DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-5013-NHL-007

A PHASE 3, DOUBLE-BLIND RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE (CC-5013) VERSUS RITUXIMAB PLUS PLACEBO IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENT LYMPHOMA

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STATISTICAL ANALYSIS PLAN

A PHASE 3, DOUBLE-BLIND RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE (CC-5013) VERSUS RITUXIMAB PLUS PLACEBO IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENT LYMPHOMA

STUDY DRUG: CC-5013

PROTOCOL NUMBER: CC-5013-NHL-007

DATE: June 21, 2018

Prepared by:
Celgene Corporation
PPD

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Statistical Therapeutic Area Head

Signature _____

Printed Name PPD Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature _____

Printed Name PPD Date _____

Lead Product Safety Physician

Signature _____

Printed Name PPD Date _____

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AE	Adverse event
AML	Acute myelogenous leukemia
APAC	Asia-Pacific region
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
BSA	Body surface area
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CMH	Cochran–Mantel–Haenszel
CR	Complete response
CrCl	Creatinine clearance
CRu	Complete response unconfirmed
CRF	Case Report Form
CT	Computed axial tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCRR	Durable complete response rate
DMC	Data Monitoring Committee
DoCR	Duration of complete response
DoR	Duration of response
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMEA	European Medicines Agency
CCI	[redacted]
CCI	[redacted]
EU	European Union
FDA	Food and Drug Administration
FL	Follicular lymphoma

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or specialist term	Explanation
GCPs	Good Clinical Practices
GCSF	Granulocyte colony-stimulating factor
GELF	Groupe D'Etude des Lymphomes Folliculaires
HP	Helicobacter pylori
CCI	[redacted]
IRC	Independent Review Committee
ITT	Intent to treat
IVRS	Interactive Voice Response System
IWG	International Working Group
IWGRC	International Working Group Response Criteria
KM	Kaplan-Meier estimate
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MALT	Mucosa-associated lymphoid tissue
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MRI	Magnetic resonance imaging
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PE	Pulmonary embolism
PET	Positron emission tomography
PFS	Progression-free survival
CCI	[redacted]
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or specialist term	Explanation
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAE	Serious adverse event
SAP	Statistical Aanalysis plan
SAS	Statistical Analysis System
SMQs	MedDRA queries
SD	Stable disease
SOC	System organ class
SPM	Second primary malignancy
TEAE	Treatment-emergent adverse event
TFR	Tumor flare reaction
CCI [redacted]	[redacted]
[redacted]	[redacted]
TTNLT	Time to next antilymphoma treatment
TTP	Time to progression
US	United States
ULN	Upper limit of normal
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's study protocol CC-5013-NHL-007 "A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Placebo in Subjects With Relapsed/Refractory Indolent Lymphoma". It contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety. The primary endpoint of the trial is PFS.

These analyses include one interim analysis for futility and one final analysis. Throughout this SAP, the treatment arms will be referred to as "experimental R2" for rituximab plus lenalidomide arm and "control R" for rituximab plus placebo arm. The purpose of the SAP is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of study data prior to database lock for the final analysis. The final SAP which may include detailed data handling conventions will be signed off prior to the database lock for the study protocol specified futility analysis for progression-free survival (PFS). All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.1.3 or higher.

3. OBJECTIVES

The primary objective of the study is:

- to compare the efficacy of rituximab plus lenalidomide to rituximab plus placebo in subjects with relapsed/refractory indolent lymphoma

Efficacy determination will be based upon PFS as the primary endpoint, as assessed by the Independent Review Committee (IRC) using the 2007 International Working Group (IWG) response criteria (IWGRC) (Cheson, 2007) but without positron emission tomography (PET).

The secondary objectives of the study are:

- to compare the safety of rituximab plus lenalidomide versus rituximab plus placebo (no formal testing will be provided)
- to compare the efficacy of rituximab plus lenalidomide versus rituximab plus placebo using other parameters of efficacy:
  - durable complete response rate (DCRR), overall response rate (ORR), complete response rate (CR rate), duration of response (DoR) and duration of complete response (DoCR) by 2007 IWGRC without PET
  - overall survival (OS), event-free survival (EFS), time to next anti-lymphoma treatment (TTNLT)

CCI [redacted]

CCI [redacted] CCI [redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This Phase 3 multicenter, double-blind, randomized study is designed to evaluate the efficacy and safety of rituximab plus lenalidomide versus rituximab plus placebo. The overall study design is described in Figure 1. The study is divided into the Screening Period, Treatment Period, and Follow-up Period. It is planned to randomize 350 subjects.

