens led to significantly longer PFS and sometimes longer OS. These regimens are R-CVP, R-CHOP and R-bendamustine. Which of these regimens are considered standard of care varies depending on the geographic location and physician preference. Furthermore, rituximab-maintenance studies have shown improved PFS, and European and US regulatory agencies recently approved rituximab as a first-line maintenance treatment for patients with follicular lymphoma whose disease has responded to initial induction therapy based upon the results of the PRIMA study (Salles, 2011).

The current study is designed to investigate the efficacy and safety of lenalidomide therapy in patients with previously untreated FL. The multicenter nature of the study provides assurance that the results are likely to have general applicability. The inclusion of a control arm, and the fact that the Investigator must select the Investigator's choice option of a standard-of-care for the patient before randomization, is intended to provide a realistic comparison to current standard-of-care in this patient population. Patient eligibility criteria are consistent with those used in other studies of this population.

Patients are required to have measurable disease to facilitate the accurate assessment of CR/CRu, which is a direct measure of the co-primary efficacy endpoint CR/CRu rate at 120 weeks. The International Working Group (IWG) response criteria were selected to provide an international standard for the assessment of lymphoma (Cheson, 1999). The use of this tool will ensure that data across centers are evaluated consistently and also allow for direct comparison to historical data. Safety will be assessed by evaluating AEs and laboratory data. AE and abnormal laboratory value severity will be graded using version 4.03 of the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE).

Known toxicities of lenalidomide, given alone or in combination with rituximab have been reported. In addition, in the clinical database and safety database of the sponsor, tumor flare, tumor lysis and venous thromboembolus have been reported.

Monitoring for tumor flare and venous thromboembolic events (VTE – including pulmonary embolism and deep vein thrombosis) will be performed along with safety measures that are routinely assessed in investigational studies of hematologic malignancies. VTE prophylaxis is recommended for patients in the lenalidomide arm who are at high risk for a thromboembolic event. VTE, TFR and TLS will be recorded as AEs.

2.2. Study Design

This multi-center, open-label study is designed to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab. The overall study design is described in Figure 1. The study is divided into the Screening Period, Treatment Period, and Follow-up Period.

Once a patient gives written consent, the patient may enter the Screening Period, which is permitted to last up to 4 weeks. During the Screening Period, the investigator will choose one standard-of-care regimen ("investigator's choice") for the patient from a list of permitted choices of rituximab-containing chemotherapy regimens. In addition, during the Screening Period, the patient will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either experimental arm (rituximab plus lenalidomide) versus control arm ("investigator's choice" of rituximab-chemotherapy).

It is noted that patient eligibility will be based on investigator assessment. However, patient's disease will be assessed by central pathology review to confirm the FL diagnosis using formalin-fixed paraffin embedded (FFPE) tumor or lymph node tissue submitted in the Screening Phase or obtained from the Screening biopsy.

The patient will enter the Treatment Period once the patient has fulfilled the required assessment in the Screening Period and has been randomized. Treatment must start as soon as possible after randomization but no later than 2 weeks after randomization. Treatment Period for each patient starts with first intake of study drug, which is defined as Study Day 1 of Cycle 1. The treatments will be given as described in detail in Section 4. The patients will receive protocol-specified treatments, until:

(1) Inability to achieve a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment),

(2) Inability to achieve a response of at least PR by 24 weeks (second CT assessment),

(3) Relapse or progression of disease,

(4) Withdrawal of consent or

(5) Unacceptable toxicity.

All randomized patients are followed for progression free survival and overall survival. This includes patients who discontinue the study early for any reason without documented evidence of disease progression.

Upon completion of the required treatments, the patient will enter the Follow-Up Period. In the follow-up period, the patients will be followed for disease progression, next lymphoma treatment (including next chemotherapy) and overall survival.

All protocol defined efficacy assessments will be conducted by Central Review including central radiology and clinical review by an Independent Review Committee (IRC). However, a patient's withdrawal from the study for disease progression or failure to achieve threshold clinical activity at the 12 and 24 week assessments [see points (1) and (2) above] will be based upon investigator assessment.

Since the study endpoint is PFS based on computed axial tomography (CT) as determined by IRC, progression will be based on CT scans.

For suspected progression based on clinical evaluation, a CT scan must be available demonstrating unequivocal progression.

For equivocal progression based on CT findings, the site Investigator will contact the principal investigator of the study to determine whether the patient should remain on the study treatment. In some cases of equivocal progression, immediate central reading of the CT scan in question may be requested prior to removing the patient from the study treatment. In such cases, if the PD is not confirmed by central radiology review, the patient should continue treatment as per protocol.

In limited instances where progression is evident only by assessments other than CT, CT scans must still be obtained along with the non-CT documentation of progression.

The same methodology will be performed for equivocal cases of threshold clinical activity at the 12 and 24 week assessments. That is, in equivocal cases of threshold clinical activity, the site investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if threshold clinical activity is confirmed by central radiological review, the patient should continue treatment as per protocol.

DSMC will conduct two early futility analyses, the first, 6 months after the 200th patient has been randomized (whatever their disease status) and the second, 120 weeks after the 200th patient has been randomized (whatever their disease status). The first futility analysis is to evaluate the complete response (CR/CRu) rate at 24 weeks (6 months) of treatment for the first 200 patients. The second futility analysis is to evaluate the complete response (CR/CRu) rate at 120 weeks for the first 200 patients.

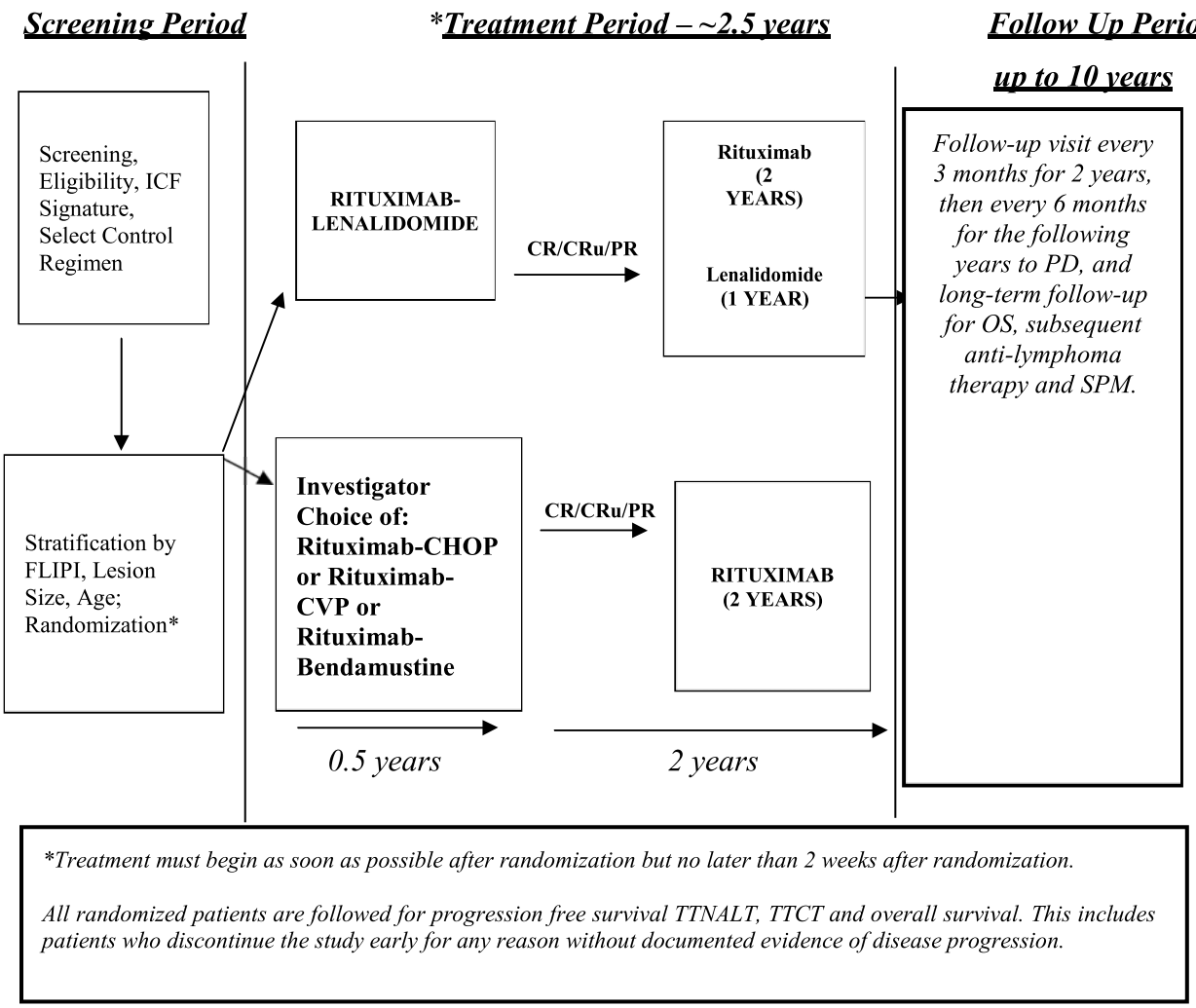
Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG (Cheson, 1999) criteriaBecause all protocol specified analyses including early futility analyses are based on IRC review, all CT scans must be sent for central review as soon as possible.

See Section 8 for a detailed description of Statistical Analyses.

The study will be conducted in compliance with Good Clinical Practices (GCPs).

Lenalidomide concentrations will be determined in patients who consent to this analysis in selected countries and sites.

Figure 1: Overall Study Design



2.3. Study Duration

The duration of the entire study will be approximately 12-13 years. Patients receive up to four weeks of screening, approximately 2.5 years of treatment and up to 10 years of follow-up.

The expected accrual duration is 40 months. Patients will be stratified by FLIPI score (0-1 v 2 v 3-5), age (>60 v ≤ 60) and longest diameter of the largest node (> 6 v ≤ 6 cm) and randomized to receive either rituximab-lenalidomide or Investigators Choice of R-CHOP, R- CVP, or R-B.

Randomized patients will receive therapy for approximately 2.5 years and followed until relapse or progression. After relapse or progression, OS, anti-lymphoma therapy and second primary malignancy (SPM) data will continue to be collected.

3. STUDY POPULATION

Patients must have an investigator-assessed diagnosis of Stage II-IV follicular lymphoma, grade 1-3a, have not been previously treated for their lymphoma other than local radiation for localized disease, have signs or symptoms of lymphoma requiring treatment, and have adequate bone marrow function, liver function and renal function.

3.1. Inclusion criteria

Patients must satisfy all the following criteria to be enrolled in the study:

1. Histologically confirmed CD20+ follicular lymphoma grade 1, 2 or 3a as assessed by the investigators:
   - a formalin fixed paraffin embedded specimen taken within 18 months before signing informed consent must be available for central review, and
   - a formalin fixed paraffin embedded bone marrow biopsy taken within 18 months before patient signing informed consent must be available for central review.
2. Have no prior systemic treatment for lymphoma.
3. Must be in need of treatment as evidenced by at least one of the following criteria:
   - Bulky disease defined as:
     - a nodal or extranodal (except spleen) mass >7cm in its greater diameter or,
     - involvement of at least 3 nodal or extranodal sites (each with a diameter greater than ≥3 cm)
   - Presence of at least one of the following B symptoms:
     - fever (>38C) of unclear etiology
     - night sweats
     - weight loss greater than 10% within the prior 6 months
   - Symptomatic splenomegaly
   - Compression syndrome (ureteral, orbital, gastrointestinal)
   - Any one of the following cytopenias due to lymphoma:
     - hemoglobin < 10g/dL (6.25 mmol/L)
     - platelets <100 x 10^9/L , or
     - absolute neutrophil count (ANC) < 1.5 x 10^9 /L
   - Pleural or peritoneal serous effusion (irrespective of cell content)
   - LDH > ULN or β2 microglobulin > ULN
4. Bi-dimensionally measurable disease with at least one mass lesion > 2 cm that was not previously irradiated.

