DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-5013-DLC-002

PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTICENTER STUDY TO COMPARE THE EFFICACY AND SAFETY OF LENALIDOMIDE (CC-5013) PLUS R-CHOP CHEMOTHERAPY (R2-CHOP) VERSUS PLACEBO PLUS R-CHOP CHEMOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED ACTIVATED B-CELL TYPE DIFFUSE LARGE B-CELL LYMPHOMA

The information contained in the attached report is the property of Celgene and should not be shared or used for any purpose other than that for which it was provided.

Celgene is committed to providing information about its clinical trials to researchers and patients with the goal of furthering science and enhancing healthcare worldwide. Laws and regulations require, however, that Celgene protects patient privacy. The company may further have legal or contractual obligations not to disclose commercial or technical information provided by or related to certain partner companies or vendors.

The attached report is presented in its original format, but certain information has been redacted in order to comply with the aforementioned obligations or to protect Celgene's confidential commercial information. The redactions are based on the following principles:

- Redacted information has been replaced by grey space, maintaining original spacing and pagination.
- Any information that might allow the identification of individuals has been redacted for anonymization.
- Attachments to this report that contain confidential information are not made available. Such attachments include those that contain identifiable patient information, such as subject listings, narratives, and profiles. They also may contain confidential commercial information such as methodologies, and hypothesis generating and exploratory analyses.
- Cross-references to these attachments (such as links to subject listings in Section 16.2) are not redacted from the body of the report. However, the hyperlinks in the electronic document are no longer functional.
- Information about Celgene vendors and their services are redacted because many contracts prohibit disclosure of that information. Further, laws and regulations prevent us from disclosing certain information about our vendors or their services because it is protected by copyright.

Information about Celgene's redaction policies and the availability of additional data from this report may be found at http://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/.

STATISTICAL ANALYSIS PLAN

PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTICENTER STUDY TO COMPARE THE EFFICACY AND SAFETY OF LENALIDOMIDE (CC-5013) PLUS R-CHOP CHEMOTHERAPY (R2-CHOP) VERSUS PLACEBO PLUS R-CHOP CHEMOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED ACTIVATED B-CELL TYPE DIFFUSE LARGE B-CELL LYMPHOMA

INVESTIGATIONAL PRODUCT (IP):	LENALIDOMIDE (CC-5013)
PROTOCOL NUMBER:	CC-5013-DLC-002
DATE Final Amendment 3	04-FEB-2019

Prepared by:

Celgene Corporation

86 Morris Avenue

Summit, NJ 07901

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP VERSION, DATE	Final, ddMMMyyyy
SAP AUTHOR	*{See appended electronic signature page}* Printed Name and Title Date
PROTOCOL TITLE	PHASE 3 RANDOMIZED, DOUBLE-BLINDED, PLACEBO CONTROLLED, MULTICENTER STUDY TO COMPARE THE EFFICACY AND SAFETY OF LENALIDOMIDE (CC-5013) PLUS R-CHOP CHEMOTHERAPY (R2-CHOP) VERSUS PLACEBO PLUS R-CHOP CHEMOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED ACTIVATED B-CELL TYPE DIFFUSE LARGE B-CELL LYMPHOMA
INVESTIGATIONAL PRODUCT	CC-5013 (lenalidomide)
PROTOCOL NUMBER	CC-5013-DLC-002
PROTOCOL VERSION, DATE	Final Amendment 3, 04 February 2019
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Statistical Therapeutic Area Head Signature *{See appended electronic signature page}* Printed Name Date	
Lead Clinical Research Physician / Clinical Research Physician Signature *{See appended electronic signature page}* Printed Name Date	
Lead Product Safety Physician Signature *{See appended electronic signature page}* Printed Name Date	

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

ABC	Activated B-cell
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
ATE	Arterial Thromboembolism
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DI	Dose Intensity
DLBCL	Diffuse Large B-cell Lymphoma
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EAIR	Exposure Adjusted Incidence Rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

EFS	Event-free Survival
EMA	European Medicines Agency
EQ-5D	EuroQuol 5 Dimension Scale
FACT-Lym	Functional Assessment of Cancer Therapy for Patients with Lymphoma
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Gene Expression Profiling
HLT	Higher Level Term
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ID	Identification Number
Ig	Immunoglobulin
IHC	Immunohistochemistry
IP	Investigational Product
IPI	International Prognostic Index
IRAC	Independent Response Adjudication Committee
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
Max	Maximum
Min	Minimum
mITT	Modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multi Gated Acquisition
NCI	National Cancer Institute
NGS	Next Generation Sequencing

ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-free Survival
Placebo-R-CHOP	Placebo plus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or equivalent chemotherapy (R-CHOP)
PP	Per-protocol
PR	Partial Response
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
R2-CHOP	Lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or equivalent chemotherapy (R-CHOP)
RDI	Relative Dose Intensity
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPM	Second Primary Malignancy
TEAE	Treatment-emergent Adverse Event
TFR	Tumor Flare Reaction
TSH	Thyroid Stimulating Hormone
TTNLT	Time to Next Lymphoma Therapy
VTE	Venous Thromboembolism
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CC-5013-DLC-002 "Phase 3 Randomized, Double-Blind, Placebo Controlled, Multicenter Study to Compare the Efficacy and Safety of Lenalidomide (CC-5013) Plus R-CHOP Chemotherapy (R2-CHOP) Versus Placebo Plus R-CHOP Chemotherapy in Subjects with Previously Untreated Activated B-cell Type Diffuse Large B-cell Lymphoma" which was issued on 16 May 2014. It contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety.

The study includes one interim analysis for futility and one final analysis. This SAP covers both interim analysis and final analysis. Throughout this SAP, the treatment arms will be referred to as R2-CHOP (lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or equivalent chemotherapy) and placebo-R-CHOP (placebo plus R-CHOP). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to the database lock and any data analysis for the interim/final analysis. This SAP will be finalized and signed off prior to the clinical database subset lock for the final analysis. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.2 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the study is to compare the efficacy of R2-CHOP versus placebo-R-CHOP.

3.2. Secondary Objectives

The secondary objective of this study is to compare the safety of R2-CHOP versus placebo-R-CHOP.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This randomized, placebo-controlled study is designed to evaluate the efficacy and safety of R2-CHOP chemotherapy versus placebo-R-CHOP chemotherapy in subjects with previously untreated CD20+, activated B-cell (ABC) type diffuse large B-cell lymphoma (DLBCL). Stratification for randomization will be employed to reduce bias related to subject international prognostic index (IPI) score, presence of bulky disease, and age. Randomization in this parallel treatment design is in a 1:1 ratio to either R2-CHOP or placebo-R-CHOP. Celgene, as well as the investigator and subject, will be blinded to treatment assignment.

This study is divided into Screening, Treatment and Follow-Up Periods as summarized below and graphically presented in the Figure 1. Details of the study design are described in Sections 4.1.1, 4.1.2 and 4.1.5 of the protocol. Details of the study treatments are described in Section 8 of the study protocol.

During the Screening Period, subjects will undergo safety and other assessments to determine eligibility for the study. If subject eligibility is confirmed, then randomization via the interactive voice response system (IVRS) is the final part of the Screening Period. Pre-specification of the optional therapies such as the extra 2 doses of single agent rituximab or consolidation radiotherapy will also be registered in IVRS prior to randomization.