Upon giving written informed consent, the subject enters the Screening Period to determine eligibility. All Screening assessments must be completed within 28 days prior to randomization. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either the experimental arm (rituximab plus lenalidomide) or control arm (rituximab plus placebo) in a 1:1 ratio.

The subject will enter the Treatment Period once the subject has fulfilled the required assessments in the Screening Period and has been randomized. The treatments will be given as described in detail in the study protocol Section 8, and must begin as soon as possible after randomization but no later than 1 week after randomization. The subjects will receive study protocol-specified treatments for a maximum of 12 cycles or until relapse or progression of disease, withdrawal of consent, or unacceptable toxicity. All randomized subjects will be assessed for disease progression (PD) and OS during the study using the schedule described in the study protocol. This includes all subjects who discontinue the study protocol-specified treatment or the study early for any reason without documented evidence of clinical and/or radiological disease progression.

Upon completion or early discontinuation of the study protocol-specified treatments (study protocol Section 8), all subjects will enter the Follow-up Period. In the Follow-up Period, subjects will be followed for disease progression, subsequent anti-lymphoma therapy CCI [redacted], development of any second primary malignancies (SPMs) and OS.

The Schedule of Study Assessments are is listed in Table 2.

Table 2: Schedule of Study Assessments

Procedure	Screening (Day -28 to Day -1)	Treatment Period 12 Months						At Treatment Discontinuation or Completion	Follow-up	
		Cycles 1 to 12: Every Cycle Day 1 (±3 days)	Additional Assessments: Cycle 1 Days 1, 8, 15, 22 (±1 day) Cycles 2 to 5 Day 1 (±3 days)	Cycle 1 Days 1, 8, 15 (±1 day)	Cycles 2 to 4 Day 15 (±1 day)	Cycle 4 & Cycle 7 Day 1 (± 3 days)	Cycle 10 Day 1 (±3 days)		If no PD then follow the CT scan assessment schedule[6] or otherwise specified	If progressed then every 6 months (±2 weeks)
Informed Consent	X	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	-	-	-	-	-	-	-	-	-
Complete Medical History	X	-	-	-	-	-	-	-	-	-
CNS Lymphoma Evaluation	X	-	-	-	-	-	-	-	-	-
Creatinine Clearance (Cockcroft-Gault estimation)	X	-	-	-	-	-	-	-	-	-
12-Lead ECG	X	-	-	-	-	-	-	-	-	-
HBV Screening	X	-	-	-	-	-	-	-	-	-
FFPE Tumor Specimen[1]	X	-	-	-	-	-	-	-	-	-
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X	-	-	-	-	-	X	X[12]	-
Vital Signs[2]	X	X	-	-	-	-	-	X	-	-
Hematology [3]	X	X	-	X	X	-	-	X	X[12]	-
Serum Chemistry[3]	X	X	-	X	X	-	-	X	X[12]	-
Serum Immunoglobulin (IgG, IgA, IgM)	X	-	-	-	-	-	X	-	-	-
Thyroid Stimulating Hormone (TSH)	X	-	-	-	-	X	X	-	-	-

CCI [redacted] CCI

Table 2: Schedule of Study Assessments (Continued)