5. Stage II, III or IV disease.
6. Must be > 18 years and sign an informed consent.
7. Performance status ≤ 2 on the ECOG scale.
8. Adequate hematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) within 28 days prior to signing informed consent, including:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 /L
   - Platelet count ≥ 75 x 10^9 /L
   - Hemoglobin ≥ 8.0 g/dl (5 mmol/L)
9. Must be able to adhere to the study visit schedule and other protocol requirements.
10. Females of childbearing potential (FCBP) receiving lenalidomide must:

    Have two negative pregnancy tests as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the patient practices complete abstinence from heterosexual contact.

    Either commit to complete abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.
11. Male patients receiving lenalidomide must[†]:

    Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

    Agree to not donate semen during study drug therapy and for 28 days after discontinuation of study drug therapy.
12. All patients receiving lenalidomide must:

    Have an understanding that the study drug could have a potential teratogenic risk.

    Agree to abstain from donating blood while taking study drug therapy and for 28 days after discontinuation of study drug therapy.

    Agree not to share study medication with another person.

    Agree to be counseled about pregnancy precautions and risk of fetal exposure

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

13. For all patients receiving Rituximab:

    Women must not breast feed and must use effective contraception must not be pregnant and agree not to become pregnant during participation in the trial and during the 6 months thereafter. Men must agree not to father a child during participation in the trial and during the 6 months thereafter.

3.2. Exclusion criteria

The presence of any of the following will exclude a patient from enrollment:

1. Clinical evidence of transformed lymphoma by investigator assessment.
2. Grade 3b follicular lymphoma.
3. Patients taking corticosteroids during the last 4 weeks, unless administered at a dose equivalent to < 10 mg/day prednisone (over these 4 weeks).
4. Major surgery (excluding lymph node biopsy) within 28 days prior to signing informed consent.
5. Seropositive for or active viral infection with hepatitis B virus (HBV):
   - HBsAg positive
   - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA

   Note:

   - Patients who are HBsAg negative, anti-HBs positive, and/or anti-HBc positive, but viral DNA negative are eligible
   - Patients who are seropositive due to a history of hepatitis B vaccine are eligible.
6. Known seropositive for, or active infection with hepatitis C virus (HCV).
7. Known seropositive for, or active viral infection with human immunodeficiency virus (HIV).
8. Life expectancy < 6 months.
9. Known sensitivity or allergy to murine products.
10. Prior history of malignancies, other than follicular lymphoma, unless the patient has been free of the disease for ≥ 10 years. Exceptions include a history of previously ***treated***:
    - Localized non-melanoma skin cancer
    - Carcinoma in situ of the cervix
11. Prior use of lenalidomide.
12. Neuropathy > Grade 1.
13. Presence or history of CNS involvement by lymphoma.
14. Patients who are at a high risk for a thromboembolic event and are not willing to take venous thromboembolic (VTE) prophylaxis.

15. Any of the following laboratory abnormalities:
    - serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT)> 3x upper limit of normal (ULN), except in patients with documented liver involvement by lymphoma
    - total bilirubin > 2.0 mg/dl (34 μmol/L) except in cases of Gilberts Syndrome and documented liver or pancreatic involvement by lymphoma
    - creatinine clearance of < 30 mL/min
16. Uncontrolled intercurrent illness.
17. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form.
18. Pregnant or lactating females.
19. Any condition, including the presence of laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study, or which confounds the ability to interpret data from the study.

4. STUDY TREATMENTS

4.1. Drugs description

Lenalidomide will be supplied as 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg capsules for oral administration and labeled as IP.

Commercially available IV formulation of Rituximab background therapy and standard of care therapy, i.e. cyclophosphamide, doxorubicin, vincristine and bendamustine will be used.

Commercially available prednisone will also be used as oral formulation. Standard of care chemotherapy must be available by prescription, generally reimbursed by the health system and used routinely in previously untreated FL patients at the center.

4.2. Treatment schedule and design

Treatment must start as soon as possible after randomization but no later than 2 weeks after randomization. Treatment Period for each patient starts with first intake of study drug, which is defined as Study Day 1 of Cycle 1.

4.2.1. Experimental Arm : Rituximab - Lenalidomide

Patients randomized to receive rituximab-lenalidomide will receive six cycles of lenalidomide 20 mg daily on days 2-22 every 28 days. Patients exhibiting a CR/CRu after six cycles then receive 12 cycles of 10 mg lenalidomide daily on days 2-22 every 28 days for a total of 18 cycles. Patients exhibiting a PR after six cycles receive an additional 3 or 6 cycles of the 20 mg lenalidomide dose until they achieve a CR/CRu at which time they receive the 10 mg lenalidomide dosing for 9 or 6 cycles respectively for a total of 18 cycles. Patients who remain in PR after the additional 6 cycles will receive 10 mg lenalidomide dosing for a total of 18 cycles.

All patients randomized to receive rituximab-lenalidomide receive rituximab, 375 mg/m^2 on days 1, 8, 15 and 22 of cycle 1, day 1 of cycles 2 to 6; and 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Lenalidomide treatment is continued for 18 cycles or until disease progression, unacceptable toxicity, or voluntary withdrawal. In addition, patients who do not achieve a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment), and patients who do not achieve a response of at least PR by 24 weeks (second CT assessment) will be withdrawn from treatment and followed for survival and PFS using the same schedule of assessments as patients continuing treatment .

Lenalidomide dosing will be based on patients creatinine clearance calculated using the Cockcroft-Gault formula. Creatinine clearance should be calculated using actual body weight.

Patients who have a creatinine clearance ≥ 60 mL/min will receive oral lenalidomide that is initiated on Day [D] 2 of Cycle 1 at a dose of 20 mg [p.o.] once daily for 21 days (D2 – D22) in each 28 day cycle.

Patients who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min] will receive a lower starting dose of lenalidomide of 10 mg once daily for 21 days (D2 – D22) in Cycle 1 and Cycle 2.

After completion of Cycle 2, if the patient remains free of Grade 3 or Grade 4 toxicity, the dose may be increased to a maximum of 15 mg once daily for 21 days (D2 – D22) starting on day 2 of cycle 3.

Lenalidomide should be taken at approximately the same time every day. There is no requirement for taking lenalidomide with or without food, or with or without certain types of foods or liquids. If a patient misses a dose of lenalidomide and it is within 12 hours of their normal dosing time, the patient should be instructed to make up the missed dose, and to then take their next dose according to their regular schedule. Lenalidomide concentration is low at 12 hours post dose, therefore making up a missed dose and then resuming regular dosing with a greater than or equal to (≥) 12 hour interval between the two doses will not cause considerable drug accumulation.

4.2.2. Control Arm : Investigators Choice

Patients randomized to receive investigators choice will receive ONE of the following

Rituximab-CHOP: with six cycles of R-CHOP in 21 day cycles followed by two 21 day cycles of 375 mg/m^2 rituximab and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles,

OR

Rituximab-CVP: with eight cycles of R-CVP in 21 day cycles; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles,

OR

Rituximab-Bendamustine: with rituximab 375 mg/m^2 (day 1) plus bendamustine 90 mg/m^2 (days 1 + 2) every 28 days for six cycles; and 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles.

Patients who do not achieve the threshold clinical activity of 1) 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment) or 2) a response by 24 weeks (second CT assessment) will be withdrawn from treatment and followed for survival and PFS using the same schedule of assessments as patients continuing treatment.

4.2.3. Rituximab background therapy

The planned dose of rituximab is 375 mg/m^2 in all regimens. Schedule is as described for individual regimens. Premedication should be administered (see package insert).

All dosage calculations for rituximab and chemotherapies will be based on the patient‘s body surface area (BSA), using actual weight for calculations. This will be determined on the first day of study drug administration of Cycle 1. For rituximab, no dosage adjustments should be performed.

For large changes in body weight compared to baseline (≥ 10%), the dose of chemotherapy may be modified accordingly. However, the same dose of rituximab should be infused regardless of any fluctuations in body weight.

In rare cases, for patients with high leukemic infiltration the very first dose of rituximab may be given as 2 parts on days 1 and 2, respectively, but the medical monitor or coordinating investigator must be contacted for prior authorization. The amounts administered on day 1 and day 2 will be at the discretion of the physician.

4.2.4. R-CHOP regimen

Standard CHOP chemotherapy consists of cyclophosphamide, doxorubicin, vincristine and prednisone.

The doses of CHOP components are:

Cyclophosphamide, 750 mg/m2 IV on day 1

Doxorubicin, 50 mg/m2 IV on day 1

Vincristine, 1.4 mg/m2 (2 mg cap) IV on day 1

Prednisone, 100 mg/day PO on days 1-5

CHOP will be administered according to the standard preparation and infusion procedures of each investigational site.

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For patient ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA but drugs other than vincristine should not be capped..

Rituximab is administered on day 1 for six cycles with CHOP in 21 day cycles followed by two 21 day cycles of 375 mg/m^2 rituximab; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert).

4.2.5. R-CVP regimen

Standard CVP chemotherapy consists of cyclophosphamide IV push, vincristine IV bolus and prednisone PO. The doses of CVP components are:

Cyclophosphamide 750 mg/m^2 day 1

Vincristine 1.4 mg/m^2 (2 mg cap) day 1,

Prednisone 40 mg/m^2 (5 days 1-5)

CVP will be administered according to the standard preparation and infusion procedures of each investigational site.

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For patient ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be

adjusted in case of are large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA but drugs other than vincristine should not be capped.

Rituximab is administered on day 1 for eight cycles with CVP in 21 day cycles: and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert).

4.2.6. R-Bendamustine regimen

Bendamustine is administered at 90 mg/m^2 on days 1 + 2 every 28 days for six cycles. Bendamustine will be administered according to the standard preparation and infusion procedures of each investigational site. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Rituximab is administered on day 1 for six cycles with bendamustine in 28 day cycles and 8 weeks later responding patients continue with 375 mg/m^2 rituximab on day 1 every 8 weeks for 12 cycles. Premedication should be administered (see package insert)

4.3. Dose Modifications

4.3.1. Lenalidomide Dose Modifications

The lenalidomide dose for each patient will be interrupted and/or modified by following the toxicity rules as described in Table 1, Table 2, and Table 3.

Basically, if a significant toxicity, defined as dose-limiting toxicity in Table 1, occurs on or after day 15 of the cycle, treatment will be held (interrupted) until the end of the cycle and the dose will then be reduced by a step (dose level -1) in the subsequent cycle.

If toxicity occurs before day 15 of the cycle, treatment will be held until recovery and restarted without dose reduction for the rest of the cycle (continue until day 21; missed doses will not be made up).

The next cycle will resume at reduced dose (dose level -1) in subsequent cycles. In those instances where in the opinion of the investigator re-challenge at the same dose level poses an unacceptable risk to the patient, treatment will be held (interrupted) until the end of the cycle and the dose will be reduced by a step in the subsequent cycle

In case of recurrence of an event during the same cycle, lenalidomide will be held until the next cycle.

Doses that were missed, due to toxicity or any other reasons, will not be rescheduled. If a dose is reduced, re-escalation is not permitted.

There will be no dose adjustment for rituximab. In case of cycle delay due to lenalidomide induced toxicity, rituximab of the next cycle will also be postponed until AE has resolved and recycling is allowed.

If dosing is interrupted for toxicity or cycle delayed, it can only be restarted if:

- The ANC is ≥ 1,000 cells/mm^3 (1.0 X 10^9/L);
- The platelet count is ≥ 50,000 cells/mm^3 (50 X 10^9/L);

- Lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity;
- Any other lenalidomide-related AE not requiring discontinuation has resolved to ≤ Grade 2 severity.