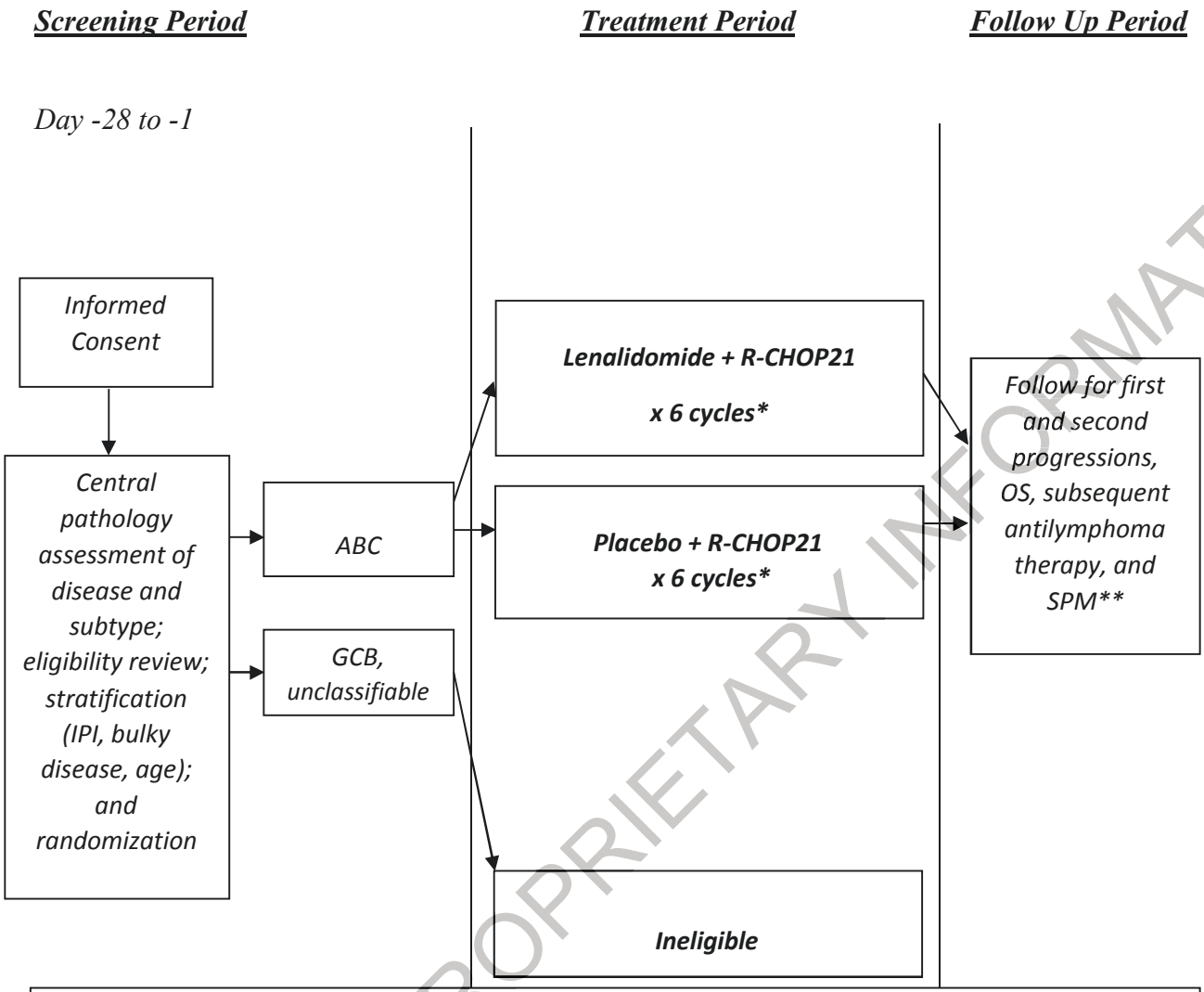
The Treatment Period begins with Cycle 1 Day 1 dosing. Subjects will receive protocol-specified treatments for 6 cycles. Treatment will continue to completion; or until the outcome of the computed tomography (CT) scan between Weeks 9 and 12 (after Cycle 3 but before Cycle 4) indicates a treatment change based on response assessment; disease progression; unacceptable toxicity; death; or withdrawal of consent, whichever occurs first.

The Follow-up Period begins upon study treatment completion or upon early discontinuation of study treatment. Subjects will be followed for first and second progressions, subsequent antilymphoma therapy, development of any second primary malignancies (SPMs), and overall survival (OS) according to the schedule described in Table 5 of the protocol.

Approximately 560 subjects will be randomized. Subjects who discontinue/withdraw from the study will not be replaced. There is one planned interim analysis for futility at 50% information level and one planned final analysis for superiority.

The study will be conducted in compliance with Good Clinical Practice (GCP).

Figure 1 Overall Study Design



* *It is permissible to administer an additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of study treatment are complete if it is considered standard of care per local practice. However, the decision to administer these extra two doses must be pre-specified in IVRS prior to randomization.*

Study treatment will continue until 6 cycles of treatment are complete; or until unacceptable toxicity; or until the outcome of the CT scan conducted once between weeks 9-12 (after Cycle 3 but before Cycle) indicates a treatment change based on response assessment; disease progression; or withdrawal of consent; whichever occurs first.

** *All subjects who discontinue treatment and who maintain consent, will proceed directly to the Follow-up Period. This includes subjects who complete the full course of treatment, who discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new antilymphoma therapy (chemotherapy, SCT, radiotherapy, etc.). During the Follow-up Period scans continue at protocol specified time points until first progression and are submitted to central radiology.*

Subjects who are alive at the time of primary analysis will still be followed exclusively for second primary malignancies, subsequent antilymphoma therapies, first and second progression and survival for up to 5 years from the date the last subject is randomized.

IPI= international prognostic index, ABC= activated B-cell, GCB= germinal center B-cell, OS=overall survival, SPM= second primary malignancy

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint

- Progression-free Survival (PFS)

4.2.2. Secondary Efficacy Endpoints

Key secondary endpoint

- Event-free Survival (EFS)

Other secondary endpoints

- Overall Survival
- Complete Response (CR) rate
- Duration of Complete Response
- Duration of Response (PR + CR)
- Time to Next Lymphoma Therapy (TTNLT)
- Objective Response Rate (ORR)
- Health-related quality of life (HRQoL) as measured by the EuroQuol 5 Dimension Scale (EQ-5D) and the Functional Assessment of Cancer Therapy for Patients with Lymphoma (FACT–Lym) standardized measures of health status

4.2.4. Safety Endpoints

- Adverse Events (AEs) including SPMs
- Physical examinations
- Vital signs

- Laboratory tests based on central laboratory

4.3. Stratification, Randomization, and Blinding

An IVRS will be employed to accomplish randomization, to record pre-specification of optional consolidation radiotherapy, and to manage subject medications.

Once the subject is determined eligible, the investigator or designee will access the IVRS within the 28-day Screening Period to obtain the randomized treatment assignment for the subject.

Subjects will be stratified as follows:

- IPI score: 2 versus ≥ 3
- Age: < 65 versus ≥ 65 years
- Presence of bulky disease: ≥ 7.0 cm (bulky) versus < 7.0 cm (non-bulky)

Subjects will be randomized in a 1:1 ratio to either R2-CHOP or placebo-R-CHOP. The subject identification number (ID) assigned by the IVRS will identify the subject for all aspects of the study. The randomization schedule will be generated by the IVRS vendor based on a permuted-block randomization method.

This study is a double-blind study, which means that Celgene, as well as the investigator and subject, will be blinded to treatment assignment (R2-CHOP or placebo-R-CHOP).

4.4. Sample Size Determination

For the primary endpoint PFS, the superiority of R2-CHOP versus placebo-R-CHOP will be tested. The hypotheses on superiority are defined as:

$$H_0: \text{HR (test versus control)} = 1 \text{ versus } H_1: \text{HR (test versus control)} < 1$$

where HR (test versus control) is the hazard ratio of R2-CHOP arm (test) over placebo-R-CHOP arm (control). One hundred and ninety-two (192) PFS events (progression or deaths) out of 560 subjects will have 90% power to detect a 37.5% hazard reduction in disease progression, ie, HR (test versus control) = 0.625 for the R2-CHOP arm versus placebo-R-CHOP arm using a 2-sided test with a significance level of 0.05. This sample size has already taken into account the pre-planned interim analysis for futility at 50% of the information.

With an adequate peak enrollment rate of 18 subjects per month that is reached in 9 months and the assumption that the median PFS in the control arm (placebo-R-CHOP) is about 24 months, it is estimated that the required 50% information, or 96 PFS events, for the interim PFS futility analysis will be available approximately 28 months from the start of enrollment, and the required 192 PFS events for the final PFS analysis will be available in about 42 months from the start of enrollment.

This sample size is calculated using the software EAST 5.4 with a β-spending function of Gamma (-4). Since there is no intention to declare efficacy at the interim PFS analysis, no α-spending function is specified. For a detailed description of stopping boundaries please refer to Section 13 Interim Analysis.

In case the event rate falls below 2 events per month before reaching 192 events, the final analysis will be performed when at least 170 events have occurred. The power of the study will be at least 86%.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

The summary tables, listings, and any supportive SAS output will include the explanatory "headers" that indicate, at a minimum:

- protocol number
- data cutoff date

The Summary tables, listings, and any supportive SAS output will include the explanatory "footers" that indicate, at a minimum:

- program source (ie, SAS program name, including the path, run date)
- data extraction date

The purpose of the data extraction date is to link the output to the database, either active or archived, that is write-protected for replication and future reference. The program run date is the output date which will appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting corresponding table and figure.

In addition, the following reporting conventions will be implemented:

- Data from all study centers will be combined for analysis;
- All stratified efficacy analyses will use the stratification factors including IPI score (2 versus ≥ 3), age (< 65 versus ≥ 65 years), and presence of bulky disease (≥ 7.0 cm [bulky] versus < 7.0 cm [non-bulky]);
- All statistical tests of the treatment effect will be conducted as 2-sided tests;
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999';
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless otherwise specified;
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, Standard Deviation (SD), first quartile (Q1), third quartile (Q3), minimum (Min), and maximum (Max) for continuous variables;
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value;
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the

parentheses. In the case the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0);

- All listings will be sorted for presentation in order of study center, subject, and date of procedure or event;
- All analysis and summary tables will have the analysis population sample size (ie, number of subjects) wherever applicable;
- Baseline is defined as the latest value collected on or before the date when the first dose of study treatment is administered. When the latest values contain retest, the retest value will be used as baseline for the analysis. 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.