Procedure	Screening (Day -28 to Day -1)	Treatment Period 12 Months						At Treatment Discontinuation or Completion	Follow-up	
		Cycles 1 to 12: Every Cycle Day 1 (±3 days)	Additional Assessments: Cycle 1 Days 1, 8, 15, 22 (±1 day) Cycles 2 to 5 Day 1 (±3 days)	Cycle 1 Days 1, 8, 15 (±1 day)	Cycles 2to 4 Day 15 (±1 day)	Cycle 4 & Cycle 7 Day 1 (± 3 days)	Cycles 10 Day 1 (±3 days)		If no PD then follow the CT scan assessment schedule[6] or otherwise specified	If progressed then every 6 months (±2 weeks)
Tumor Flare and Tumor Lysis Assessments[4]	-	-	-	X	-	-	-	-	-	-
Pregnancy Testing - for FCBP with Regular or No Menstrual Cycles	Once between Days -10 to -14, and within 24h prior to C1D1	Weekly during first 28 days; every cycle on Day 1 thereafter						X	-	-
Pregnancy Testing - for FCBP with Irregular Menstrual Cycles	Once between Days -10 to -14, and within 24h prior to C1D1	Weekly during first 28 days; every cycle on Days 1 and 14 thereafter						X	-	-
Birth Control and Lenalidomide Counseling[5]	Once between Days -10 to -14	X	-	-	-	-	-	X	-	-
Distribute Lenalidomide Counseling Sheet[5]	X	X	-	-	-	-	-	X	-	-
Adverse Events	X	After signing the informed consent document through 28 days after last dose.								
Assessment of Second Primary Malignancy (SPM)[6]	X	After signing the informed consent document up to and including a follow-up period of up to 5 years from the date of the last subject randomized								
Prior/Concomitant Medications/ Procedures / Record Hospitalizations	X	After signing the informed consent document through 28 days after last dose.								
Physical Examination	X	X	-	-	-	-	-	X	X[12]	-
B Symptoms	X	X	-	-	-	-	-	X	X[12]	-

CCI [redacted] CCI

Table 2: Schedule of Study Assessments (Continued)

Procedure	Screening (Day -28 to Day -1)	Treatment Period 12 Months						At Treatment Discontinuation or Completion	Follow-up	
		Cycles 1 to 12: Every Cycle Day 1 (±3 days)	Additional Assessments: Cycle 1 Days 1, 8, 15, 22 (±1 day) Cycles 2 to 5 Day 1 (±3 days)	Cycle 1 Days 1, 8, 15 (±1 day)	Cycles 2 to 4 Day 15 (±1 day)	Cycle 4 & Cycle 7 Day 1 (± 3 days)	Cycles 10 Day 1 (±3 days)		If no PD then follow the CT scan assessment schedule[6] or otherwise specified	If progressed then every 6 months (±2 weeks)
CT or MRI of Neck, Chest, Abdomen and Pelvis and Response Assessment [7]	X	**Years 1-3:** Every 12 weeks (± 1 week) **Year 4:** Every 16 weeks (± 1 week) **Year 5:** Every 6 months (± 2 weeks) **Years onwards:** Every year (± 3 weeks) **and up to PD**								-
CCI [redacted]										
Bone Marrow Biopsy	X[9]	For subjects with radiological CR/CRu and conditions as defined in protocol section 6.2.1								
Upper Gastrointestinal Endoscopy and Gastric Biopsy[10]	X	**Years 1:** Cycle 7 Day 1 (± 2 weeks); After cycle 12 (+ 2 months) **Year 2-3:** Every 6 months (± 2 weeks) **Year 4 onwards**: Every year (± 2 weeks) **and up to PD or CR**								-
Dispense Study Drug[11]	-	X	-	-	-	-	-	-	-	-
Rituximab[11]	-	-	X	-	-	-	-	-	-	-
Study Drug Return/ Accountability	-	X	-	-	-	-	-	X	-	-
Subsequent Anti-Lymphoma Therapie CCI [redacted]	-	-	-	-	-	-	-	X	-	X

Note: Safety assessments (including labs) must be performed prior to dosing at each treatment visit.
C1D1: Cycle 1 Day 1; CBC: Complete blood count; CNS: Central nervous system; CRF: Case report form; CT: Computed tomography; ECG: Electrocardiogram; FCBP: females of childbearing potential; FFPE: Formalin-fixed paraffin embedded; HBV: Hepatitis B virus; MRI: magnetic resonance imaging; CCI [redacted] TLS: Tumor lysis syndrome; TSH: Thyroid stimulating hormone.

1. If an FFPE tumor block cannot be sent, one hematoxylin and eosin (H and E) stained slide and 10 unstained slides or 11 unstained slides will be acceptable.
2. Vital signs include weight, height (only at Screening), blood pressure, temperature, and pulse.
3. 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 C1D1.