These conditions must be met on Day 1 of each cycle to initiate dosing for the cycle. If these conditions are not met on Day 1 of a new cycle, the patient will be evaluated once every seven days and a new cycle of treatment with lenalidomide will not be initiated until the toxicity has resolved as described above. When a cycle is delayed, both drugs (rituximab and lenalidomide) should be delayed. If a new cycle is delayed for more than 28 days, the Medical Monitor must be notified.

Table 1: Lenalidomide Dose Modification Rules

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Grade 3 Neutrophil count decreased (neutropenia) (one time reading)	Follow CBC at least every seven days.
Neutrophil count decreased (Neutropenia) Sustained (≥ 7 days) Grade 3 OR ≥ Grade 3 associated with fever (temperature ≥ 38.5° C) OR Grade 4	• If neutropenia has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow CBC every seven days • If neutropenia occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • Use of G-CSF, is permitted if the ANC is below 500 during a cycle at the discretion of the Investigator as per ASCO and ESMO guidelines. • In both cases, restart subsequent cycle at next lower dose
Platelet count decreased (Thrombocytopenia) ≥ Grade 3 (platelet count < 50,000 cells/mm^3 [50x10^9/L])	• If thrombocytopenia has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow CBC every seven days • If thrombocytopenia has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose

Table 1: Lenalidomide Dose Modification Rules (Continued)

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Allergic reaction or hypersensitivity **Grade 2** Grade 3-4	• If allergic reaction has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If allergic reaction has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose • Permanently discontinue lenalidomide study drug
Constipation Grade 1-2 ≥ Grade 3	• Initiate bowel regimen and maintain dose level • If constipation has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If constipation has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Vascular access complication (Venous thrombosis/embolism) ≥ Grade 3	• Hold (interrupt) dose and start anticoagulation; restart at Investigator's discretion (maintain dose level)
Peripheral neuropathy Newly developed ≥ Grade 3 (applies only to those neuropathies which begin or worsen while on study)	• If neuropathy has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If neuropathy has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Tumor Flare Reaction (TFR)* Grade 1-2 Grade 3-4	• Continue lenalidomide, maintain dose level • At the investigator's discretion may initiate therapy with NSAIDs, limited duration corticosteroids, and/or narcotics • Initiate therapy with NSAIDs, corticosteroids, and/or narcotics • If TFR has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle, and follow at least every seven days • If TFR has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose

Table 1: Lenalidomide Dose Modification Rules (Continued)

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Tumor Lysis Syndrome (TLS)** Laboratory TLS or Grade 1 TLS	• Continue lenalidomide (maintain dose), or at the investigator's discretion, continue lenalidomide and reduce dose by one level at the start of the subsequent cycle • Provide vigorous intravenous hydration and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy is appropriate (if approved by the local Health Authority) as needed to reduce hyperuricemia • Hospitalization will be at investigator's discretion
Grade 2-4	• If TLS has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If TLS has occurred before day 15 and resolved to Grade 0 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose • If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following re-initiation of lenalidomide
Other lenalidomide related non- hematologic AEs ≥ Grade 3	• If AE has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If AE has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Hypothyroid	
If the TSH is > ULN and patient is clinically euthyroid	• repeat TSH on Day 1 of next cycle. • No dose decrease or interruption
If TSH is > ULN for more than 2 cycles, or if patient has clinical symptoms of hypothyroidism;	• Endocrinology evaluation is recommended and thyroid hormone replacement is allowed if clinically indicated. • No dose decrease or interruption

Table 1: Lenalidomide Dose Modification Rules (Continued)

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Hyperthyroid If TSH < ~~U~~LN and patient is clinically euthyroid,.	• repeat TSH every 3 months. • No dose decrease or interruption
If TSH <~~U~~LN at repeat evaluation and patient is clinically euthyroid	• recommend endocrine evaluation. • No dose decrease or interruption
If TSH < ~~U~~LN and patients have symptoms of hyperthyroid (tremor, tachycardia, unintentional weight loss, or *new onset* night sweats),	• Hold lenalidomide for remainder of cycle. • Obtain endocrine evaluation and workup for alternative etiologies. • Repeat TSH level on day 1 of next cycle and contact PI. • If endocrine evaluation rules out hyperthyroidism, restart lenalidomide at the same dose at next cycle • If hyperthyroidism confirmed and alternative etiologies eliminated, restart lenalidomide dosing at next lower dose in the next cycle.

*AEs are graded using the NCI CTCAE v 4.03; however TFR will be graded using NCI CTCAE v 3.0 as subsequent versions do not contain a provision for TFR.
** AEs are graded using the Cairo-Bishop toxicity grade

Please note that Leucopenia and Lymphopenia are not part of the dose modification rules, only Neutropenia grade 3 or 4 requires dose modification.

Table 2: Lenalidomide Dose Modification Rules for Rash

DLT, based on NCI CTCAE Toxicity Grade	Action Required < Day 15	Action Required ≥ Day 15
Rash[a] Grades 1-2	• Start supportive measuresb if grade 2 • No dose adjustment	• Start supportive measures if grade 2 • No dose adjustment
Grade 3 (Non- desquamating or non- blistering)	• Hold (interrupt) dose. • Start supportive measures. • Evaluate weekly • If rash resolves to ≤ grade 1 prior to day 21 restart at the • same dose level and continue to • Day 21. • Restart subsequent cycle at next lower dose.	• Hold (interrupt) lenalidomide for remainder of cycle. • Start supportive measures. • Evaluate weekly until rash • ≤ grade 1. • Restart subsequent cycle at next lower dose.
Grade 4[c]	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures
Desquamating (blistering) rash Any Grade[c]	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures

[a] AEs are graded using the NCI CTCAE v 4.03; however rash will be graded using NCI CTCAE v 3.0.

[b] Suggested supportive measures – 1) initiate daily oral antihistamines, for example, loratine 10 mg PO dialy, ceterizinge 10 mg PO dialy or diphenhydramine 25 mg PO daily; 2) Short courses of low-dose steroids for example, prednisone 10 mg PO x 3 days or hydrocortisone 20 mg PO QAM, 10 mg PO QPM x 3 days. It is recommended that the daily oral anti-histamines treatment be continued for the rest the of the lenalidomide treatment.

[c] In cases of severe (grade 4 or desquamating) rash, prompt dematologic evaluation with skin biopsy and workup for alternate causes is strongly recommended.

Table 3: Lenalidomide Dose Modification Rules For Abnormal Liver Function*

DLT, based on NCI CTCAE Toxicity Grade	Action Required
ALT grade 2 (>3 - 5 x UNL) **and** Total bilirubin grade 1 (> ULN - 1.5 x ULN)	• Continue study drug: re-test at next scheduled visit • No dose modification
ALT ≥ grade 3 (>5 x ULN) **or** Total bilirubin ≥ grade 2 (> 1.5 x ULN)	• hold (interrupt dose) for the rest of the cycle and follow weekly ALT and total bilirubin until return to baseline • Resume the same dose of study drug if recovery (return to baseline) from the event is ≤ 14 days. • If recovery is prolonged beyond 14 days, weekly testing of liver functions should occur during that cycle and then the study drug dose should be decreased by one level at the start of the next cycle.

*For patients with Gilberts Syndrome or liver involvement by lymphoma, dose reductions should be made in consultation with the medical monitor.

4.3.2. Lenalidomide Dose Reductions Levels

The daily dose of lenalidomide may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction per cycle. Once a patient's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase. Refer to Table 4 for patients starting at the 20 mg dose, and to Table5 for patients starting at the 10 mg dose.

Table 4: Dose Reduction Levels from 20 mg Start Dose

Starting Dose	**20 mg daily on Days 2-22, every 28 days**
Level –1 Dose	15 mg daily on Days 2-22, every 28 days
Level –2 Dose	10 mg daily on Days 2-22, every 28 days
Level –3 Dose	5 mg daily on Days 2-22, every 28 days
Level –4 Dose	2.5 mg daily on Days 2-22, every 28 days

Table 5: Dose Reduction Levels from 10 (or 15) mg Start Dose

Starting Dose	10 mg daily on Days 2-22, every 28 days
Level A Dose*	15 mg daily on Days 2-22, every 28 days
Level –1 Dose	5 mg daily on Days 2-22, every 28 days
Level –2 Dose	2.5 mg daily on Days 2-22, every 28 days

*After completion of Cycle 2, if the patient remains free of Grade 3 or Grade 4 toxicity, the dose may be increased to a maximum of 15 mg once daily for 21 days (D2 – D22) starting on day 2 of cycle 3. The same dose reduction rules as in Table 4 would then apply.

Table 6: Dose Reduction Levels from the Cycle 13 - 10 mg Dose*

Starting Dose	10 mg daily on Days 2-22, every 28 days
Level –1 Dose	5 mg daily on Days 2-22, every 28 days
Level –2 Dose	2.5 mg daily on Days 2-22, every 28 days

*All patients receive the 10 mg lenalidomide dose from cycle 13 through cycle 18. Patients exhibiting CR/CRu after 6 and before 12 cycles begin the 10 mg lenalidomide at the next cycle.

Patients with no dose reduction or dose reduction to 15 mg or 10 mg during cycles 1-12 continue with 10 mg. Patients who dose reduced to 5 mg or 2.5 mg during cycles 1-12 continue with 5 mg and 2.5 mg respectively.

4.3.3. Dose Adjustment for Patients in the Control Arm

Patients will be evaluated for adverse events at each visit with the NCI CTCAE v 4.03 used as a guide for the grading of severity. The dose of Investigator's Choice for each patient will be interrupted and modified according to the clinical practice of the Investigator's institution, and in line with the approved prescribing information including administration, warnings, precautions, contraindications, and adverse reactions, as applicable.

4.4. Method of Treatment Assignment

The treatment assignment will occur in the screening period, once all the required screening procedures have been completed, and all required data have been submitted to the IVRS/IWRS system.

Investigators will select one protocol specified standard of care chemotherapy (i.e., bendamustine, CHOP or CVP) for their patient during screening and enter this data into IVRS/IWRS. Standard of care chemotherapy must be available by prescription, generally reimbursed by the health system and used routinely in previously untreated FL patients at the center.

Patients will be stratified by FLIPI score (0-1 v 2 v 3-5), age (>60 v $\leq$ 60) and longest diameter of the largest node (> 6 v $\leq$ 6 cm) and randomized to receive either rituximab-lenalidomide or Investigators Choice of R-CHOP, R-CVP, or R-B.

4.5. Drug Dispensation and accountability

4.5.1. Packaging and labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

4.5.2. Study Drug Receipt and Storage

The Investigator, or designee, is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug shipping order/packing slip.

The Investigator, or designee, will verify the accuracy of the information on the study drug shipping order/packing form and call the IVRS to register/activate the study drug received at the site.

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

The study drug should be stored as directed on the respective package labels.

4.5.3. Drug Dispensing Requirements

In investigational studies, study drug will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of study patients. Once trained these healthcare staff will counsel study patients prior to study drug being dispensed to ensure that the study patient (FCBP & males) has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the study patient understands the risks associated with lenalidomide. This step will be documented by completing the Education and Counseling Guidance Document (Appendix 20.8), and no study drug will be dispensed until this step occurs. Counseling includes verification with the study patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet will be supplied as described in Appendix 20.8.

4.5.4. Special Handling Instructions

Health care providers should consider wearing gloves when directly handling Revlimid (lenalidomide) capsules followed by standard hand washing. All patients should not handle or administer lenalidomide unless they are wearing gloves. All patients should not extensively handle or open lenalidomide capsules and should maintain storage of capsules in the packaging until ingestion.