5.2. Analysis Populations

In this study the following four populations will be defined and used in the analysis and presentation of the data.

5.2.1. Intent-to-treat Population

The Intent-to-treat (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 are initially assigned.

5.2.2. Modified Intent-to-treat Population

The modified Intent-to-treat (mITT) population is defined as all subjects who satisfy the following conditions:

- are randomized
- have received at least one dose of investigational product
- are CD20+, ABC type DLBCL as determined by Central Pathology
- are previously untreated
- have measurable disease at baseline
- have at least one post-baseline tumor assessment or died after randomization but before the assessment

The mITT population will be used as supportive analysis for efficacy. Subjects will be analyzed according to the treatment arm to which they are initially assigned.

5.2.3. Safety Population

The Safety population is defined as all subjects who have received at least one dose of investigational product.

The Safety population will be used for all safety analyses. Subjects will be analyzed according to the treatment which they actually received.

6. SUBJECT DISPOSITION

All subjects randomized will be included in subject disposition analyses listed below.

The following analysis populations will be summarized and the median follow-up time (months) in each population will be calculated and reported:

1. ITT population
2. mITT population
3. Safety population

The study treatment includes a combination of both lenalidomide or placebo with R-CHOP. Each of the components (lenalidomide/placebo or R-CHOP) may be interrupted or even discontinued due to its own reasons, however, the study treatment should be viewed as an integrated unit (R2-CHOP or placebo-R-CHOP). Subjects who completed both 6 cycles of lenalidomide/placebo and 6 cycles of R-CHOP are considered to have completed the protocol specified study treatment. Subjects who discontinued either lenalidomide/placebo or R-CHOP during or before Cycle 6 are not considered to have completed the protocol specified study treatment.

The pre-specified optional extra 2 doses of rituximab and consolidation radiotherapy are not considered as study treatment for data analysis purpose.

Subject disposition will be reported in the ITT, mITT, and Safety populations separately for the following categories:

1. Subjects completed 6 full cycles of the protocol specified study treatment
2. Subjects completed 6 cycles of R-CHOP but prematurely discontinued lenalidomide/placebo
   - primary reason for lenalidomide/placebo discontinuation
3. Subjects completed 6 cycles of lenalidomide/placebo but prematurely discontinued R-CHOP
   - primary reason for R-CHOP discontinuation
4. Subjects prematurely discontinued both lenalidomide/placebo and R-CHOP
   - primary reason for lenalidomide/placebo discontinuation
   - primary reason for R-CHOP discontinuation
5. Subjects prematurely discontinued lenalidomide/placebo while ongoing on R-CHOP
   - primary reason for lenalidomide/placebo discontinuation
6. Subjects prematurely discontinued R-CHOP while ongoing on lenalidomide/placebo
   - primary reason for R-CHOP discontinuation
7. Subjects ongoing on both lenalidomide/placebo and R-CHOP
8. Subjects entered the Follow-up Period
9. Subjects ongoing in the Follow-up Period

10. Subjects discontinued from the Study
    - primary reason for study discontinuation

Subjects in the categories of 4-8 are not considered to have completed the protocol specified study treatment.

A summary table of randomized subjects by country and site will be provided. A summary table of all screen failure subjects by screen failure reason will also be provided. Screened subjects include all patients who have signed ICF.

Separate listings will be provided for subjects who completed the protocol specified study treatment, for subjects who did not complete the study specified study treatment, and for subjects who are ongoing on the treatment. Further listing will be provided for randomized subjects excluded from the mITT and Safety populations with primary reasons for exclusions. A separate listing will be provided for subjects not randomized (ie, Screen Failures), including the primary reason for failing screening.

7. PROTOCOL DEVIATIONS

The protocol deviations and important protocol deviations are identified and assessed by the clinical research physician or designee following company standard operational procedure. The protocol deviations and important protocol deviations will be summarized by treatment arm in the ITT population.

A by-subject listing of subjects with protocol deviations and important protocol deviations in the ITT population will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for the ITT, safety, and mITT populations. Individual subject listings will be provided to support the summary tables.

8.1. Demographics

The following demographics will be summarized by treatment arm:

1. Age (years)
2. Weight (kg)
3. Height (cm)
4. Body Mass Index (BMI) (kg/m^2)
5. Body Surface Area (BSA) (m^2)
6. Sex
7. Race
8. Ethnicity
9. Reproductive Status

Continuous variables will be summarized descriptively (n, Mean, SD, Median, Q1, Q3, Min, Max), and categorical variables will be summarized with frequency counts.

8.2. Baseline Characteristics

The following baseline clinical characteristics will be summarized by treatment arm:

1. Eastern Cooperative Oncology Group (ECOG) performance score
2. Baseline creatinine clearance (CrCl) (mL/min) and CrCl category
3. Disease stage of DLBCL at diagnosis
4. Baseline electrocardiogram (ECG)
5. IPI score from IVRS
6. Lactate dehydrogenase (LDH)
7. White blood cell (WBC) count
8. Presence of bulky disease from IVRS
9. Bone marrow involvement
10. Subjects with pre-specified optional two extra doses of rituximab

11. Subjects with pre-specified optional consolidation radiotherapy

8.3. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The version of the MedDRA will be indicated in the footnote of relevant tables based on the current version used in the clinical data.

A summary of medical and surgical history will be presented by MedDRA system organ class (SOC) and preferred term (PT), for the ITT population. A similar summary will be generated for the currently active abnormalities only and ITT population, by SOC and PT.

A frequency tabulation of the number of subjects who had at least one prior venous thromboembolism (VTE) event will be produced by treatment arm, for the Safety population. The VTE events include deep venous thrombosis, pulmonary embolism, and other venous thrombosis. In addition, the number of subjects with various number of thrombosis risk factors (0, 1, 2, 3, ≥4) will be summarized. There are 16 thrombosis risk factors considered: Protein C deficiency, Protein S deficiency, Anti-thrombin-3 deficiency, Activated protein C resistance, Prothrombin gene mutation, Elevated homocysteine level, Antiphospholipid syndrome, Lupus Anticoagulant, Estrogen-use, Immobilization, Trauma within past 3 months, Post-operative, Obesity, Tamoxifen use, Central Venous Access Device, and Other.

By-subject listings will display medical history and history of VTE events including all relevant data collected on the CRF, for the ITT population.

8.4. Prior Therapy

This study is to investigate the treatment effect on subjects with previously untreated ABC type DLBCL, thus, all subjects enrolled into the study will not have prior therapy for DLBCL. However, for subjects with bulky disease, systemic symptoms, compressive disease, elevated bilirubin due to lymphoma, or rapidly progressing adenopathies, pre-phase treatment with corticosteroids according to local practice is permitted prior to beginning the Treatment Period, at the discretion of the investigator. It is recommended to limit the pre-phase treatment to up to 100 mg / day prednisone or equivalent for 10 days.

A frequency tabulation of the number of subjects who received the pre-phase prednisone or equivalent will be produced as part of prior medications, for the safety population.

8.5. Prior and Concomitant Medications

Medications initiated prior to the start of study treatment and continued after the start of study treatment will be counted as both prior and concomitant medications.

8.5.1. Prior Medications

Prior medications are defined as non-study medications that were started before the date of the first dose of study treatment. A summary showing the number and percentage of subjects who took prior medications will be presented for the safety population according to the World Health Organization Drug Dictionary (WHO-DD) coding system Anatomical Therapeutic Chemical (ATC) classification and drug preferred term. In addition, pre-phase Corticosteroid use will be summarized.

8.5.2. Concomitant Medications

Concomitant medications are defined as any non-study medications that were taken while the subject is on the study treatment through 28 days after the last non-zero dose of lenalidomide/placebo or any component of R-CHOP, including the optional two additional doses of single agent rituximab if administered, whichever is later. They include the medications that were initiated before the first dose of study treatment and continued during the study treatment as well as medications that were initiated between the date of the first dose of study treatment through 28 days after the last non-zero dose of lenalidomide/placebo or any component of R-CHOP, including the optional two additional doses of single agent rituximab if administered, whichever is later.

A summary showing the number and percentage of subjects who took concomitant medications will be presented for the safety population by WHO therapeutic drug class and generic drug name.

Any medications that were initiated more than 28 days after the last non-zero dose of lenalidomide/placebo or any component of R-CHOP, including the optional two additional doses of single agent rituximab if administered, are not considered concomitant medications. However, all non-study medications will be included in by-subject listings.

Growth factors usage will be summarized in three ways. The number of subjects who received at least one growth factor will be summarized, and the days of each growth factor usage will be summarized in terms of median, min, and max. The number of person-cycles with at least one growth factor usage during treatment (Cycle 1 – Cycle 6) will be calculated, and similarly, the number of person-cycles with a particular growth factor usage will be calculated, and the days of usage will be summarized in terms of median, min, and max. Additionally, by cycle analysis will be performed for the number of subjects who received at least one growth factor, and the days of each growth factor usage will be summarized in terms of median, min, and max.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided in the Safety population. By-subject listings will be included to support the tabulations described in this section.