4. The site should make every effort to contact the subject on Day 5 (± 1 day) of the first cycle to inquire about the subject'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 (see protocol section 9.3.1 for more details).
5. All subjects enrolled into this study must conform to all aspects of the lenalidomide pregnancy prevention risk management plan (standalone document, see study protocol Section 18.6).
6. Medical history of any prior cancer other than the disease under study will be reported and, in addition, SPMs will be monitored as events of interest and must be reported as serious adverse events (SAE) regardless of the treatment arm the subject is in. This includes any second primary malignancy, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the Informed consent (ICD) up to and including the follow-up period and until 5 years after the last subject randomized. 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 (eg, any confirmatory histology or cytology results, X-ray reports, CT scan reports, etc.).
7. Efficacy assessment to be performed until progression or relapse. See study protocol Section 6.2.1 for more details.

CCI [redacted]

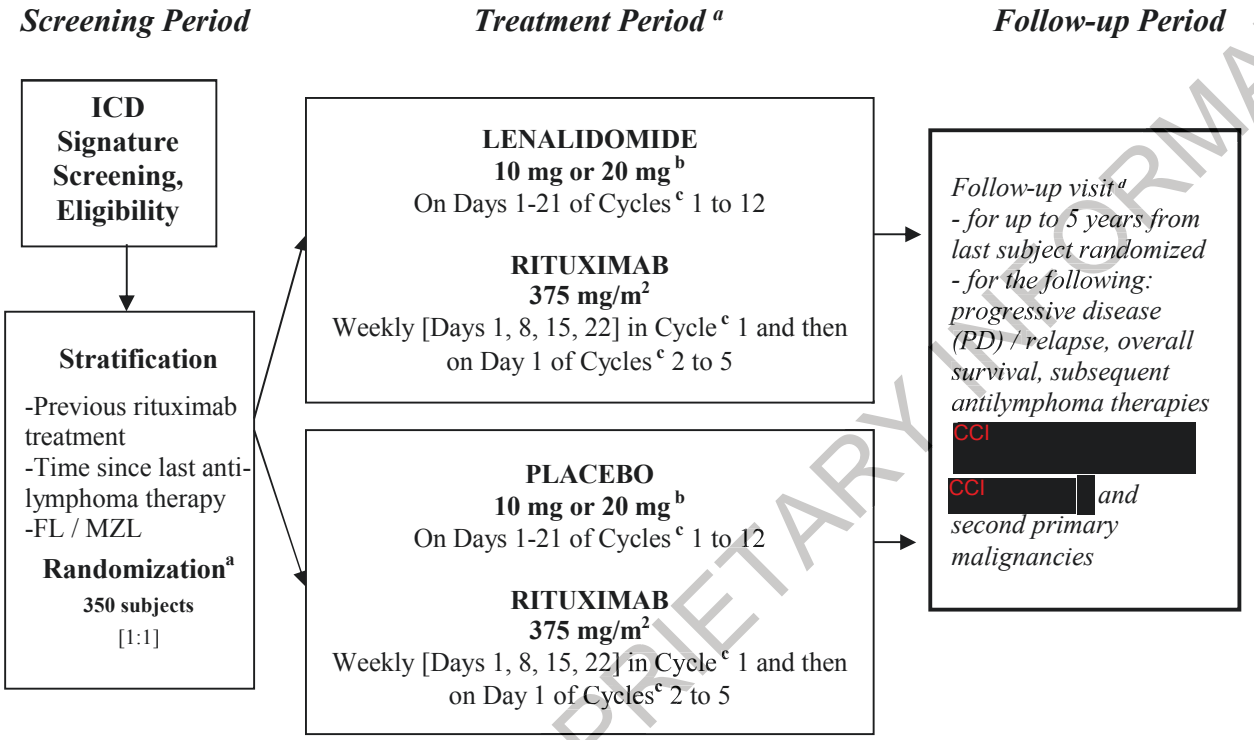
9. Bone marrow biopsy is required at Screening (for staging) only for subjects with abnormal CBC. See study protocol Sections 6.1 and 6.2.1 for more details.
10. Upper gastrointestinal endoscopy including biopsies (from stomach, duodenum, gastroesophageal junction and from any abnormal-appearing site) is required only in subjects with gastric mucosa-associated lymphatic tissue (MALT) lymphoma. See study protocol Sections 6.1 and 6.2.1 for more details.
11. See study protocol Sections 8.1 and 8.2 for more details regarding treatment administration. There is no window for study drug administration.
12. During Follow-up, at same time as the CT/MRI scan evaluation and every 6 months (± 2 weeks) after year 5 (see protocol section 6.4).