4.5.5. Record of Administration

Accurate recording of all study drug administration will be made in the appropriate section of the patient's CRF and source documents.

4.5.6. Accountability and destruction

An accurate accounting of the dispensing/return of study drug for each study patient will be maintained in source documents on an ongoing basis by a member of the study site staff. Additionally, if any study drug is lost or damaged or if the study patient misses a dose, this information should be documented in the study patient's CRF and source documents.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

4.5.7. Compliance

For the oral medications of lenalidomide, study personnel will review the dosing instructions with the patient prior to dispensing the study drug. The patient will be instructed to return the study drug bottle, including any unused study drug, to the site at the next visit. Patient compliance will be noted on the appropriate CRFs and source records based on a capsule count. To monitor treatment compliance, reconciliation of capsules will be done at each scheduled study visit.

5. STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS

5.1. Study flow chart

See Figure 1.

5.2. Screening Examination and Procedures

See Table 1 – Schedule of Assessments.

Patients will be screened for protocol eligibility during a period of no more than 4 weeks prior to randomization as outlined in the Schedule of Study Assessments.

Screening assessments and recording of AEs/SAEs will begin once the patient has signed the informed consent form.

The patient's eligibility (inclusion and exclusion criteria) has to be evaluated during the screening period prior to randomization.

5.2.1. Demographic Information

- Written Informed Consent
- Complete medical history (including previous cancer)
- Physical examination performed within 2 weeks prior to the first day of treatment
- Age, gender
- Weight, height and BSA
- Vital signs (including Blood Pressure, pulse and temperature)

5.2.2. Histological diagnosis

FFPE tumor block of diagnostic tumor tissue taken within the 18 months before signing the informed consent must be confirmed to be available at the time of randomization and must be submitted to central pathology within 12 weeks after randomization.

If block cannot be sent, an H&E slide and 10 unstained slides will be acceptable.

Pathology reports associated with these tissues are also required and will be sent to the central pathology laboratory with the tissue and/or slides. The sponsor will provide detailed instructions and materials for sample handling and shipping. *Note that diagnosis based on fine needle aspirations is not considered acceptable pathologic data for entry into this study.*

Eligibility will be based on local pathology review; confirmation of diagnosis by central pathology laboratory is not required for entry or initiation of treatment. If tumor tissue was not collected within 18 months prior to the patient signing the informed consent, a newly obtained tumor biopsy (excisional or core) is required.

5.2.3. Tumor and disease staging

- CT/MRI of neck, chest, abdomen and pelvis is required to locally confirm measurable disease of at least 2 cm. CT is to be performed with contrast unless it is medically contraindicated. This scan may be used as the baseline CT scan if it is obtained within 6 weeks prior to randomization.
- Evaluation of all involved nodal and extra-nodal sites of lymphoma.
- Assessment of spleen and liver enlargement based on CT scan or physical examination.
- FDG-PET scan (optional). FDG-PET is to be submitted in addition to CT/MRI data, not in lieu of it.
- Patients with a presence of CNS lymphoma involvement are excluded from the study. Patients with suspicion of CNS involvement must undergo neurologic evaluation and CT/MRI of head and lumbar puncture to exclude CNS disease.
- Paraffin fixed bone marrow biopsy taken within 18 months of patient signing the informed consent or if bone marrow block are not available 5 representative, unstained slides must be submitted to central pathology within 12 weeks after randomization.

  The pathology reports must also be submitted. Although receipt of the blocks or slides by central pathology is required, the outcome of the central review of the slides is not part of the eligibility requirements.

  If bone marrow biopsy was not collected within 18 months of signing the informed consent, a newly obtained bone marrow biopsy is required. Bone marrow aspirate will not be acceptable.
- B-symptoms
- FLIPI and FLIPI 2 (See Appendix 20.4)
- Ann Arbor staging (See Appendix 20.5)
- ECOG performance status (See Appendix 20.6)

5.2.4. Laboratory assessments

- Compete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC) and platelet count.
- sodium, potassium, calcium,
- phosphorous,
- glucose,
- uric acid,

- alkaline phosphatase, AST, ALT, total protein, albumin, total bilirubin,
- chloride,
- blood urea nitrogen,
- lactate dehydrogenase (LDH), β2-microglobulin
- TSH
- Creatinine
  (creatinine clearance will be calculated by the Cockcroft-Gault formula)

Cockcroft-Gault estimation of creatinine clearance (CrCl):

Serum creatinine units mg/dL => for females, the formula is multiplied by 0.85.

CrCl (mL/min) = [(**140 – age** (years)) x (**weight** [kg])] / [**72** x (**serum creatinine** [mg/dL])];

Serum creatinine units µmol/L => A = 1.23 for men and A = 1.04 for females.

CrCl (mL/min) = [(**140 – age** (years)) x (**weight** [kg]) x **A**] / (**serum creatinine** [µmol/L]);

Creatinine clearance should be determined utilizing actual body weight (Cockcroft, 1976; Luke, 1990).

Eligibility for the study is based on the local laboratory results.

Laboratories used for hematological and biochemical tests and assays including ongoing pregnancy tests during the study are individual centre laboratories. All the laboratories must provide their normal values and an updated accreditation for quality control.

However, if Screening labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.

5.2.5. Cardiac function evaluation

- 12-Lead ECG is performed at Screening and as clinically indicated thereafter.
- Left VEF (measured by Ultrasound echocardiography or scintigraphy) according to physician decision (if patient planned to receive anthracycline).

5.2.6. Serologies and specific laboratory assessments

- Hepatitis B screening includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs)
- Two pregnancy tests for females of childbearing potential (FCBP) – 1) one during screening period (all FCBP) and 2) one within 24 hours prior the start of lenalidomide (only for FCBP randomized in experimental arm).

Please note that following laboratory assessments are optional and will be performed only by selected sites and countries.

- FcgR polymorphism is measured in peripheral blood cells once during screening.

- Blood MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation in peripheral blood or other MRD assays.
- Bone marrow MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation or other MR.
- Serum immunoglobulin levels
- Peripheral blood immunophenotyping (Total T cells and B cells, as well as CD4/CD8 and NK cells)
- Tetanus (T-cell dependent) and pneumococcal (Pure B cell) response specific serum IgG
- Lymphoma cells (%)

5.2.7. Quality of life assessments

- EORTC QLQ-C30 (Appendix 20.3)
- EQ-5D (Appendix 20.3)

5.2.8. Selection of Standard-of-Care regimen (Investigator's Choice)

The intent of this study is to compare the rituximab plus lenalidomide regimen to standard-of-care rituximab-chemotherapy regimens in use in a particular country, geographic region or institution.

Therefore, during the Screening Phase, prior to randomization, Investigators will select one regimen from a choice of protocol specified choices of standard-of-care chemotherapy regimens from the choices described in Section 8.2 for their patient during screening and enter this choice into IVRS/IWRS.

Standard of care chemotherapy regimen must be available by prescription, generally reimbursed by the health system and used routinely to treat previously untreated FL patients at the center.

After randomization, study drug is dispensed on Day 1 for lenalidomide patients or Investigator's Choice patients assigned to oral prednisone (R-CHOP or R-CVP). For Cycle 1 only, a 2 weeks window between randomization and Cycle1 Day 1 is allowed; however, the Screening period must remain within 28 days of Cycle 1 Day 1 dosing.

5.3. Evaluation during treatment and follow-up

Serial assessments of safety and efficacy will be performed as outlined in the Schedule of Study Assessments (Table 1). Patients in both arms will follow comparable assessment schedules. Note that for the first year of maintenance rituximab cycles are administered every 56 days and lenalidomide cycles every 28 days. To balance patient contacts during this time, patients in the rituximab arm will call the site/or call center for a phone call interview every 28 days after each rituximab treatment (for months without rituximab administration) during the first year of maintenance. Laboratories used for hematological and biochemical tests and assays including ongoing pregnancy tests during the study are individual centre laboratories.

5.3.1. Evaluation during each cycle of treatment

- Physical examination (including weight, vital signs and ECOG PS) at day 1 ofevery treatment cycle
- Serum chemistry laboratory evaluations (sodium, potassium, chloride, calcium, phosphorus, BUN, creatinine, glucose, albumin, total protein, ALP, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid) within 48 hours of Day 1 of everytreatment cycle

Note that the Cycle 1 Day 8 (±1 day) and 15 (±1 day) and Cycle 2-4 Day 15 (±1day) chemistry labs are required only for patients in the experimental arm and suggested for patients in the control arm to monitor for tumor lysis.

- Hematology laboratory evaluations (RBC count, hemoglobin, hematocrit, WBC count and differential, ANC, and platelet count) within 48 hours of Day 1 of every treatment Cycle

Note that the Cycle 1 Day 8 (±1 day) and 15 (±1 day) and Cycle 2-4 Day 15 (±1day) hematology labs are required only for patients in the experimental arm and suggested for patients in the control arm to monitor for cytopenias. The cycles 5-6 Day 15 hematology labs are required for all patients.

However, if Screening or standard of care labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1

- TSH to be performed until week 76 and will follow the same schedule as the CT scans. See Section 10.3.2 for more details on the CT scan schedule. However if the lab for Day 1 of the cycle are drawn within the given window as specified for CT scan, it need not be repeated again.
  - It is recommended that the patient be monitored for TLS during the first week of cycle 1. The site should make every effort to contact the patient on Day 5 (± 1 day) of the first cycle to inquire about the patient's condition and to make sure that he/she is continuing with TLS prophylaxis measures by keeping hydrated and taking the TLS prophylaxis as instructed. Any patient contact that is made on Day 5 (± 1 day) should be documented in patient's medical record and any AEs that are discovered should be captured on the CRF.
  - Pregnancy tests for females of childbearing potential (FCBP) will be performed weekly during the first cycle, every 28 days (Day 1 of every cycle) during treatment and at Day 28 following study drug discontinuation as described in Appendix 20.8.

5.3.2. Evaluation of response

- All response assessments will be determined from first dose date and will follow the counting of calendar days and not the dosing cycles.
- Patients with negative bone marrow at screening require no further bone marrow biopsy. Patients with positive bone marrow at screening must have a post-screening bone marrow biopsy to confirm CR/CRu within 28 days of first achieving

radiological, clinical and biochemical CR/CRu. Post-screening bone marrow biopsies taken when the patient is not in CR/CRu that are negative also require no further bone marrow biopsy. At 120 weeks, patients with a positive bone marrow at screening who are in radiological, clinical and biochemical CR/CRu and who have not had a negative post-screening bone marrow biopsy must have a repeat bone marrow biopsy at this time to confirm CR/CRu.

- CT scans using contrast media are the preferred radiology method (MRI is allowed in case of contraindications to the use of CT scans):
  - 12 weeks after the first dose date (-1 week/+2 weeks),
  - 24 weeks after the first dose date (-1 week/+4 weeks),
  - 36 weeks after the first dose date (-1 week/+ 2 weeks),
  - 52 weeks after the first dose date (-1 week/+ 2 weeks),
  - 76 weeks after the first dose date (-1 week/+ 3 weeks),
  - 100 weeks after the first dose date (-1 week/+ 3 weeks),
  - 120 weeks after the first dose date (-1 week/+ 4 weeks),
  - and then every 6 months (± 4 weeks) for 5 years and then every year (± 4 weeks) until disease progression or relapse.
- FDG-PET scan (will be optional). FDG-PET is to be submitted in addition to CT/MRI data, not in lieu of it:
  - 24 weeks after the first dose date (-1 week/+4 weeks),
  - 76 weeks after the first dose date (-1 week/+ 3 weeks),
  - 120 weeks after the first dose date (-1 week/+ 4 weeks).
- Physical examination (including ECOG PS and B symptoms) during each response assessment by CT scans. However if the physical examination for Day 1 of the cycle is drawn within the given window as specified for CT scan it need not be repeated again.
- Serum chemistry (LDH) during each response assessment by CT scans. However if the lab for Day 1 of the cycle are drawn within the given window as specified for CT scan, it need not be repeated again

Since the study endpoint is PFS based on CT, FDG PET scan is not the basis for disease progression. For suspected progression based on FDG-PET, a CT scan must be available demonstrating unequivocal progression.