As presented in Section 6, study treatment consists of both lenalidomide/placebo and R-CHOP. Although either lenalidomide/placebo or R-CHOP, or both, may be discontinued early due to its own toxicity, the study treatment is viewed as an integrated regimen (R2-CHOP or placebo-R-CHOP). A subject is classified as "Completed the Protocol Specified Study Treatment" only if the subject completed 6 full cycles of both lenalidomide/placebo and R-CHOP.

All treatment exposures (duration in weeks and in cycles), dose modifications, and treatment compliance scores will be summarized based on the first 6 cycles. For subjects with optional extra 2 cycles of rituximab, a separate summary will be provided for these extra 2 cycles of rituximab in terms of cumulative dose, dose intensity, and relative dose intensity.

9.1. Treatment Duration and Cycles

Lenalidomide/Placebo Treatment Duration (weeks) is defined as:

[(date of end of lenalidomide/placebo) – (date of first lenalidomide/placebo) + 1]/7

Date of first lenalidomide/placebo is defined as the date of the first non-zero dose of lenalidomide/placebo.

Date of end of lenalidomide/placebo is defined as follows:

- For subjects who completed 6 full cycles of lenalidomide/placebo, the end of lenalidomide/placebo is defined as Day 21 of Cycle 6, which is referred to as "date of completion" recorded on the eCRF called Treatment Disposition - Lenalidomide/Placebo.
- For subjects who prematurely discontinued lenalidomide/placebo before or during Cycle 6, the end of lenalidomide/placebo is the date either the investigator or subject decided to prematurely discontinue lenalidomide/placebo, which is referred to as "date of discontinuation" recorded on the eCRF called Treatment Disposition - Lenalidomide/Placebo.

R-CHOP Treatment Duration (weeks) is defined as:

[(date of end of R-CHOP) – (date of first R-CHOP) + 1]/7

Date of first R-CHOP is defined as the date of the first non-zero dose of rituximab, cyclophosphamide, doxorubicin, vincristine, or prednisone or equivalent, whichever is earlier.

Date of end of R-CHOP is defined as follows:

- For subjects who completed 6 full cycles of R-CHOP, the end of R-CHOP is defined as Day 21 of Cycle 6, which is referred to as "date of completion" recorded on the eCRF called Treatment Disposition - RCHOP.
- For subjects who prematurely discontinued R-CHOP before or during Cycle 6, the end of R-CHOP is the date either the investigator or subject decided to prematurely discontinue

R-CHOP, which is referred to as "date of discontinuation" recorded on the eCRF called Treatment Disposition - RCHOP.

R-CHOP Individual Component Duration (weeks) is defined as:

[(date of end of individual component) – (date of first dose of individual component) + 1]/7

Date of first dose of individual component is defined as the date of the first non-zero dose of the individual component.

Date of end of individual component is defined as follows:

- For subjects who completed 6 full cycles of the individual component, the end of individual component is defined as Day 21 of Cycle 6, which is referred to as "date of completion" recorded on the eCRF called Treatment Disposition - RCHOP.
- For subjects who prematurely discontinued the individual component before or during Cycle 6, the end of individual component is the date either the investigator or subject decided to prematurely discontinue the individual component.

Total Treatment Duration (weeks) is defined as:

[(date of end of treatment) – (date of first treatment) + 1]/7

Date of first treatment is defined as the date of first lenalidomide/placebo or the date of first R-CHOP, whichever is earlier.

Date of end of treatment is defined as the date of end of lenalidomide/placebo or the date of end of R-CHOP, whichever is later.

Please note that the pre-specified optional extra 2 doses of single agent rituximab at Cycles 7 and 8 should not be counted as study treatment, therefore should be excluded in treatment duration calculation.

Descriptive statistics will be provided for the total treatment duration (weeks) as well as lenalidomide/placebo treatment duration and R-CHOP treatment duration.

Total Treatment Cycles is defined as the greatest number of cycles of either lenalidomide/placebo or R-CHOP a subject completed. If a subject discontinued R-CHOP during Cycle 3 and then discontinued lenalidomide/placebo during Cycle 6, the subject is considered as completed 2 cycles of R-CHOP and 5 cycles of lenalidomide/placebo, the total number of treatment cycles is 5. If a subject discontinued R-CHOP during Cycle 3 and completed all 6 cycles of lenalidomide/placebo, the total number of treatment cycles is 6.

Lenalidomide/Placebo Treatment Cycles is defined as the number of cycles of lenalidomide/placebo the subject completed.

R-CHOP Treatment Cycles is defined as the number of cycles of R-CHOP the subject completed.

R-CHOP Individual Component Cycles is defined as the number of cycles of the individual component the subject completed.

The number and percentage of subjects who completed up to 6 cycles of total treatment will be provided by each category (ie, < 1 cycle, 1 cycle through 6 cycles). In addition, the number and percentage of subjects who completed up to 6 cycles of lenalidomide/placebo or R-CHOP will be provided separately.

9.2. Cumulative Dose

Cumulative dose will be calculated for each individual drug of study treatment (lenalidomide/placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or equivalent). Cumulative dose is defined as the sum of all doses of that drug taken across the treatment period in mg (for lenalidomide/placebo and prednisone or equivalent) or mg/m^2 (for rituximab, cyclophosphamide, doxorubicin, and vincristine). For placebo, the nominal doses recorded on the case report form (CRF) will be used, rather than "zero mg".

Descriptive statistics of cumulative dose will be provided separately for lenalidomide/placebo, rituximab, and each component of chemotherapy.

9.3. Dose Intensity

Dose Intensity (DI) during the treatment is defined as the cumulative dose (in mg or mg/m^2) divided by the number of actual dose exposure days. The days with no dose or zero dose recorded on the CRF are excluded from the denominator.

Dose intensity will be calculated separately for each drug of study treatment, and descriptive statistics will be provided.

9.4. Relative Dose Intensity

Relative Dose Intensity (RDI) is defined as 100 times the dose intensity divided by the planned dose intensity.

Planned DIs are:

1. For lenalidomide/placebo: 15 mg per day
2. For rituximab: 375 mg/m^2 per day
3. For cyclophosphamide: 750 mg/m^2 per day
4. For doxorubicin: 50 mg/m^2 per day
5. For vincristine: 1.4 mg/m^2 per day, noting that there might be a lower planned dose intensity (maximum 2 mg per day) for obese or very tall subjects, however, obese or very tall subjects are not well defined for programming purpose, thus, 1.4 mg/m^2 per day has to be used for DI calculation
6. For prednisone: 100 mg per day

Relative dose intensity for each drug of study treatment will be categorized into ≤ 75%, > 75% to ≤ 90%, > 90% to ≤ 100%, and > 100%, and frequency counts will be provided by treatment arm. For rituximab, the Cumulative Dose, Dose Intensity, and Relative Dose Intensity will be summarized separately for Cycle – Cycle 6 and during the extra 2 cycles.

9.5. Dose Reduction/Interruption

Dose reduction/interruption due to AE and other reasons will be summarized by treatment arm. For lenalidomide/placebo, dose reduction is defined as any non-zero reduced dose. For any R-CHOP drugs, dose reduction is defined as any non-zero dose with >20% reduction from the planned dose for the first dose, or any non-zero dose with >20% reduction from the previous dose for subsequent doses, with AE or any other reason recorded on the CRF for the dose assignment. Dose interruption is defined as any zero dose of lenalidomide/placebo or any R-CHOP drugs with AE or any other reason recorded on the CRF for the dose assignment. Time to first dose reduction/interruption will be calculated from the first dose of any study drug.

The overall number and percentage of subjects who have at least one dose reduction/interruption for lenalidomide/placebo and R-CHOP will be separately provided for each reason by treatment arm. Time to first dose reduction/interruption due to any reason will be descriptively provided. Time to first dose reduction/interruption due to AE will also be descriptively provided.

In addition, the percent of cycles with dose reduction/interruption due to AE will be determined for each subject for lenalidomide/placebo and R-CHOP separately and summarized by treatment arm. The percent of cycles with dose reduction/interruption due to AE for lenalidomide/placebo is defined as the number of cycles during which the dose of lenalidomide/placebo was reduced/interrupted due to AE divided by the total number of cycles of study drug the subject received. The percent of cycles with dose reduction/interruption due to AE for R-CHOP is defined as the number of cycles during which the dose of any component of R-CHOP was reduced/interrupted due to AE divided by the total number of cycles of study drug the subject received. The ratio is then multiplied by 100 for easy interpretation.

The percent of cycles with dose reduction/interruption due to AE will be reported as 5 categories: 0% of cycles, > 0 to ≤ 25% of cycles, > 25 to ≤ 50% of cycles, > 50 to ≤ 75% of cycles, and > 75 to ≤ 100% of cycles. The number and percentage of subjects in each category will be reported for lenalidomide/placebo and R-CHOP separately by treatment arm.