Efficacy determination for the primary endpoint will be based upon PFS as determined by the IRC.

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study according to DMC charter.

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

Figure 1: Overall Study Design



CrCl = creatinine clearance; ICD = informed consent document; FL = follicular lymphoma; MZL = marginal zone lymphoma; PD = progressive disease.

[a] Treatment must begin as soon as possible after randomization but no later than 1 week after randomization.
[b] 10 mg if CrCl ≥ 30 mL/min but < 60 mL/min; 20 mg if CrCl ≥ 60 mL/min.
[c] Cycle defined as Lenalidomide / Placebo cycle of 28 days (21 days treatment and 7 days rest period)
[d] All randomized subjects are followed for disease progression and overall survival using the same schedule described in Table 1. This includes patients who discontinue the protocol-specified treatment or the study early for any reason without documented evidence of PD or relapse.

4.1.1. Study Population

The study population includes relapsed and refractory indolent lymphoma subjects who:

- must have an investigator-assessed diagnosis of relapsed/refractory indolent lymphoma, defined in this clinical trial as grade 1, 2 or 3a follicular lymphoma or marginal zone lymphoma,
- must have been previously treated for their lymphoma with systemic therapy (chemotherapy, immunotherapy, or chemoimmunotherapy),
- must be refractory to or have relapsed after their last treatment,
- must have received at least 2 previous doses of rituximab and must not be rituximab-refractory (as of study protocol Amendment 3), and
- must have at least one measurable lesion by computed axial tomography (CT) or magnetic resonance imaging (MRI) scan, and must have adequate bone marrow function, liver function and renal function.

Definitions:

- Relapsed lymphoma: relapsed after initial response of CR to prior therapy.
- Progressive lymphoma: PD after initial response of PR or stable disease (SD) to the prior therapy.
- Refractory lymphoma: subject who received a non-rituximab containing systemic therapy and who experienced the best response of PD to this therapy.
- Rituximab-refractoriness:
  - did not respond (at least a PR) to rituximab or R-chemoregimen therapy and/or
  - time to disease progression < 6 months after last rituximab dose.
- Rituximab-sensitive marginal zone lymphoma (MZL) or FL:
  - Responded (at least a PR) to rituximab or rituximab-chemoregimen therapy and
  - Time to disease progression ≥ 6 months after last rituximab dose

4.1.2. Treatment Assignment

It is planned to randomize 350 subjects in a 1:1 rate to experimental arm (175 subjects) or control arm (175 subjects):

Experimental Arm (Experimental R2): rituximab plus lenalidomide

- Rituximab, 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 through 5,

  plus

- Lenalidomide, 20 mg once daily on Days 1 through 21 every 28 days up to 12 cycles.

Control Arm (Control R)**:** rituximab plus placebo

- Rituximab, 375 mg/m^2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 through 5,

  plus

- Placebo (identical matched capsule), once daily on Days 1 through 21 of every 28-day cycle up to 12 cycles.

4.1.3. Screening Period

Upon giving written informed consent, the subject will enter the Screening Period to determine eligibility (the Screening Period timing begins on the day [Day −28] the first study procedure is performed after the subject has provided written informed consent). All screening assessments must be completed within 28 days prior to randomization. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either the experimental arm (rituximab plus lenalidomide) or control arm (rituximab plus placebo).

Subject eligibility will be based on investigator assessment of the pathologic diagnosis. However, subject's disease diagnosis will be assessed retrospectively by central pathology to confirm the FL or MZL diagnosis. Thus, the investigator must confirm that archival formalin-fixed paraffin embedded (FFPE) tumor or lymph node tissue specimen exists during the Screening Phase. If an archival specimen is not available for submission, then a rebiopsy is required prior to randomization. All tumor specimens must be sent to the central pathology laboratory, preferably during the screening period and no later than 8 weeks after randomization. Confirmation of FL or MZL by the central pathologist is not required for entry into the study.

4.1.4. Treatment Period

The Treatment Period begins with Cycle 1 Day 1 dosing of the therapy drugs and must begin as soon as possible after randomization but no later than 1 week after randomization. The subjects will receive protocol-specified treatments and efficacy and safety assessments for a maximum of 12 cycles, or until relapse or progression of disease, withdrawal of consent, or unacceptable toxicity. A central laboratory will be used for the analysis of hematology and serum chemistry. Clinical decisions and dose modifications during the study can be based on local laboratory results.