All protocol defined efficacy assessments will be conducted by Central Review including central radiology and clinical review by an IRC. Since the study endpoint is PFS based on CT as determined by IRC, progression will be based on CT scans.

For suspected progression based on clinical evaluation, a CT scan must be available demonstrating unequivocal progression.

For equivocal progression based on CT findings, the site Investigator will contact the principal investigator of the study to determine whether the patient should remain on the study treatment. In some cases of equivocal progression, immediate central reading of the CT scan in question may be requested prior to removing the patient from the study treatment. In such cases, if the PD is not confirmed by central radiology review, the patient should continue treatment as per protocol.

In limited instances where progression is evident only by assessments other than CT, CT scans will still be provided along with the non-CT documentation of progression.

The same methodology will be performed for equivocal cases of threshold clinical activity at the 12 and 24 week assessments. That is, in equivocal cases of threshold clinical activity, the site investigator will contact the principal investigator of the study to determine whether the patient should remain on the study. In some cases immediate central reading of the CT scan in question may be requested prior to removing the patient from the study. In such cases, if threshold clinical activity is confirmed by central radiological review, the patient should continue treatment as per protocol.

5.3.3. Quality of Life Assessments

- EORTC QLQ-C30: Follow the same schedule as described for CT scans in Section 10.3.2.
- EQ-5D: Follow the same schedule as described for CT scans in Section 10.3.2 with the exception that EQ-5D assessments continue beyond disease progression/relapse until the end of follow-up period.

5.3.4. Specific laboratory assessments

Please note that following laboratory assessments are optional and will be performed only by selected sites and countries.

- Blood MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation in peripheral blood or other MRD assays at the following time points : 24 weeks (-1 week/+4 weeks), 76 weeks (-1 week/+ 3 weeks), 120 weeks (-1 week/+4 weeks).
- Bone marrow MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation or other MRD assays at the following time points : 24 weeks (-1 week/+4 weeks), 120 weeks (-1 week/+4 weeks) and only for patients with bone marrow involved by lymphoma at screening.
- Serum immunoglobulin levels are measured at the following time points: 24 weeks (- 1 week/+4 weeks), 52 weeks (- 1 week/+2 weeks), 76 weeks (- 1 week/+3 weeks), 100 weeks (- 1 week /+3 weeks), 120 weeks (-1 week /+4 weeks).
- Peripheral blood immunophenotyping (Total T cells and B cells, as well as CD4/CD8 and NK cells) are at the following time points: 24 weeks (-1 week/+4 weeks), 76 weeks (-1 week/+3 weeks), 120 weeks (-1 week/+4 weeks).

- Tetanus (T-cell dependent) and pneumococcal (Pure B cell) response specific serum IgG is measured at 24 weeks (-1 week/+ 4 weeks) and 120 weeks (-1 week/+ 4 weeks) after the first dose date in patients with documentation of prior vaccination who consent to this additional assessment.

5.3.5. Assessments for Venous Thromboembolitic events (VTE)

VTE including Deep vein thrombosis and pulmonary embolism will be assessed.

Deep vein thrombosis in Non-Hodgkin's Lymphoma

Ottinger et al (1995) analyzed incidence, risk factors, causes and prognostic significance of venous thromboembolism (VTE) in high-grade non-Hodgkin's lymphoma (HG-NHL) in a prospective clinical trial. In 593 patients, they reported a 6.6% incidence of VTE, with 77% of all cases occurring before or within the first 3 months of chemotherapy. Vessel compression by HG-NHL was identified as the leading cause of VTE.

In lymphoma patients receiving lenalidomide, DVT and PE were reported in 7 (3.2%) and 6 (2.8%) of 266 patients with relapsed or refractory aggressive NHL receiving lenalidomide in clinical studies NHL-002 and NHL-003 (Wiernik 2006; Witzig, 2011). DVT and PE were reported in 0 (0%) and 1 (2.3%) of 43 patients with indolent relapsed refractory NHL (Witzig, 2009). Anti-thrombotic prophylaxis was not suggested in NHL-001 or NHL-002 but required for patients considered to be high risk of developing DVT in NHL-003.

Unlike the increased risk of DVT reported when adding lenalidomide to dexamethasone in multiple myeloma patients, there is no evidence to suggest an increased risk of DVT in lymphoma patients receiving lenalidomide as single agent.

Nonetheless, in the current study, it is recommended that patients randomized to the rituximab-lenalidomide who are considered to be at high risk for DVT receive anti-thrombotic prophylaxis (see Section 9.1.2) and all patients will be closely monitored for VTE including Deep vein thrombosis and pulmonary embolism.

5.3.6. Assessment for Treatment Discontinuation

- Physical examination including vital signs and ECOG PS
- Hematology and serum chemistry laboratory evaluations
- Adverse events including SPM
- Hospitalization
- Concomitant medication
- Study drug return/accountability
- Subsequent anti-lymphoma therapy
- EORTC QLQ-C30 and EQ-5D questionnaires
- Pregnancy Test for FCBP

5.4. Follow-up assessments

Follow-up period will start at the end of treatment (120 weeks) or at treatment discontinuation (if applicable). Adverse events and hospitalization will be recorded up to 28 days after the last dose of study drug (s).

Patient will be followed every 3 months (± 2 weeks) for the first two years and every 6 months (± 4 weeks) up to end of follow-up period.

For patients who have completed treatment or discontinued treatment due to reasons other than progressive disease or relapse follow-up assessments include:

- Physical examination including ECOG PS
- Hematology laboratory evaluations (RBC count, hemoglobin, hematocrit, WBC count and differential, ANC, and platelet count) every 3 months (± 2 weeks) for the first two years and every 6 months (± 4 weeks)
- LDH will follow the CT scan assessment schedule as described in Section 10.3.2
- CT scans will follow the assessment schedule as described in Section 10.3.2
- Optional Serum immunoglobulin levels every 6 months/24 weeks (± 4 weeks) for 1 year of follow-up will only be performed by selected sites and countries.
- Overall survival
- SPM

- EORTC QLQ-C30 and EQ-5D questionnaires will follow the CT scan assessment schedule as described in Section 10.3.2

For patients who discontinue treatment due to progressive disease or relapse, follow-up assessments include:

- Overall survival,
- Subsequent anti-lymphoma therapy (including the time of and best response to the first anti-lymphoma treatment regimen utilized after discontinuation from the treatment)
- Subsequent anti-lymphoma chemotherapy (including the time of and best response to the first anti-lymphoma chemotherapy utilized after discontinuation from the treatment)
- EQ-5D questionnaire
- SPM and relevant information

5.5. Progression/Relapse

Relapse/progression will be determined as per Cheson1999 criteria (see Appendix 20.1). Progressive disease should be based on CT scan.

A pathological confirmation by biopsy of the lesion should be done if possible.

6. STUDY PROCEDURES

6.1. Informed consent

Written informed consent written and approved in compliance with local regulatory authority will be obtained from each patient prior to being randomized in the trial. Specific informed consent should be signed for biological studies and genetic analysis. The informed consent for biological studies and genetics analysis should be signed before sampling.

The patient and the investigator will date and sign the informed consent form.

The investigator shall provide a copy of the signed consent to the study patient; the original shall be maintained in the investigator's study file.

6.2. Pathological diagnosis

Histopathology central review process has become in the last years a common and prerequisite procedure for clinical trials in the field of lymphomas. It requires both a histopathological and immunohistochemical approach using an appropriate panel of antibodies according to the morphological pattern and, in some instances, further molecular or genetic analysis. A mandatory pathological review will be organized for all patients included in the trial. The goal of this central review will be to confirm the diagnosis and to classify precisely the malignancy according to the WHO classification 2008.

Therefore for each patient, the investigator will be requested to submit a registration form along with a copy of the histopathological report where the name and address of the pathologist having diagnosed the lymphoma will be easily identified as well as a copy of the bone marrow report.

All the requested tumor paraffin embedded blocks from the formalin fixed sample (that was used for diagnosis), or 10 unstained slides, and bone marrow biopsy (or 5 unstained slides with H&E) will be collected.

At reception, routinely stained sections will be assessed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a pathological review will be organized, and a consensus diagnosis will be entered on the review form. This review form will then be sent to the clinical coordinator and to the pathologist coordinator.

Initial tumor block will also be used to make tissue microarray (TMA) and tissue core for DNA extraction; both will be used to study the expression of markers known to influence the prognosis of follicular lymphoma.

When the review process is completed, tissue array and tissue core analysis are completed, a pathological report will be sent to the initial pathologist as well as the investigator at the enrolling centre and the remaining pathologic material will be sent back to the initial pathologist.

6.3. CT scan Review

CT scans must be performed according to the quality requirements detailed in the imaging manual. Specifically, all CT scans must be performed using IV contrast, a slice thickness of $\leq$ 5mm and must include thoracic, abdominal, neck and pelvic anatomical regions.

A central review of CT scan is mandatory and organized. For each patient, when applicable, data and images of CT scan performed at following timepoints will be reviewed by a panel of CT experts:

- screening
- 12 weeks after the first dose date (-1 week/+2 weeks),
- 24 weeks after the first dose date (-1 week/+ 4 weeks),
- 36 weeks after the first dose date (-1 week/+ 2 weeks),
- 52 weeks after the first dose date (-1 week/+ 2 weeks),
- 76 weeks after the first dose date (-1 week/+ 3 weeks),
- 100 weeks after the first dose date (-1 week/+ 3 weeks),
- 120 weeks after the first dose date (-1 week/+ 4 weeks). Scans at 120 weeks which are not performed as specified or are otherwise unevaluable must be repeated,
- Every 6 months (± 4 weeks) for 5 years and then every year (± 4 weeks) until disease progression or relapse,
- to document progression/relapse.

The central analysis of the imaging should be done according to IWG response criteria (Cheson, 1999) for the NHL.

For CTs, the reviewer panel is composed by 3 CT experts for review of the CTs according to the following rules:

- 2 reviewers will analyze the CT scans independently.
- In case of disagreement between the 2 reviewers, the 3rd reviewer will analyze the CT exams independently.

6.4. PET scan Review

A central review of the FDG-PET scan is organized. For each patient when applicable, the data and images of FDG-PET scan performed at following time points will be reviewed by a panel of PET experts:

- screening
- 24 weeks after the first dose date (-1 week/+ 4 weeks),
- 76 weeks after the first dose date (-1 week/+ 3 weeks),
- 120 weeks after the first dose date (-1 week/+ 4 weeks).

For FDG-PETs, The reviewer panel is composed by 3 nuclear physicians for review of the PETs according to the following rules:

- 2 reviewers will analyze the PET scans independently.
- In case of disagreement between the 2 reviewers, the 3rd reviewer will analyze the PET exams independently.

7. CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

7.1. Premature withdrawal from trial intervention

Circumstances that lead to premature withdrawal of a patient from the trial must be reported by the investigator on the appropriate CRF page.

Criteria for patient withdrawal include (but are not limited to):

- Death,
- Toxicity (adverse event),
- Disease progression/relapse,
- Concomitant disease,
- Non compliance (including loss of patient to follow-up),
- Voluntary withdrawal,
- Major protocol violation, including initiation of alternate anti-neoplasic therapy.

Patients should however remain in the trial for the purposes of follow-up and data analysis.