9.6. Treatment Compliance

The R2-CHOP or placebo-R-CHOP regimen will be administered over a 21-day cycle (with the possible exception of Cycle 1, which may last 22 days). In each cycle of treatment lenalidomide/placebo should be administered for 14 days, prednisone or equivalent for 5 days, and rituximab, cyclophosphamide, doxorubicin, and vincristine for 1 day.

For each component of the IPs, the treatment compliance rate (%) for each subject will be defined below.

Lenalidomide/placebo compliance rate (%) = 100 x $\frac{cumulative\ dose\ of\ lenalidomide/placebo}{210\ mg\ \text{x}\ \#\ of\ lenalidomide/placebo\ cycles\ the\ subject\ received}$

Rituximab compliance rate (%) = 100 x $\frac{cumulative\ dose\ of rituximab}{375\ mg/m^2\ \text{x}\ \#\ of\ R-CHOP\ cycles\ the\ subject\ received}$

Cyclophosphamide compliance rate (%) = 100 x $\frac{cumulative\ dose\ of\ cyclophosphamide}{750\ mg/m^2\ \text{x}\ \#\ of\ R-CHOP\ cycles\ the\ subject\ received}$

Doxorubicin compliance rate (%) = 100 x $\frac{cumulative\ dose\ of\ doxorubicin}{50\ mg/m^2\ \text{x}\ \#\ of\ R-CHOP\ cycles\ the\ subject\ received}$

Vincristine compliance rate (%) = 100 x $\frac{cumulative\ dose\ of\ vincristine}{1.4\ mg/m^2\ \text{x}\ \#\ of\ R-CHOP\ cycles\ the\ subject\ received}$

Prednisone compliance rate (%)

$$= 100\ \text{x}\ \frac{cumulative\ dose\ of\ prednisone}{500\ mg\ \text{x}\ \#\ of\ R-CHOP\ cycles\ the\ subject\ received}$$

For each component of the IPs, the treatment compliance rate (%) will be presented with the following categories: < 75%, ≥ 75% to ≤ 100%, > 100% to < 120%, and ≥ 120%.

10. EFFICACY ANALYSIS

All efficacy evaluations will be conducted in the ITT population. Supportive analysis of the primary and key secondary efficacy endpoints in the mITT population will be conducted for the final analysis.

Statistical comparisons will be made between R2-CHOP and placebo-R-CHOP arms. Efficacy results that will be considered statistically significant after consideration of the strategy for controlling the family-wise Type 1 error rate are described in Section 10.1, Multiplicity. All statistical tests will be 2-sided at the significance level of $\alpha = 0.05$, and the corresponding p-values and 2-sided 95% CIs for intended point estimates will be reported.

Derived efficacy parameters will be displayed in a by-subject listing, and further listings will present all relevant information from the Independent Response Adjudication Committee (IRAC) assessments, survival status, subsequent anti-lymphoma therapy, and ECOG performance status.

10.1. Multiplicity

A step-down procedure will be used to control the family-wise Type 1 error rate for the primary efficacy endpoint PFS and the key secondary efficacy endpoint EFS. The primary efficacy endpoint PFS will be tested first. The key secondary efficacy endpoint EFS will only be tested if the primary efficacy endpoint demonstrates superiority at $\alpha = 0.05$ level for R2-CHOP over placebo-R-CHOP. The analyses will be based on the ITT population.

10.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, which is defined as the time (months) from the date of randomization to the date of disease progression or death (any cause), whichever occurs earlier. Relapse from CR will be considered as disease progression throughout this document. Disease progression will be determined based on the Revised Response Criteria for Malignant Lymphoma (**Error! Reference source not found.**, 2014). The PFS analysis based on the IRAC assessment will serve as the primary analysis. The PFS analysis based on the local investigator's assessment will serve as the sensitivity analysis.

Subjects who did not experience disease progression and who did not die before the clinical data cutoff date will be censored at the date of last adequate response assessment.

In addition, the following two sets of censoring rules will be applied to the PFS analysis.

The first set of censoring rules will follow the Food and Drug Administration's (FDA's) "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (FDA, 2007). Specifically, subjects who received new anti-lymphoma therapy without objective disease progression will be censored at the date of the last adequate response assessment prior to the new anti-lymphoma therapy. The analysis with this set of censoring rules will serve as the primary analysis for PFS. The detailed censoring rules are illustrated in the Table 2 below.

Table 2: Censoring Rule for PFS Endpoint (Primary Analysis)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented at or between scheduled visits	Date of first adequate assessment[a] showing disease progression	Event (Progressed)
Progression or death documented immediately after two or more missed scheduled tumor assessments	Date of last adequate assessment[a] with evidence of no progression	Censored
Death at or between scheduled visits	Date of death	Event (Died)
Progression or death after subsequent systemic anti-lymphoma therapy started[b]	Date of last adequate assessment[a] with evidence of no progression prior to the start of subsequent systemic anti-lymphoma therapy	Censored
No progression or death	Date of last adequate assessment[a] with evidence of no progression prior to the start of subsequent systemic anti-lymphoma therapy (if any).	Censored

FDA = Food and Drug Administration.
[a] Adequate assessment is defined as documented assessment recorded in the clinical data.
[b] The pre-specified optional extra 2 doses of rituximab and consolidation radiotherapy are not considered as subsequent systemic anti-lymphoma therapy, if determined before randomization.
Note: Only the first applicable date (either progressed or censored) will be assigned to each subject.
Source: FDA's "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (FDA, 2007).

In order to avoid possible informative censoring, eg, the administration of new anti-lymphoma therapy may be related to factors associated with the actual survival time, a sensitivity analysis for PFS will be performed using the second set of censoring rules that follows the European Medicines Agency's (EMA's) guideline "Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man" (EMA, 2012). Specifically, disease progression will be counted as PFS event regardless of whether subjects receive new anti-lymphoma therapy or miss more than one assessment prior to that. The detailed censoring rules are illustrated in the Table 3 below:

Table 3: Censoring Rule for PFS Endpoint (Sensitivity Analysis)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented at or between scheduled visits	Date of first adequate assessment[a] showing disease progression	Event (Progressed)

Progression documented after two or more missed scheduled tumor assessments	Date of first adequate assessment[a] showing disease progression	Event (Progressed)
Death after two or more missed scheduled tumor assessments	Date of death	Event (Died)
Death at or between scheduled visits	Date of death	Event (Died)
Progression after subsequent systemic anti-lymphoma therapy started[b]	Date of first adequate assessment[a] showing disease progression	Event (Progressed)
No progression or death	Date of last adequate assessment[a] with evidence of no progression	Censored

EMA = European Medicines Agency.
[a] Adequate assessment is defined as documented assessment recorded in the clinical data.
[b] The pre-specified optional extra 2 doses of rituximab and consolidation radiotherapy are not considered as subsequent systemic anti-lymphoma therapy, if determined before randomization.
Note: Only the first applicable date (either progressed or censored) will be assigned to each subject.
Source: EMA's guideline "Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man" (EMA, 2012).

These censoring rules will be applied to determine PFS events as assessed by IRAC and by investigator separately.

The final analysis for PFS will be conducted when a total of at least 192 PFS events in the ITT population occurred by IRAC assessment and PFS events will be re-determined per Table 2 censoring rule. In case the event rate falls below 2 events per month before reaching 192 events, the final analysis will be performed when at least 170 events have occurred. The power of the study will be a least 86%.

The survival distribution of PFS will be estimated using Kaplan-Meier method (without adjusting for the stratification factors) and graphically presented. The median PFS time (in months) including 2-sided 95% CI for each treatment arm will be provided. In addition, the PFS rate at every 6 months will be provided along with its standard error.

The stratified log-rank test will be performed to evaluate treatment efficacy for the primary analysis. The stratification factors for analysis include IPI score (2 versus ≥ 3), presence of bulky disease (≥ 7.0 cm [bulky] versus < 7.0 cm [non-bulky]), and age (< 65 versus ≥ 65 years). The experimental arm
(R2-CHOP) will be declared superior if the 2-sided p-value from the stratified log-rank test is ≤ 0.05 in favor of the experimental arm. The un-stratified log-rank test will be performed as sensitivity analysis.

Conventionally, hazard ratio with 2-sided 95% CI will be estimated using the Cox proportional hazards model adjusting for the stratification factors. Proportional hazard assumption will be evaluated. Sensitivity analyses will be provided if deemed appropriate.

In summary, the final PFS analysis will be performed based on IRAC assessments as well as based on investigator assessments, using the censoring rules in Table 2 and Table 3 below:

Table 3, both in ITT and mITT populations. The stratified PFS analysis based on IRAC assessments using the censoring rules in Table 2 in the ITT population is the primary analysis, and other PFS analyses in the ITT population are sensitivity analyses. All analyses in the mITT population are supportive.

10.3. Analyses of Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed in the ITT population. The key secondary endpoint will also be analyzed in the mITT population.