All randomized subjects will be followed for disease progression and OS using the same schedule as described in protocol's Schedule of Study Assessments. This includes all subjects who discontinue the protocol-specified treatment or the study early for any reason without documented evidence of disease progression. A subject's withdrawal from the protocol-specified treatment for disease progression will be based upon investigator assessment.

4.1.5. Follow-up Period

The Follow-up Period begins upon study treatment completion or discontinuation. 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 anti-lymphoma / salvage therapy (chemotherapy, stem cell transplants, radiotherapy, etc.). In the Follow-up Period, the subjects will be followed for disease progression, OS, subsequent anti-lymphoma therapies, CCI and SPMs. The Follow-up period ends when subjects complete the 5 year follow up after the last subject has been randomized.

4.2. Study Endpoints

Progression free survival (PFS), best overall response including ORR, CR rate, durable CR rate, and DOR will be assessed per2007 IWGRC (Cheson, 2007) by IRC assessments. Investigator assessments will also be provided for sensitivity analyses. In addition to CT/MRI scan to assess response and progression, subjects with gastric MALT lymphoma will also undergo endoscopy as part of response assessment.

All following endpoints are further defined in Section 11.1 CCI .

The protocol-specified primary efficacy endpoint is:

- Progression-free survival (PFS)

The protocol-specified secondary endpoints are:

- Overall survival (OS)
- Durable complete response rate (DCRR)
- Overall response rate (ORR)
- Complete response rate (CR)
- Duration of response (DoR)
- Duration of complete response (DoCR)
- Event-free survival (EFS)
- Time to next anti-lymphoma treatment (TTNLT)
- Safety (type, frequency, and severity of adverse events [AEs], and relationship of AEs to study drug or comparator)

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4.3. Stratification, Randomization, and Blinding

The randomization procedure will be accomplished by a validated interactive voice response system (IVRS), using the method of randomly permuted block within strata, stratified by the following:

- previous rituximab treatment (yes; no),
- time since last anti-lymphoma therapy (≤ 2; > 2 years), and
- disease histology (FL; MZL).

4.4. Sample Size

The basis for the power and sample size determination will be a test of the equality of the overall time-to-event (ie, PFS) curves between experimental and control treatment groups using a stratified log-rank test. The primary efficacy endpoint is PFS. To fulfill the primary objective of the study, it must be shown that the experimental arm is superior to the control arm on the primary endpoint at one-sided $\alpha = 0.025$ level. It is hypothesized that the median PFS is 17.6 months in the experimental arm and 11 months in the control arm (corresponding hazard ratio [HR] of 0.625, assume that FL and MZL subjects have the same median PFS). For 90% power to detect this difference with 1-sided $\alpha = 0.025$, a total of 193 PFS events will be required.

Based on the rate of accrual anticipated in this study, and annual dropout rate of 5%, it is planned to randomize a total of approximately 350 subjects in a 1:1 ratio to the 2 treatment arms and the study duration to reach the PFS events is expected to be 43 months.

Sample size and power were calculated using the East® Version 5.4 software system (Cytel Inc, 675 Massachusetts Avenue, Cambridge, MA 02139; http://www.cytel.com).

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the following:

- Program source (eg, SAS program name, including the path, that generates the output) and
- Data extraction date (eg, the database lock date, run date)

The purpose of the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference. An output date will also 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.

5.1.1. Dates Handling

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS unless specified otherwise). 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, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are 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 dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events 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 16.1 (eg, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug 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 are not otherwise 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 (see Section 5.1.2 below).