7.2. Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states their wish not to contribute further data to the study, the relevant sponsor contact should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. However, data up to the time of consent withdrawal will be included in the data reported for the study.

7.3. Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained by investigator since one year and at least three unsuccessful documented attempts of contact are available in source documentation.

8. ADVERSE EVENTS

8.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

Signs, symptoms or physical findings indicative of lymphoma or progression of lymphoma should not be reported as an adverse event or serious adverse event. However, if a finding cannot be attributed with certainty to lymphoma or progression of lymphoma, this finding must be reported as an adverse event or serious adverse event, as applicable. For examples, 1) a finding of dyspnea or pleural effusion in a patient experiencing disease progression outside of the mediastinum or lung must be collected as an AE or SAE as applicable while dyspnea or pleural effusion in a patient experiencing disease progression in the mediastinum or lung may be judged to be results of disease progression and therefore not reported as an AE or SAE; 2) a finding of bowel obstruction in a patient experiencing disease progression outside of the bowel must be collected as an AE or SAE as applicable while bowel obstruction in a patient experiencing disease progression in the bowel may be judged to be results of disease progression.

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the patient's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the patient signs informed consent to 28 days after the last dose of study drug(s). AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the patient's source documents. All SAEs must be reported (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

8.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

8.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

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

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

SPM will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the patient is in (see Section 7.5). This includes any SPM, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the ICD up to and including the follow-up period of up to 10 years. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and patient's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.

- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- A procedure or hospitalization for progression/relapse investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling).
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen 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 study drug(s), action taken regarding study drug(s), and outcome.

8.2.2. Severity

For both AEs and SAEs, the Investigator must assess the severity of the event.

The severity/intensity of AEs will be graded based upon the patient's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the NCI CTCAE should be evaluated for severity/intensity according to the following scale:

Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5 = Death - the event results in death]

Specific NCI Working Group or other criteria pertinent to the indication may also be used as applicable.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on patient/event *outcome* or *action* criteria associated with events that pose a threat to a patient's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

8.2.3. Causality

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

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

If an event is assessed as suspected of being related to a comparator, ancillary or additional study drug(s) that has not been manufactured or provided by Sponsor, please provide the name of the manufacturer when reporting the event.

8.2.4. Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

8.2.5. Action Taken

The Investigator will report the action taken with study drug(s) as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

8.2.6. Outcome

All SAEs that have not resolved upon discontinuation of the patient's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

8.3. Abnormal laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;

- requires treatment, modification/ interruption of study drug(s) dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

The investigator has to notify in the patient's medical file all the abnormal laboratory values considered as clinically significant (write next to each abnormal laboratory value assessed as clinically significant "CS", or precise in the medical report).

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

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

8.4. Pregnancy

The Lenalidomide Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. Refer to approved product/prescribing information for further information on rituximab pregnancy restrictions.

8.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on IP, or within 28 days of the patient's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the patient instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form. The exposure of any pregnant female (eg, caregiver or pharmacist) to lenalidomide is also an immediately reportable event.

The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female patient until completion of the pregnancy, and must notify immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

8.4.2. Male Patients

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The event must also be reported immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form.

8.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page of the CRF. Signs, symptoms or physical findings indicative of lymphoma or progression of lymphoma should not be reported as serious adverse event. However, if a finding cannot be attributed with certainty to lymphoma or progression of lymphoma, this finding must be reported as an adverse event or serious adverse event, as applicable. All SAEs must be reported (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

SPM will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the patient is in. This includes any SPM, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the ICD up to and including the follow-up period of 10 years. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and patient's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study drug(s)) that occur during the study (from the time the patient signs informed consent to 28 days after the last dose of study drug (s), and those made known to the Investigator at anytime thereafter that are suspected of being related to study drug(s). SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a patient died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with the IRB/EC.

Safety Queries

Queries pertaining to SAEs will be communicated to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g., missing causality assessment) may be handled by phone.

8.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Drug Safety of the sponsor or its authorized representative will determine the expectedness of events suspected of being related to lenalidomide based on the Investigator Brochure.

Adverse events such as disease progression, death related to disease progression (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the sponsor to regulatory authorities.

The sponsor or its authorized representative shall notify the Investigator of the following information

- Any AE associated with the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to patients.

The Investigator must keep copies of all pertinent safety information on file.

8.7. Follow up of Serious Adverse events

Any SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported as soon as information becomes available.

9. STATISTICAL CONSIDERATIONS

This phase 3 study (RV-FOL_Gelarc-0683C) is a companion to the RV-FOL-Gelarc-0683 study with a combined enrollment target of 1000 patients and will enroll up to 250 patients. The data from both studies will be collected into one database and the statistical analyses as described in this Section will be performed on the combined total of patients enrolled into both studies. A single data safety monitoring committee (DSMC), central pathology, and Central Independent Review committee (IRC) will be utilized for these two studies.

9.1. Overview

The objective of this statistical analysis is to investigate efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma.

Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG (Cheson, 1999) criteria.

All statistical analyses specified in this protocol will be conducted using *SAS*® version 9.1.3 or higher.

9.2. Study Population Definitions

For this study, the following three populations will be defined and used in the analysis and presentation of the data.

Intent-to-treat (ITT) population: The ITT population is defined as all patients who are randomized into the trial, regardless of whether they received study treatment or not.

The ITT population will be used for the primary efficacy analysis. Patients will be analyzed according to the treatment arm to which they are initially assigned.

Modified ITT (mITT) population: The mITT population is defined as all randomized patients who have received at least one dose of study drug, have confirmed diagnosis of follicular lymphoma with no prior systemic treatment for lymphoma, have baseline and at least one post-baseline tumor assessment for efficacy.

The efficacy analysis will also be performed on the mITT population as supportive evidence and/or sensitivity analysis. Patients will be analyzed according to the treatment arm to which they are initially assigned.

Safety population: The safety population is defined as all patients who have received at least one dose of study drug. The safetypopulation will be used for all safety analysis. Patients will be analyzed according to the treatment which they actually received.

9.3. Sample Size and Power Considerations

Sample size calculation is based on providing adequate power to evaluate treatment effect on the co-primary efficacy endpoints.

The co-primary efficacy endpoints are complete response (CR/CRu) rate at 120 weeks and PFS.

It is hypothesized that the complete response (CR/CRu) rate at 120 weeks is 60% in the control arm and 72% in the experimental arm. For 90% power to detect this difference with two-sided $\alpha = 0.05$, a total of 644 patients (322 in each arm) will be required. The power calculation for the response rates is performed using EAST v5.4 software based on the large sample z-test with unspooled variance estimate.

It is hypothesized that the median PFS is 83 months in the control arm, and there is a 30% increase in the median PFS in the experimental arm (corresponding hazard ratio of 0.7692). For 80% power to detect this difference with two-sided $\alpha = 0.05$, a total of 456 progression/relapse/death events will be required.

Considering the sample size requirements for both co-primary endpoints, it is planned to enroll a total of approximately 1000 patients into the study.

Therefore, for an enrollment rate of 10 patients per month in the first six months, 25 patients per month in the next 11 months, and 30 patients per months thereafter with 6% dropout rate per year, a total of 1000 patients in 1:1 ratio to the two treatment arms (500 in each arms) will be needed, with a 40-month accrual period and up to 10 years follow-up. The analysis of PFS will occur in about 142 months when the required 456 progression/relapse/death events are expected to be observed.

The assumptions used in sample size calculations are derived from available literature, especially from the published results of PRIMA and STiL studies. For the proposed sample size of N = 1000, it should be noted that any reasonable deviations from these assumptions have limited impact on the power of the test. For example, if the complete response (CR/CRu) rate at 120 weeks is down to 50% in the control arm instead of 60%, the proposed sample size of 1000 patients still have roughly 97% power to detect a 12% rate difference. If the median PFS reduces to 70 months in the control arm instead of 83 months, it still requires a total of 456 events to detect a 30% increase in the median PFS, and the only impact is that the study duration will be reduced to 113 months if 1000 patients are to be randomized.

9.4. Background and Demographic Characteristics

Patient's age, height, weight, and baseline characteristics will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum), while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

Patient's demographics and baseline characteristics will be summarized for the ITT population. Patient disposition (analysis population allocation, randomized, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment arms. Protocol deviations will be summarized using frequency tabulations.

9.5. Efficacy Analysis

9.5.1. Co-Primary Efficacy Endpoints

Complete Response (CR/CRu) Rate at 120 weeks

The tumor response data will be assessed by the IRC using the IWG (Cheson, 1999) criteria.

Progression Free Survival (PFS)

PFS is an accepted endpoint of clinical benefit for previously untreated FL patient and was the basis for the recent approval of rituximab maintenance in this population (Salles, 2011). The disease progression status will be assessed by IRC using the IWG (Cheson, 1999) criteria. PFS is defined as the time from randomization into the study to the first observation of documented disease progression or death due to any cause. If a patient has not progressed or died, PFS will be censored at the time of last visit with adequate assessment. If a patient received other anti-cancer treatment for follicular lymphoma before progression, the CT/MRI assessments should continue as scheduled until disease progression or death which will be counted as events.

Various censoring rules will be considered in sensitivity analyses. Detailed censoring rules for PFS will be provided in the Statistical Analysis Plan based on "Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics" (see reference http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf) and "Methodological Considerations For Using Progression-Free Survival As Primary Endpoint In Confirmatory Trials For Registration" (http://www.emea.europa.eu/pdfs/human/ewp/26757506en.pdf).

9.5.2. Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed using appropriate statistical methods.

- Complete Response (CR) Rate at 120 weeks by IWG 1999
- Event Free Survival (EFS) by IWG 1999
- Time to Next Anti-Lymphoma Treatment (TTNLT)
- Overall Survival (OS)

EFS will be measured from the date of randomization to the date of first documented progression, relapse, and initiation of a new anti-lymphoma treatment or death by any cause. Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

TTNLT will be measured from the date of randomization to the date of first documented administration of any new anti-lymphoma treatment (chemotherapy, radiotherapy, radio-immunotherapy, immunotherapy). Patients continuing in response or who are lost to follow-up will be censored on their last visit date. Patients who died (due to any cause) before having received a new anti-lymphoma treatment will be included in the statistical analysis with death being counted as an event.

The OS will be measured from date of randomization to the date of death. Patients who die, regardless of the cause of death, will be considered to have had an event. Patients who withdraw consent for the study will be considered censored at the time of withdrawal. Patients who complete the study and are still alive at the time of the clinical data cut-off date will be censored. All patients who were lost to follow-up prior to the clinical data cut-off date will also be considered censored at the time of last contact.

9.5.3. Analysis Method

The co-primary efficacy endpoints are the complete response (CR/CRu) rate at 120 weeks and the PFS. The primary efficacy analysis will be based on the ITT population. Analysis based on the mITT population is supportive.

For the co-primary endpoint CR/CRu rate at 120 weeks, the number and percent of patients with CR/CRu at 120 weeks will be tabulated by treatment arm. The experimental arm will be declared superior if the two-sided p- value from a chi-square test is ≤ 0.05 in favor of the experimental arm. The primary analysis will be performed using a stratified Cochran-Mantel-Haenszel (CMH) test to adjust for possible confounding effects of the stratification factors: FLIPI score (0-1 vs 2 vs 3-5), Age (>60 vs $\leq$ 60), longest diameter of the largest node (> 6 v $\leq$ 6 cm). The un-stratified test will be a supportive analysis.

For the co-primary endpoint PFS, the Kaplan-Meier estimates of PFS function will be provided. If a patient has a missing or incomplete CT scan, all other available CT scans or MRIs of the patient will still be used for the analysis. The experimental arm will be declared superior if the two-sided p-value from a stratified log-rank test is ≤ 0.05 in favor of the experimental arm.