All secondary efficacy endpoints will be analyzed at the time of final PFS analysis.

10.3.1. Key Secondary Endpoint

The key secondary efficacy endpoint is EFS, which is defined as the time (months) from randomization until occurrence of one of the following events, whichever occurs first:

- Disease progression
- Initiation of subsequent systemic anti-lymphoma therapy
- Death due to any cause

Pre-specified optional therapies such as the extra 2 doses of single agent rituximab after Cycle 6 or consolidation radiotherapy will not count as an EFS event (initiation of subsequent systemic anti-lymphoma therapy) if the decision to treat and the location to be treated is determined prior to randomization.

Subjects who did not experience any of these events defined in the categories above before the clinical data cutoff date will be censored at date last known alive.

The primary EFS will be EFS incorporating the IRAC assessments, while EFS incorporating investigator assessments will be supportive.

The survival distribution of EFS will be estimated using Kaplan-Meier method (without adjusting for the stratification factors) and graphically presented. The median EFS time (in months) including 2-sided 95% CI for each treatment arm will be provided. In addition, the EFS rate at every 6 months will be provided along with its standard error.

The stratified log-rank test will be performed to evaluate treatment efficacy. The stratification factors for analysis include IPI score (2 versus ≥ 3), presence of bulky disease (≥ 7.0 cm [bulky] versus < 7.0 cm [non-bulky]), and age (< 65 versus ≥ 65 years). The experimental arm will be declared superior if the 2-sided p-value from the stratified log-rank test is ≤ 0.05 in favor of the experimental arm. The unstratified log-rank test will be performed as sensitivity analysis.

Conventionally, hazard ratio with 2-sided 95% CI will be estimated using the Cox proportional hazards model adjusting for the stratification factors. But the treatment effect will be determined

by the p-value from the stratified log-rank test, not by this 95% CI for the hazard ratio. In addition, hazard ratio with 2-sided 95% CI will be estimated using the Cox proportional hazards model without adjusting for the stratification factors

To control the family-wise Type 1 error rate, the sequential gate keeping approach is used so that the EFS analysis result in the ITT population is interpretable only if the primary PFS analysis result demonstrates superiority at $\alpha = 0.05$ level for R2-CHOP over placebo-R-CHOP.

10.3.2. Other Secondary Endpoints

The other secondary endpoints are OS, CR rate, ORR, Duration of Response, Duration of CR, TTNLT, and HRQoL as measured by EQ-5D and FACT-Lym. Since only the primary endpoint PFS and the key secondary endpoint EFS are considered for controlling the family-wise Type 1 error rate, any statistically significant treatment effect on these other secondary endpoints cannot be interpreted as confirmatory, but rather informatory.

Overall survival is defined as the time (months) from randomization until death due to any cause. Subjects who withdrew consent for the study will be censored at the time of withdrawal. Subjects who are still alive before the clinical data cutoff date and subjects who are lost to follow-up will be censored at date last known alive.

Overall survival will be analyzed in the same way as for the PFS and EFS except for its own censoring rule as described in the above paragraph. In addition, the OS rate at every 6 months will be provided along with its standard error.

10.3.2.1. Complete Response Rate and Objective Response Rate

The CR rate is defined as the percentage of subjects who ever achieved a complete response after initiation of the study treatment and prior to initiation of subsequent systemic anti-lymphoma therapy. Objective response rate is defined as the percentage of responders, defined as subjects who ever achieved at least a partial response (PR) after initiation of the study treatment and prior to initiation of subsequent systemic anti-lymphoma therapy. Subjects who do not have any adequate response assessments during this period will not be considered as responders.

The CR rate and ORR will be tested by Cochran-Mantel-Haenszel (CMH) method with the three stratification factors as strata. The stratification factors include IPI score (2 versus ≥ 3), presence of bulky disease (≥ 7.0 cm [bulky] versus < 7.0 cm [non-bulky]), and age (< 65 versus ≥ 65 years). The un-stratified (ie, Pearson's chi-squared) test will also be performed as a sensitivity analysis.

The CR rate and ORR based on IRAC assessment and investigator assessment will be analyzed separately.

A cross-tabulation of the best responses by IRAC assessment versus best responses by investigator assessment will also be presented.

10.3.2.2. Duration of Complete Response

Duration of complete response will be calculated for complete responders only. It is defined as the time (months) from documented initial complete response prior to initiation of subsequent systemic antilymphoma therapy until documented disease progression or death, whichever occurs earlier. Subjects who have not progressed or died at the time of the analysis will be censored at the date of last response assessment demonstrating no disease progression. Subjects who change treatment without evidence of disease progression will be censored at the last assessment showing no progression prior to treatment change.

Duration of complete response will be analyzed in the same way as for the OS except for its own censoring rule as described in the above paragraph.

Duration of complete response based on IRAC assessment and investigator assessment will be analyzed separately.

10.3.2.3. Duration of Response

Responders will be defined as subjects who ever achieved at least a partial response (PR) after initiation of the study treatment and prior to initiation of subsequent systemic anti-lymphoma therapy. Duration of response will be calculated for responders only. It is defined as the time (months) from documented initial response prior to initiation of subsequent systemic antilymphoma therapy until documented disease progression or death, whichever occurs earlier. Subjects who have not progressed or died at the time of the analysis will be censored at the date of last response assessment demonstrating no disease progression. Subjects who change treatment without evidence of disease progression will be censored at the last assessment showing no progression prior to treatment change.

Duration of response will be analyzed in the same way as for the OS except for its own censoring rule as described in the above paragraph.

Duration of response based on IRAC assessment and investigator assessment will be analyzed separately.

10.3.2.4. Time to Next Lymphoma Therapy (TTNLT)

Time to next lymphoma therapy is defined as the time (months) from randomization to the time of treatment change for the next lymphoma treatment. Subjects without treatment change will be censored at date last known alive. Pre-specified optional therapies such as the extra 2 doses of single agent rituximab after Cycle 6 or consolidation radiotherapy will not count as treatment change for the next lymphoma therapy if the decision to treat and the location to be treated are determined prior to randomization.

Time to next lymphoma therapy will be analyzed in the same way as for the OS except for its own censoring rule as described in the above paragraph.

10.3.2.5. Health-related Quality of Life

Data on HRQoL will be collected using the standardized EQ-5D and FACT-Lym health measurement instruments. The detailed analysis of ED-5D and FACT-Lym will be addressed in a separate analysis plan and performed by an external vendor.

10.4. Subgroup Analysis

In order to accurately evaluate treatment effect in a more homogeneous population, the primary endpoint PFS, key secondary endpoint EFS, and modified PFS will also be analyzed within the following subgroups:

- IPI score (2 versus ≥ 3);
- Presence of bulky disease (≥ 7.0 cm [bulky] versus < 7.0 cm [non-bulky]);
- Age (< 65 versus ≥ 65 years versus ≥ 80 years);
- Sex (male versus female);
- Baseline creatinine clearance (≥ 30 to < 60 mL/min versus ≥ 60 mL/min).
- Additional Cycle(s) of Rituximab (Yes vs No)
- Pre-phase steroid (Yes vs No)
- Central Pathology Lab (for primary endpoint only)

These subgroup analyses are almost identical to the PFS and EFS analysis specified in Sections 10.2 and 10.3.1 with two exceptions. The treatment effect will be evaluated by unstratified log-rank test and the hazard ratio will be estimated using the Cox proportional hazards model without adjusting for the stratification factors.

These subgroup analyses will be performed in the ITT population.

10.6. Assessing Study Center Effect and Treatment-by-Center Interaction

This study is a multicenter study and has planned to involve approximately 150 study sites to randomize a total of 560 subjects. No single site will have a sufficient number of subjects to allow a meaningful evaluation of the site effect and treatment-by-site interaction effect; therefore, data from all sites will be pooled together in analysis.

11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. All analyses of safety data will be conducted in the Safety population.

The safety analysis will include AEs, laboratory evaluations, vital signs, physical examinations, and multi gated acquisition (MUGA) scans.

11.1. Adverse Events

All adverse events will be coded using the MedDRA®. The version of the MedDRA will be indicated in the footnote of relevant AE tables based on the current version used in the clinical data.

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs) which are defined as any AEs that started between the date of first dose of study treatment and 28 days after the date of last non-zero dose of lenalidomide/placebo or any component of R-CHOP, including the optional two additional doses of single agent rituximab if administered, whichever is later.

A treatment-related TEAE is defined as a TEAE which the investigator considered suspected of being related to any component of the study drug.

TEAEs related to lenalidomide/placebo are those TEAEs that have "suspected" relationship to lenalidomide/placebo.

TEAEs related to R-CHOP are those TEAEs that have "suspected" relationship to rituximab, cyclophosphamide, doxorubicin, vincristine, or prednisone or equivalent.

The frequency of TEAEs will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher, except for tumor flare reaction (TFR), which will be defined using CTCAE version 3. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or death (Grade 5).