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

5.1.2. 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:

- For all safety analyses, study days on or after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study medication (eg, rituximab or lenalidomide, whichever is earlier) plus 1 day; study days before the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study medication. Note that Study Day 1 is the first day of treatment of study drug. There is no day zero, and negative study days are reflective of observations obtained during the baseline/screening period. All effort should be made to avoid incomplete study drug start date.
- For all efficacy analyses, time-to-event days for efficacy endpoints will be calculated as the difference between the date of interest and the randomization date plus 1 day.
- Age (expressed in days) is calculated as follows:

  AGE = DATE of RANDOMIZATION – DATE of BIRTH + 1.
- If the date of randomization is not available (ie, screen failure), then the date of informed consent is used. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:
- WEEKS = DAYS / 7.
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:
- MONTHS = DAYS / 30.4375

5.2. Analysis Populations

The primary efficacy analyses will be performed on the Intent-to-treat (ITT) population for the primary and secondary endpoints. Primary and secondary endpoints will also be analyzed for the modified Intent-to-treat (mITT) population. Sensitivity analyses will be conducted for the primary and secondary endpoints based on the ITT population. All ITT and mITT analyses will be based on randomized treatment groups.

Safety analyses will be conducted only on the Safety population.

5.2.1. Intent-to-Treat Population (ITT)

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 are initially assigned.

5.2.2. Modified ITT (mITT)

The mITT population is defined as all randomized subjects who have received at least 1 dose of study medication, have confirmed diagnosis of relapsed/refractory FL or MZL by central pathology review except SMZL which was based on local pathology assessment, and have baseline (Screening) 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 are initially assigned

5.2.3. Safety Population

The safety population is defined as all subjects who have received at least one dose of study medication.

The safety population will be used for all safety analysis. Subjects will be analyzed according to the treatment which they initially received.

5.2.4. Subgroup Analyses

In addition to analyses that include the ITT population, PFS (primary endpoint per 2007 IWGRC) and ORR (per 1999 IWGRC) will be performed for subgroups to compare treatments within stratification factors: previous rituximab treatment (yes; no), time since last anti-lymphoma therapy (≤ 2; > 2 years); histology (FL; MZL). Separate efficacy analyses for FL and MZL subjects will be also performed. For these stratification factors, data collected by CRF will be used in subgroup analyses.

Subgroup analyses may also be performed on other important factors such as demographic and baseline characteristics as needed:

- Age (< 65; ≥ 65 years)
- Sex (male; female)
- Race (White; Other Races)
- Region (the United States [US], the European Union [EU], Asian-Pacific Region and Brazil[Other])
- FLIPI (>=3 ; <3) for FL subjects only;
- Number of prior anti-lymphoma regimens (1 ; >1) ;
- Ann Arbor Stage at Enrollment (I-II; III-IV)

- Prior Rituximab containing chemotherapy regimen (Yes or No)
- Refractory to last prior regimen (Yes; No)
- High tumor burden perGELF, (Salles et al., Lancet 2010, 377:42-51) (Yes; No)
- Chemoresistant (<PR or PD <=6 months from last chemotherapy, Yes; No)
- Unfit for Chemotherapy (defined by Age>=70, or if 60-69 years old AND CrCL<60 mL/min or ECOG PS>=2, Yes; No)

Definitions:

- Prior Rituximab containing chemotherapy regimen (Yes; No):

  Prior rituximab containing chemotherapy regimen requires that rituximab AND one or more chemotherapeutic agents are used in the same regimen (at least one regimen, no requirement on which line the regimen is used).

- High tumor burden (Yes; No):

  High tumor burden condition is met when a subject meets at least one of the following criteria at baseline:

  - A nodal or extranodal (except spleen) mass >7cm in greater diameter
  - Involvement of at least 3 nodal or extra-nodal sites (each with a diameter greater than 3 cm)
  - Symptomatic splenomegaly (>16 cm)
  - Compression syndrome (ureteral, orbital, gastrointestinal)
  - Pleural or peritoneal serous effusion (irrespective of cell content)
  - B-symptoms
  - Any one of the following:
    - hemoglobin < 10g/dL (6.25 mmol/L)
    - absolute neutrophil count (ANC) < 1.5 x 109 /L
    - platelets <100 x 109/L
  - Baseline Lactate dehydrogenase (LDH) > upper limit of normal (ULN)

- Chemoresistant (Yes; No):

  Chemoresistant criteriaon is met when a subject meets one of the either conditions below:

  - the best overall response to last chemotherapy treatment is SD or PD
  - the best overall response to last chemotherapy treatment is PR, CRu, or CR, but progression occurs within 6 months after completion of treatment

- Unfit for Chemotherapy (Yes; No):

  Subjects who are unfit for chemotherapy meet one of the either conditions below:

- age ≥70;
- if age ≥ 60 and age < 70, with at least one of the following:
  - CrCl is ≥30 mL/min AND < 60mL/min
  - ECOG Performance Status ≥ 2.