Conventionally, hazard ratio with two-sided 95% confidence interval (CI) will be estimated using the Cox proportional hazards model. But the treatment effect will be determined by the p-value, not by this 95% CI. The un-stratified log-rank test will be a supportive analysis. Subgroup analysis for PFS will be performed as appropriate.

The secondary efficacy endpoints are CR rate at 120 weeks, EFS, TTNLT, and OS. In order to control an overall two- sided 0.05 study-wise Type I error rate, a fixed-sequence gate-keeping procedure will be employed to interpret the analysis results of these secondary efficacy endpoints in the order of CR rate at 120 weeks, EFS, TTNLT, and OS.

Step 1: If the result of CR rate at 120 weeks fails to reach the 2-sided 0.05 significance level, no efficacy claims will be made for these secondary endpoints. If the p-value from the CR rate at 120 weeks ≤ 0.05, the efficacy claim for CR rate at 120 weeks will be made, and further testing will be performed in the Step 2.

Step 2: If the result of EFS analysis fails to reach the 2-sided 0.05 significance level, no efficacy claims will be made for the remaining three secondary endpoints. If the p-value from the EFS analysis ≤ 0.05, the efficacy claim for EFS will be made, and further testing will be performed in the Step 3.

Step 3: If the result of TTNLT analysis fails to reach the 2-sided 0.05 significance level, no efficacy claims will be made for the remaining two secondary endpoints. If the p-value from the TTNLT analysis ≤ 0.05, the efficacy claim for TTNLT will be made, and further testing will be performed in the Step 4.

Step 4: If the result of OS analysis fails to reach the 2-sided 0.05 significance level, no efficacy claim will be made for the OS endpoints. If the p-value from the OS analysis ≤ 0.05, the efficacy claim for the OS be made.

9.6. Safety Analysis

Safety analysis will include all patients in the Safety population.

Study medication exposure will be summarized for each treatment arm including duration of study medication, total dose taken, and dose reductions.

Adverse events, vital sign measurements, clinical laboratory measurements, and concomitant medications will be summarized by treatment arm.

AEs will be coded according to medical dictionary for drug regulatory activities (MedDRA) and classified using the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE). The incidence rates of AEs will be tabulated by system organ class and preferred term. Subsets of AEs to be summarized include serious AEs (SAEs), AEs of interest including SPM, events of all CTCAE grade severities, suspected treatment-related AEs, and events that resulted in withdrawal of study medication. The most severe grade of each preferred term for a patient will be utilized for summaries of adverse events by NCI CTCAE grade. All AEs with corresponding attributes will be displayed in a by-patient listing. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, suspected treatment-related events, and serious adverse events will also be displayed in separate

by-patient listings.

9.7. Interim Analysis

9.7.1. Interim Analysis for futility

For the co-primary endpoint of the complete response (CR/CRu) rate at 120 weeks, two interim analyses for futility are pre-planned:

- The first interim analysis will be performed when the first 200 patients have their response assessments done at 6 months oftreatment, or have had disease progression or died prior to this timepoint.
- The second interim analysis will be performed when the first 200 patients have their response assessments done at 120 weeks, or have had disease progression or died prior to this timepoint.

The intention of these two interim futility analyses is to assess risk-benefit and ensure patient safety. The proposed futility boundaries are non-binding. The results of these two futility analyses will be reviewed by the independent DMC to make recommendation of go/no go.

There is no plan to claim efficacy superiority based on these interim results, therefore, no Type I error rate adjustment is needed.

For the first futility analysis, possible results of the CR/CRu rate at 120 weeks for 644 patients will be simulated according to the following assumptions. The simulated results will then be analyzed to establish the first futility boundary.

Based on the PRIMA study results, the following assumptions are made for simulations:

1. For the first 100 patients in the control arm when their response data at 6 months are observed, their observed CR/CRu rate at 6 months is estimated approximately 58% to 62%, and their observed ORR is approximately 88% to 92%.
2. In the control arm, among the patients who have CR/CRu observed at 6 months there will be a 0.75 probability for them to remain in CR/CRu at 120 weeks, and among the patients who have PR observed at 6 months there will be a 0.50 probability for them to convert to CR/CRu at 120 weeks.
3. For the next 222 patients in the control arm whose response data at 6 months have not been observed yet at the first futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be (the observed CR/CRu rate at 6 months from the first 100 patients) x 0.75 + (the observed PR rate at 6 months from the first 100 patients) x 0.50.

4. For the first 100 patients in the experimental arm when their response data at 6 months are observed, their observed CR/CRu rate and PR rate at 6 months estimated in a wider range for the purpose to establish the first futility boundary.
5. In the experimental arm, among the patients who have CR/CRu observed at 6 months there will be a 0.90 probability for them to remain in CR/CRu at 120 weeks, and among the patients who have PR observed at 6 months there will be a 0.60 probability for them to convert to CR/CRu at 120 weeks.
6. For the next 222 patients in the experimental arm whose response data at 6 months have not been observed yet at the first futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be (the observed CR/CRu rate at 6 months from the first 100 patients) x 0.90 + (the observed PR rate at 6 months from the first 100 patients) x 0.60.

The Table 7 below shows the likelihood of achieving a superiority result based on the observed CR/CRu rates at 6 months for the first 200 patients. The futility boundary of the first futility analysis is that if the observed CR/CRu ratio (experimental arm/control arm) at 6 months is 0.80 or lower, the trial should be recommended to stop considering both the efficacy and safety outcome.

Table 7: 1st Futility Analysis Simulation Results

Observed CR/CRu Rate Ratio (experimental arm / Control arm) **at 6 Months, N=200 pts**	Conditional Power: Average Likelihood of Achieving Statistically Significant Results at α= 0.05 Level on CR/CRu at 30 months (N=644 pts)
0.88	**11.99%**
0.85	**5.58%**
0.82	**0.86%**
0.80	**0.21%**
0.75	**0.01%**
0.70	**0%**

For the second futility analysis, possible results of the CR/CRu rate at 120 weeks for 1000 patients will be simulated according to the following assumptions. The simulated results will then be analyzed to establish the second futility boundary.

1. For the first 100 patients in the control arm when their response data at 120 weeks are observed, their observed CR/CRu rate at 120 weeks is estimated approximately 60% to 66%.
2. For the next 400 patients in the control arm whose response data at 120 weeks have not been observed yet at the second futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be equal to the observed CR/CRu rate at 120 weeks from the first 100 patient.

3. For the first 100 patients in the experimental arm when their response data at 120 weeks are observed, their observed CR/CRu rate at 120 weeks is estimated in a wider range for the purpose to establish the second futility boundary.
4. For the next 400 patients in the experimental arm whose response data at 120 weeks have not been observed yet at the second futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be equal to the observed CR/CRu rate at 120 weeks from the first 100 patient.

The Table 8 below shows the likelihood of achieving a superiority result based on the observed CR/CRu rates at 120 weeks for the first 200 patients. The futility boundary of the second futility analysis is that if the observed CR/CRu ratio (experimental arm/control arm) at 120 weeks is 0.98 or lower, the trial should be recommended to stop based on this efficacy and safety outcome.

Table 8: 2nd Futility Analysis Simulation Results

Observed CR/CRu Rate Ratio (experimental arm / Control arm) **at 120 Weeks, N=200 pts**	Conditional Power: Average Likelihood of Achieving Statistically Significant Results at α = 0.05 Level on CR/CRu at 30 months (N=1000 pts)
1.08	**36.6%**
1.06	**23.8%**
1.04	**13.8%**
1.02	**3.6%**
1.00	**1.4%**
0.98	**0.5%**
0.96	**0.1%**

9.7.2. Interim Analysis for efficacy

The co-primary endpoint PFS will be analyzed as an interim analysis at the timepoint when the co-primary endpoint CR/CRu rate at 120 weeks is reported, i.e., when all randomized patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment.

In order to control the overall alpha for PFS, an alpha spending function of Gamma Family with parameter -2.5 will be applied.

9.8. Final Analysis

The final analysis will be performed:

- for the co-primary endpoint CR/CRu rate at 120 weeks: when all randomized patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment,
- for the co-primary endpoint PFS: when the required 456 progression/relapse/death events have occurred among all randomized patients.

The secondary endpoint CR rate at 120 weeks will be analyzed when all randomized patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment.

In order to control the alpha for the other secondary endpoints EFS, TTNLT and OS, the final analysis of these endpoints will be performed at the time of the final PFS analysis, and only descriptive statistics (Kaplan-Meier estimates, median, etc.) will be reported without formal statistical comparison at the time of the final CR/CRu rate at 120 weeks analysis.

10. STUDY COMMITTEES

10.1. Independent Data Safety Monitoring Committee (DSMC)

An independent external Data Safety Monitoring Committee (DSMC) will periodically review ongoing safety data throughout the study and make recommendations to the sponsor for any safety concerns.

In addition, the DSMC will also review efficacy data for futility. In particular, DSMC will conduct two early futility analyses. The first futility analysis is to evaluate the complete response (CR/CRu) rate as determined by IRC at 6 months of treatment for the first 200 patients. The DSMC will also review the results of the pre-planned interim analysis described above.

10.2. Independent Review Committee (IRC)

For complete response rate assessment an independent review of all CT scans according to an independent review charter.

Bone marrow re-examinations will be conducted at the clinical sites.

Patients with negative bone marrow at screening require no further bone marrow biopsy. Patients with positive bone marrow at screening must have a post-screening bone marrow biopsy to confirm CR/CRu within 28 days of first achieving radiological, clinical and biochemical CR/CRu. Post-screening bone marrow biopsies taken when the patient is not in CR/CRu that are negative also require no further bone marrow biopsy. At 120 weeks, patients with a positive bone marrow at screening who are in radiological, clinical and biochemical CR/CRu and who have not had a negative post-screening bone marrow biopsy must have a repeat bone marrow biopsy at this time to confirm CR/Cru.

11. REFERENCES

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. The secondary efficacy objectives in the protocol are updated to allow adjustment for multiplicity. The number of secondary efficacy endpoints is reduced to three: EFS, TTNLT, and OS. The other secondary objectives (TTF, TTNCT, ORR and health related quality of life questionnaire EORTC QLQ C30) are moved to the exploratory endpoints.

   Justification: The secondary endpoints are revised in accordance with FDA feedback regarding multiplicity. In addition, TTF is not an efficacy endpoints clearly stated in the FDA Guidance; TTNCT is very similar to TTNLT and it will not add value but consume alpha; Similarly, ORR is also moved to exploratory since CR rate is being assessed as co-primary endpoint.

2. The overall survival (OS) will be calculated from the time of randomization.

   Justification: In response to FDA feedback the statistical plan was updated for calculation of OS from the time of randomization.

3. Lenalidomide dose adaptation rules are amended. In addition, dose adaption for thyroid stimulating hormone (TSH) abnormality and guidance on management of rash have been added.

   Justification: To improve patient compliance with dosing and study visit schedule, mid-cycle dose reductions are not allowed. During a cycle, only dose interruption and restart at the same dose level are allowed depending upon when the AE occurred and at the discretion of the treating physician. Based upon the two coordinating investigators recommendation dose adaptation for TSH and guidance on management of rash have been added.

4. The PK substudy is removed from the protocol.

   Justification: The sparse PK is removed from the study for the following reasons:

   a. A preliminary analysis with PK data from multiple disease indications indicate that type of cancer does not affect PK of lenalidomide.

   b. Drug-drug interactions between lenalidomide and rituximab is not anticipated, as they do not share the same clearance pathway.

   c. Sparse PK data without intensive PK data are difficult to analyze.

   d The drug exposure at one dose level of lenalidomide plus high exposure variability with the sparse PK is not wide enough for a meaningful exposure-response analysis in this study.

   e. An integrated PK/PD report utilizing historical data in MM/MDS and newly collected data in MCL/CLL is planned to be generated. This report will show that PK of lenalidomide is not sensitive to the type of cancer, and thus it may be used to support the future filling for FL.