If a subject experiences the same AE more than once with different toxicity grade, then the event with the highest grade will be tabulated once in "by grade" tables. If a subject experiences multiple AEs under the same preferred term (system organ class), then the subject will be counted only once for that preferred term (system organ class).

11.1.1. Overview of TEAE

The number and percentage of subjects experiencing TEAEs will be summarized in the following categories by treatment arm:

- All TEAEs
- Treatment-related TEAEs
- All TEAEs with CTCAE Grade 3 or higher

- Grade 3 or 4 TEAEs
- Treatment-related TEAEs with CTCAE Grade 3 or higher
- Treatment-related Grade 3 or 4 TEAEs
- All serious TEAEs
- Treatment-related serious TEAEs
- All TEAEs leading to discontinuation of lenalidomide/placebo
- All TEAEs leading to discontinuation of R-CHOP
- All TEAEs leading to discontinuation of both lenalidomide/placebo and R-CHOP
- All TEAEs leading to lenalidomide/placebo dose reduction/interruption
- All TEAEs leading to dose reduction/interruption in any component of R-CHOP
- All Grade 5 TEAEs

11.1.2. TEAEs by System Organ Class and Preferred Term

In addition to summary tables for an overview of TEAEs, the number and percentage of subjects experiencing TEAEs will be tabulated by treatment arm and the MedDRA SOC and PT, in the same categories as listed in Overview of TEAE as well as additional categories as listed below:

- All TEAEs leading to discontinuation of each component of R-CHOP
- All TEAEs leading to dose reduction/interruption in any component of R-CHOP
- All TEAEs by maximum CTCAE Grade
- Pre-treatment AEs
- Common TEAEs (defined as events occurring for more than 5% of subjects in a treatment arm)
- TEAEs by cycle of onset

Treatment-emergent adverse events will also be summarized in terms of exposure adjusted incidence rate (EAIR) per 100 person-years by treatment arm. For a particular TEAE, the EAIR per 100 person-years is defined as:

$$\frac{total\ \#\ of\ that\ TEAE\ from\ all\ subjects\ during\ the\ entire\ study}{\sum(date\ of\ end\ of\ treatment - date\ of\ first\ treatment + 1)/(365.25 * 100)}$$

where the denominator is the sum of total dose exposures counting all subjects in terms of 100 person-years. Please refer to Section 9.1 for definition of date of end of treatment and date of first treatment.

In addition, the number and percentage of subjects experiencing any TEAE will also be summarized by SOC and PT in the following subgroups:

- Age (< 65 versus ≥ 65 years versus ≥ 80 years)
- Sex (male versus Female)
- Baseline creatinine clearance (≥ 30 to < 60 mL/min versus ≥ 60 mL/min)
- IPI score (2 versus ≥ 3)
- Presence of bulky disease (≥ 7.0 cm [bulky] versus < 7.0 cm [non-bulky])

The AE tables will be presented in descending order of frequency by SOC, and descending order of PT within each SOC. The frequency is determined by the R2-CHOP arm. A table of TEAEs by decreasing frequency of PT only, and a table of TEAEs by decreasing frequency of SOC only will be provided separately.

All AEs with corresponding attributes will be displayed in a by-subject listing. AEs leading to discontinuation from or reduction/interruption of treatment, events classified as NCI CTCAE grade 3 or higher, SAEs, selected AEs, and neoplasms benign, malignant and unspecified (including cysts and polyps) will also be displayed in separate by-subject listings.

11.1.3. Death

The number of deaths and the primary cause of death will be tabulated by treatment arm. The tabulation will include all deaths that occurred from the first dose of study treatment, deaths that occurred from the first dose of study treatment until 28 days after the last non-zero dose of lenalidomide/placebo or any component of R-CHOP, including the optional two additional doses of single agent rituximab if administered, whichever is later, and deaths that occurred more than 28 days after the last non-zero dose of lenalidomide/placebo or any component of R-CHOP, including the optional two additional doses of single agent rituximab if administered, whichever is later. All deaths will be presented in a by-subject listing, and a further listing will display deaths within 28 days of last non-zero dose of lenalidomide/placebo or any component of R-CHOP, including the optional two additional doses of single agent rituximab if administered, whichever is later.

11.2. Selected Adverse Events

11.2.1. AE of Special Interest

AE of special interest (AESI) categories will use standardized MedDRA query (SMQ) (search strategy according to MedDRA Version as used for AE coding), sub-SMQ, SOC, higher level term (HLT), or list of PTs. The SPMs are selected AEs, but the assessment of SPMs will be directly from the SPM clinical dataset and described in Section 11.2.2. The following AESI categories which are representative of the important identified and potential risks in the Revlimid Risk Management Plan will be included in the analysis:

- Neutropenia
- Infection
- Thrombocytopenia

- Bleeding
- Cardiac Arrhythmias
- Cardiac Failure
- Ischaemic Heart Disease (including Myocardial Infarction)
- Arterial Thromboembolism (ATE) Events
- Venous Thromboembolism (VTE) Events
- Renal Failure
- Peripheral Neuropathy
- Diarrhea
- Constipation
- Cutaneous Reactions
- Hypersensitivity
- Angioedema
- Hepatic Disorders
- Tumour Lysis Syndrome
- Tumor Flare Reaction
- Teratogenicity
- Interstitial Lung Disease (Interstitial pneumonitis)
- Mixed Thromboembolism

Please note that these AESI categories might be updated/revised each time when the MedDRA version is updated.

The number and percentage of subjects by SOC and PT will be summarized for the following AE categories:

- Treatment-emergent AESIs
- Grade 3 or 4 treatment-emergent AESIs
- Treatment-emergent serious AESIs

11.2.2. Second Primary Malignancy

Events of SPMs will be tabulated by treatment arm for the following categories:

- All SPMs (invasive and non-invasive SPMs)
- All invasive SPMs (hematologic and solid tumor SPMs)
- All hematologic SPMs

- All solid tumor SPMs
- All non-invasive SPMs (non-melanoma skin cancers)

For each of the above SPM categories, SPMs will be further tabulated using the MedDRA preferred term. Each subject is counted only once within each SPM category as well as within each preferred term.

Additionally, the number and percentage of subjects with SPMs who died and those who did not die will be tabulated by SPM category.

It should be noted that these analyses with regard to SPMs are based on the number of subjects with at least one SPM and not the total number of SPMs.

For each SPM category, time to onset will be calculated as time (in months) from the start of the study treatment to the onset of the SPM for each affected subject. For the subjects with more than one new malignancy within an SPM category, the onset of the earliest SPM will be used. Time to onset will be summarized descriptively by treatment arm for each SPM category.

For each SPM category, the incidence rate per 100 person-years will be calculated as: (the number of subjects with any SPM in the SPM category/total person-years) * 100. Total person-years are defined as the total time from the date of first treatment to the first onset date of the specified SPM for subjects with the specified SPM plus the total time from the date of first treatment to the date of the last follow-up or death for subjects without the specified SPM. Incidence rates per 100 person-years and the 95% confidence intervals will be calculated for each treatment arm and SPM category.

By-subject listings of SPMs, demographic and baseline characteristics, prior cancer history and assessments, prior cancer regimen treatments and procedures (each for subjects with SPM), and SPM regimen treatments and procedures will be provided. Subjects with SPM before any salvage therapy, and after any salvage therapy will also be presented in listings along with the response and survival status of subjects with SPM.

11.3. Clinical Laboratory Evaluations

Clinical laboratory values from the central laboratories will be graded according to CTCAE version 4.03 or higher for applicable tests.

Laboratory values at baseline, at each post-baseline visit and change from baseline will be descriptively summarized by treatment arm. Important laboratory parameters (hemoglobin, absolute neutrophil count, platelet count) at baseline and at each post-baseline visit will be graphically presented.

The frequency distributions for shift from baseline to the worst (maximum) grade post-baseline will be presented by treatment arm for each laboratory test. For each laboratory test the baseline grade and the worst grade post-baseline will be determined for each subject. For laboratory values that are normal or slightly abnormal without a grade, the Grade 0 (G0) is assumed.

In addition, the frequency of subjects with values below, within, and above the normal ranges at baseline and at each post-baseline visit will be summarized by treatment arm.

Listings of clinical laboratory data from central laboratory with abnormal flags will be provided by subjects and tests. Listings will also be provided for the local laboratory data.

11.3.1. Hematology

Laboratory hematology tests include: hemoglobin, hematocrit, WBC count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.

11.3.2. Clinical Chemistry

Laboratory chemistry tests include: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate transaminase (AST), bilirubin (total), calcium, chloride, creatinine, glucose, phosphorous, potassium, sodium, total protein, blood urea nitrogen (BUN), LDH, and uric acid.

11.3.3. Other Laboratory Tests

Other laboratory tests include: serum immunoglobulin (Ig) measurement includes IgA, IgG, IgM, and thyroid stimulating hormone (TSH).

For female subjects of childbearing potential, the pregnancy test results (negative, positive) will be summarized for each visit by treatment arm and all pregnancy data will be displayed in a by-subject listing.