5. Modified visit schedule to reduce the number of visits in Cycle 1; Day 2 and Day 4 visits have been removed from first cycle of treatment, with a recommended monitoring for TLS during first week of cycle 1 and telephone contact added at Day 5 of the first cycle.

Justification: Tumor lysis syndrome (TLS) is characterized by metabolic abnormalities that can occur during rapid tumor breakdown in response to anti-cancer treatment. TLS is common in patients with NHL or acute leukemia (Howard et al, 2011, NEJM 364: 1844), but it is uncommon among the patients with follicular lymphoma unless the patient has high WBC counts or receives anti-CD20 treatment.

Although rare, TLS has been reported in NHL patients treated with lenalidomide, either as monotherapy or in combination with rituximab. One case of grade 1 TLS was reported in the 309 relapsed/refractory NHL patients receiving lenalidomide monotherapy in three Celgene sponsored phase 2 studies. In a single-center, open-label Phase II investigator study, Dutia et al. (2009), evaluating the use of lenalidomide plus rituximab in patients with relapsed or refractory indolent B-cell NHL, two of the first four patients (with no TLS prophylaxis) receiving lenalidomide dose of 25 mg developed tumor lysis. After initiating TLS prophylaxis with allopurinol, no further TLS events were recorded in 12 additional patients receiving 20 mg lenalidomide dose (Total N=16) (Dutia et al., 2009, ASH abstract #1679).

TLS and tumor flare reaction (TFR) have commonly been observed in patients with CLL, who were treated with lenalidomide. In some CLL patients, tumor flare and tumor lysis have been life-threatening and fatal. Based on early CLL results from CC-5013-CLL-001, frequent monitoring visits were included during the first cycle in protocols evaluating lenalidomide in CLL and lymphoma patients, including the current study. Since then, more experience with lenalidomide in CLL populations has been gained with the current CLL-008 data that support the reduced monitoring visit frequency to ease the burden on subjects without compromising their safety. Celgene reviewed safety data from the first 55 subjects (26 received lenalidomide) enrolled into the CLL-008 study. No clinical TLS was reported. One case of laboratory TLS was reported however it could not be confirmed according to the Cairo-Bishop definition and didn't result in any dose modification.

Results to date, demonstrate that with implementation of TLS prophylaxis, TLS risk (which was the basis for the very frequent visits) could be mitigated.

In the current FL study, the patients randomized to the rituximab-lenalidomide:

- receive allopurinol prophylaxis and are strongly recommended to be well hydrated especially during the first week of lenalidomide administration.
- have 6 visits during the 28 days of Cycle 1 on Days 1, 2, 4, 8, 15, 22 with blood draws on Days 1, 2, 4, 8, 15

The amendment proposes to reduce the cycle 1 monitoring visits from 6 to 4 as follows:

- have 4 visits during the 28 days of Cycle 1 on Day 1, Day 8, Day 15, Day 22 of Cycle 1 with blood draws on Days 1, 8, 15

- Strong recommendation to monitor the patient during the first week of Cycle 1 and telephone contact for Day 5 of the first cycle

The amendment also includes several other clarifications and corrections

1. Change of name and contact info of 2nd /back-up medical monitor and Celgene study manager, new personnel added for biological studies and change name for GELA to LYSA.
2. Clarification of total number of patients enrolled in the US will be up to a maximum of 250 patients
3. Updated the inclusion criterion #3 regarding 'need for treatment' to include the choice of 'LDH >ULN or β2 microglobuline >ULN'
4. Clarified the exception for exclusion criterion #5 regarding patients who are seropositive for HBV, that the patient who are HBsAg negative, anti-HBs positive and/or anti-HBc positive but viral DNA negative are eligible.
5. Updated the definition of high risk patients for VTE prophylaxis to include ' Bulky disease'
6. Clarification of the window (2 weeks) allowed after randomization but prior to start of the treatment
7. Clarification that the first rituximab dose (C1D1) for patients with high leukemic infiltration in rare cases may be given as 2 parts - on day 1 and day 2, respectively upon prior authorization from the medical monitor or coordinating PI.
8. Clarification of the window (6 weeks) allowed for the baseline/screening CT scan prior to the randomization.
9. Updated the windows for the CT scans and FDG-PET assessments during the study to accommodate the 2 week window provided for the treatment start post randomization
10. AE terms in the lenalidomide dose modification rule table updated to be consistent with the CTCAE v 4.0
11. Clarification for consistency that the immunophenotyping, MRD, anti-tetanus, anti pneumococcal tests are optional in the table of assessment and also in section 10.3.5. Clarification of the optional lymphoma cells collection.
12. Clarification of the repeat bone marrow biopsy requirements for patients in the study who have achieved CR at 6 months and 120 weeks.
13. Updated the Response assessment section to include LDH assessment with the caveat that it need not be repeated if the Day 1 blood draw falls within the given windows as specified for the CT scan.
14. Updated the AE section to clarify that signs and symptoms related to PD will not be collected as AE or SAE.
15. Updated the follow-up section to be consistent with the figure and section 6.3 in regards to the assessment for the patients with PD/relapse.
16. For consistency, throughout the protocol 'subject' was replaced with 'patient'.

17. Clarification of the assessments for treatment discontinuations (section 10.3.8) to be consistent with table for schedule of assessments.
18. Clarification of the follow-up assessment based on the patients disease status and also to be consistent with figure 2 and section 6.3.
19. Added name lenalidomide prior to (CC-5013) to the header
20. Updated the window for Day 1 assessments and clarified windows for Day 8 (cycle 1) and Day 15 (Cycles 1 - 6) assessments.
21. Figure 1 updated to include the window for treatment start after randomization and clarification regarding follow-up visits.
22. Clarification regarding capping of vincristine dose in the control arm R-CHOP or R-CVP regimens.
23. Clarification regarding use of growth factors according to ASCO or ESMO guidelines and also the examples of growth factors that may be prescribed for rescue from severe hematologic events.
24. Updated section on drug dispensation and accountability to clarify about study drug receipt and storage, drug dispensing requirement, handling and recording drug administration.
25. Updated Apendix A to include definition of stable disease (SD).
26. Following clarification and correction in Table for schedule of assessments –
    a. Updated windows for Day 1 of each cycle from 3 to 2 days to be consistent with that in section 10.3.1
    b. Added Day 15 hematology assessment for cycles 5 and 6
    c. Added TSH, B symptoms, LDH, and β2 microglobuline assessments to the table
    d. Added window (±1 day) for Day 8 and Day 15 assessments of Cycle 1, window (± 1 day) for Day 15 assessment during cycle 2-6 and window (+/- 4 weeks) to the treatment discontinuation column
    e. Deleted sparse PK assessment
    f. Added footnote for the optional sub studies (immunophenotyping, MRD, anti-tetanus, anti pneumococcal) for clarification
    g. Deleted serum chemistry row and added LDH to the follow-up assessment table
    h. Deleted CT/MRI, FDG-PET scan, PFS/TTF/EFS, Response Assessments, and Bone marrow biopsy for the End of Treatment column as these assessment will be as per protocol specified schedule.
    Justification: CT schedule should be independent of treatment until disease progression and equally applied to both treatment arms. There is no need to do an additional CT if treatment discontinued due to toxicity at some arbitrary time point.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Prednisone has been updated to predonisolone because prednisone is not approved in Japan.
- Clarified the definition of response of at least a PR for the threshold clinical activity at 24 weeks (second CT assessment).
- Clarified calculation of Creatinine clearance utilizing actual body weight.
- Corrected the TSH level information for hyperthyroid.
- Updated sections 8.1., 8.5.2., 8.5.3., 13.6., 16.6., 17.2.,17.3., 17.4., 18.2., 18.3., and 18.6 to meet local regulatory requirements.
- Updated the Pregnancy Prevention Risk Management Plan to meet the requirements for Japan
- Updated information about study personnel and incorporated editorial changes.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Change the timing of CR/CRu at 120 weeks from N = 644 to all randomized subjects.

Complete Response (CR/CRu) rate at 120 weeks from randomization and PFS are the co-primary endpoints. Both will be assessed by IRC according to IWG (Cheson, 1999) criteria. In the current protocol, the analysis of CR/CRu rate at 120 weeks will be based on the first 644 subjects randomized. It is important and logical to utilize full information on all patients randomized. This will also mean that at the time of analysis of the coprimary endpoint, all patients will have completed treatment which means that the study integrity will not be compromised if the results are released. This also provides increased power for various proposed subgroup analyses with more subjects in each subgroup. After consultation with the study scientific committee, it was recommended to amend the study protocol to conduct the primary analysis of CR/CRu rate at 120 weeks based on all randomized subjects.

This change is made in the following Sections:
Statistical Analysis Sample Size
Synopsis Interim analysis for efficacy
Synopsis final analysis
Section 14.3
Section 14.72
Section 14.8
Table 9

- Add an interim analysis for PFS

The co-primary endpoint PFS will be also analyzed as an interim analysis when the primary analysis of CR/CRu rate at 120 weeks based on all randomized subjects is performed. In order to control the overall alpha for PFS, an alpha-spending function of Gamma Family with parameter -2.5 will be applied. It is estimated that around 270 PFS events (or 0.60 information) would occur at the interim PFS analysis. A statistically significant treatment effect on PFS will be reached if the two-sided p-value ≤ 0.016 at the interim PFS analysis, and ≤ 0.043 at the final PFS analysis. If the actual number of PFS events greatly deviates from 270 at the time of the interim PFS analysis, the interim alpha spending will be adjusted accordingly using the same alpha spending function based on the actual number of PFS events and information level.

This change is made in the following Sections:
Synopsis Interim analysis for efficacy
Section 14.7.2

- Add CR at 120 weeks as the first secondary endpoint.

CR rate as a component of CR/CRu is of particular scientific and clinical importance (for example, a recently completed meta-analysis indicate an improvement in CR rate at 30 months predicts PFS very well (Sargent, DJ, et.al., J Clin Oncol 33, 2015 (suppl; abstr 8504)). Therefore, CR rate at 120 weeks is being upgraded as the first secondary efficacy endpoint. This

change also allows adequate power for testing the CR rate at 120 weeks. In order to control an overall two-sided 0.05 study-wise type I error rate due to multiple testing, a sequential gate keeping approach will be used, that is testing on CR rate at 120 weeks will be conducted only if superiority of CR/CRu at 120 weeks is demonstrated.

This change is made in the following Sections:

Synopsis Study Objectives
Synopsis Analysis Plan
Synopsis Final analysis
Section 5.2
Section 14.3
Section 14.5.2
Section 14.5.4
Section 14.8

The amendment also includes several other minor clarifications and corrections, including

- Change in Medical Monitor
- Change in Lead Study Manager
- Clarification in Table 1
- Clarification of necessity and timing of post screening bone marrow biopsies
- Specified actual body weight should be used in creatinine clearance calculation
- Clarification on the use of steroids needed for the well being of the patient
- Ibuprofen was cited as an alternative to acetaminophen for rituximab premedication
- Provide guidance to investigators that abnormal lab values considered clinically significant must be notated as such.
- Clarification that bone marrow reexamination will be conducted at the clinical sites.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Re-insertion of Sections 13.4.1 and 13.4.2

  In drafting Amendment #2, Sections 13.4.1 and 13.4.2 from Amendment #1 were inadvertently removed. They are added back into Amendment #3.

- Added language to refer to the product/prescribing information regarding rituximab pregnancy restrictions

This language was added to alert investigators to refer to the current prescribing information for rituximab pregnancy restrictions.

This change is made in Section 13.4.

The amendment also includes a few minor clarifications and corrections.