11.4. Vital Sign Measurements

Vital signs include weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature, and pulse. The normal ranges of vital signs are defined below:

- SBP Normal (90 – 119 mmHg, inclusive)
- DBP Normal (60 – 79 mmHg, inclusive)
- Body Temperature Normal (36.1 – 37.8 °C, inclusive)
- Pulse Normal (60 – 100 bpm, inclusive)

Vital signs at baseline, at each post-baseline visit and change from baseline will be descriptively summarized by treatment arm.

In addition, the frequency distributions for shift from baseline to the treatment discontinuation/completion visit in below, within, or above the normal ranges will be displayed in cross–tabulations for each treatment arm.

All vital sign results will also be presented in a by-subject listing.

11.5. Physical Examination

Physical examination findings at baseline and each post-baseline visit will be summarized in frequency tables and displayed in a by-subject listing.

11.6. Cardiac Function Tests

The baseline ECG interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant' by treatment arm with the other baseline characteristics (see Section 8.2).

The results of MUGA scan or echocardiography at baseline, at end of treatment and change from baseline will be descriptively summarized by treatment arm. In addition, the frequency distributions for shift from baseline to end of treatment in left ventricular ejection fraction (LVEF) category 'LVEF < 45%' and 'LVEF ≥ 45%' will be displayed in cross–tabulations for each treatment arm. A by-subject listing will display all LVEF results.

12. QUALITY OF LIFE ANALYSIS

Data on the standardized EQ-5D and FACT-Lym health measurement instruments will be collected in this study and analyzed as other secondary endpoints that are described in the Section 10.3.2.5.

13. INTERIM ANALYSIS

An interim analysis for futility only is planned for the PFS at 50% information level, ie, when there are 96 PFS events assessed by IRAC and PFS events will be re-determined as per Table 2 censoring rule in the ITT population. All subjects who have been randomized by the clinical data cutoff date for the interim analysis will be included in the interim analysis.

The PFS analysis specified in the Section 10.2 will be examined at interim for futility. The futility determination will be based on the PFS by IRAC assessment using Table 2 censoring rule. The other PFS analyses are sensitivity analyses.

A stratified log-rank test will be performed, and its p-value will be compared with the futility boundary. The boundary for declaring futility of the experimental arm (R2-CHOP) to the control arm (Placebo-R-CHOP) is based on a ß-spending function of Gamma (-4) with overall $\beta = 90\%$.

If a 2-sided p-value from the stratified log-rank test is ≤ 0.8373 in the direction in favor of the experimental arm at the interim analysis, the trial should continue until the required 192 PFS events in the ITT population are observed.

If the 2-sided p-value is > 0.8373 or the log-rank test finds in favor of the control arm at the interim analysis, the Data Monitoring Committee (DMC) may recommend stopping the trial for futility. However, this futility boundary is a non-binding boundary, which means that the study does not have to stop if the futility boundary is crossed at the interim analysis. The study can continue, if so desired, to the final analysis for efficacy without inflating the Type 1 error or losing power.

The analysis of PFS by investigator assessment and PFS using Table 3 censoring rule will also be provided. In order to avoid potential multiplicity issues, the stopping rule for futility analysis is solely based on the primary analysis of PFS, ie, the PFS by IRAC assessment using Table 2 censoring rule.

The results of other efficacy endpoints such as EFS, OS, and ORR may be provided if it is desirable to review them by DMC.

No subgroup analysis will be performed. The interim analysis will be based on ITT population only.

13.1. General Information

A DMC composed of oncologists and a biostatistician, who are all independent of and external to Celgene, will review ongoing safety data throughout the study according to the DMC charter, and may review interim efficacy data for futility. The DMC will make recommendations regarding the continuation of the study, potential amendments, or necessary safety measures.

13.2. Statistical Approaches for Control of Alpha

Since there is no intention to declare efficacy at the interim PFS analysis, no penalty in α should be imposed. Treatment efficacy will be declared at the final PFS analysis if a 2-sided p-value ≤ 0.05 in favor of the experimental arm after the required 192 PFS events in the ITT population are observed.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

16. REFERENCES

Cheson B, Fisher R, Barrington S, Cavalli F, Schwartz L, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-68.

European Medicines Agency (EMA), Appendix 1 to the Guideline on the Evaluation of Anticancer Medical Products in Man. EMA/CHMP/27994/2008/Rev.1; 13 December 2012.

Food and Drug Administration (FDA), Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. Rockville, MD; 2007.

Roschewski M, Pittaluga S, Dunleavey K, Kong K, Shovlin M, Jaffe E, etal. DNA sequencing-based monitoring of serum predicts clinical relapse before CT imaging in diffuse large B-cell lymphoma. Blood (American society of Hematology Annual Meeting Abstract), 2013; 122 (21): 1767.

17. APPENDICES

17.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the date9. format in SAS). Since medical history and prior medication often have incomplete dates, they can be reported as a character string in the YYYY-MM-DD format. Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedures are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure is present and should only be missing when a procedure is marked as NOT DONE in the database. Procedure dates will not be imputed.

- **Log Dates** are the dates recorded in CRF data logs. Specifically, they are the start and end dates for AEs and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 17.2.1. However, in listings, log dates will be shown as recorded without imputation.

- **Milestone Dates** are dates of protocol milestones such as randomization, study treatment start date, study termination, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.

- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but otherwise are not subject to imputation.

- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

17.1.1. Calculation Using Dates

Calculations using dates (eg, subject's age or relative day after the first dose of study medication) will adhere to the following conventions:

- **Study days** after the start day of study treatment will be calculated as the difference between the date of interest and the first date of dosing of study medication plus 1 day. The calculation algorithm for relative study days is:

Study Days = (Target Date – Study Day 1) + 1

where Study Day 1 is the date when the first dose of study treatment is administered. Negative and zero study days are reflective of observations obtained during the baseline/screening period.

- **Age** (expressed in days) is calculated as:

  Age = Consent Date – Date of Birth + 1

  In practice, age will be transformed into years by dividing the difference by 365.25 days, then truncating.

  - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year.
  - The calculated age using Consent Date and Date of Birth will be preferred in analysis. When either date is not available, it is permissible to use the age recorded directly on CRF or in IVRS.

- Intervals that are presented in weeks will be transformed from days into weeks by using (without truncation) the following conversion formula:

  Weeks = Days / 7

- Intervals that are presented in months will be transformed from days into months by using (without truncation) the following conversion formula:

  Months = Days / 30.4375

17.1.2. Calculation of Cycles

The study treatment regimen includes both lenalidomide/placebo and R-CHOP. The cycle of lenalidomide/placebo and R-CHOP will be recorded on dose log page of CRF by the investigator.

The Cycle 1 Day 1 (C1D1) is defined as the date of the earliest non-zero dose of lenalidomide/placebo or any drugs in R-CHOP that are administered within Cycle 1. Likewise, the Cycle i Day 1 (CiD1), i = 2, 3, 4, 5, and 6, is defined as the date of the earliest non-zero dose of lenalidomide/placebo or any drugs in R-CHOP that are administered within Cycle i, provided that the drug was not discontinued in previous cycle.

The total treatment cycles are defined as the longest cycles of lenalidomide/placebo or R-CHOP the subject completed. If the subject completed 3 cycles of R-CHOP and 6 cycles of lenalidomide/placebo, the total treatment cycles is 6.

17.2. Date Imputation Guideline

17.2.1. Impute Missing Adverse Events/ Prior or Concomitant Medications Dates

For AE and concomitant medications data, the incomplete or missing start or stop date will be imputed according to the following rules. The purpose of this imputation is to determine if an AE is treatment-emergent or not, and if a non-study medication is a prior medication or concomitant medication.

These missing dates will be imputed for the analysis derived datasets only. The missing dates in the original clinical datasets will not be imputed. In listings the log dates will be shown as recorded without imputation.

Incomplete Start Date:

Missing day and month

- If the year is **prior to** the year of the first day on study medication, then 31 Dec will be assigned to the missing fields.
- If the year is **same** as the year of the 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 **after** the year of the first day on study medication, then 1 Jan will be assigned to the missing fields.

Missing day only

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

Missing day, month, and year

- The date of the first dose of study medication will be assigned to the missing fields.

Please note that 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.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

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

Missing day only

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

Missing day, month, and year

- The date of the last dose of study medication will be assigned to the missing fields.

Please note that if the start date is non-missing and the imputed stop date is before the start date, the stop date will be imputed by the start date.

17.2.2. Impute Incomplete Dates of PD, second PD, and Subsequent Anti-Lymphoma Therapy

- If only day is missing, the first day of the month will be assigned.
- If both month and day are missing, the first day of January will be assigned.
- If day, month, and year are all missing, date of randomization will be assigned.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName:
Title:
Date: Friday, 29 March 2019, 10:05 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

UserName:
Title:
Date: Monday, 01 April 2019, 01:12 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

UserName:
Title:
Date: Monday, 01 April 2019, 08:58 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========