The planned subgroup analyses may not be performed on the population with insufficient number of subjects or insufficient information.

6. SUBJECT DISPOSITION

For all enrolled subjects, subject disposition will be tabulated using frequency and percent. Subject disposition includes the number of subjects in the following populations by treatment arm: ITT, mITT, and safety populations.

Primary reasons for discontinuation from each study treatment will be collected on the CRF and will be listed in subject data listings as well as summarized, using frequency and percent, for all randomized subjects including the following categories:

- Adverse event(s)
- PD or relapse
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation
- Other

for each study drug and overall treatment.

Number of subjects who are ongoing in treatment, number of subjects who are ongoing in follow-up, and number of subjects who completed treatment (maximum of 12 cycles) will also be tabulated.

Number and percent of subjects who entered the follow-up phase with or without progression will be summarized. Primary reasons for study discontinuation will be collected on the CRF and will be listed in subject data listings as well as summarized, using frequency and percent, for all randomized subjects including the following categories:

- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation

Duration of study participation, defined as from date of randomization to date of discontinuation of the study (or the date of last visit), will be summarized.

Subject listings will be provided for randomized subjects, subjects discontinued from treatment, subjects discontinued from study, and subjects who are excluded with the reason. The screen failures will be tabulated by unmet inclusion/exclusion criteria. A summary tabulation will be provided for subjects enrolled by study center and country/region.

7. PROTOCOL DEVIATION/VIOLATIONS

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

Protocol deviations will be summarized using frequency tabulations and listed under individual subject listings with no derivation as this information is from the clinical trial monitoring system.

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

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics and baseline characteristics will be carried out for the ITT population and the mITT population. Baseline is defined as the last measurement prior to or on the date of the first dose of any study medication (or the last measurement prior to or on the date of randomization in case the first dose date is missing). When there are retested values, the retest value that is the closest to and prior to or on the first dose date will be used for the analysis. Individual subject listings will be provided to support the summary tables.

Summary statistics (mean, standard deviation, median, minimum, and maximum) will be provided for variables measured on a continuous scale, e.g., age, height, and weight. The frequency distribution (n, %) will be provided for those variables measured on a nominal scale.

8.1. Demographics

Subjects' age, height, weight, and other baseline characteristics (e.g., baseline vital signs and selected safety laboratory values) will be summarized using descriptive statistics, while sex, and other categorical variables (e.g., age categories <65; ≥65 years, reasons to start the treatment, reasons for considering rituximab monotherapy), baseline electrocardiogram (ECG) interpretation, baseline Eastern Cooperative Oncology Group (ECOG) performance status, will be provided using frequency tabulations.

8.2. Baseline Characteristics

The following items will be summarized by treatment arm.

- Body surface area (BSA)
- Histology (FL, MZL)
- Grade (1,2, 3a) for FL subjects
- Follicular Lymphoma International Prognostic Index (FLIPI) category: High (≥3), Intermediate (2), Low (0,1) for FL subjects
- Number of prior antilymphoma regimens: 1,>1
- Subtype for MZL subjects (exrtranodal MZL, nodal MZL, splenic MZL)
- Stage at initial diagnosis
- Stage at enrollment
- Bulky disease (yes, no)
- Patients whose first relapse/progression documented within 2 years of initial diagnosis (yes, no)
- Creatinine clearance (ml/min) and its categories (≥30 mL/min and <60 ml/min, ≥60 ml/min)
- Baseline B symptom present (yes, no)

- Lactate dehydrogenase (LDH): Elevated, Normal
- Bone marrow involved (Yes, No)
- Ann Arbor Stage (1-2; 3-4)
- Early relapse for FL subjects (Yes; No)
- Prior Rituximab containing chemotherapy regimen (Yes or No)
- Refractory to last prior regimen (Yes; No)
- High tumor burden (GELF) (Yes; No)
- Chemoresistant (Yes; No)
- Chemotherapy eligible (Yes; No)
- Unfit for Chemotherapy (Yes; No)

8.3. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 20.0 or later. 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) in descending order of frequency by SOC, and then within each SOC by descending order of PT by the rituximab plus lenalidomide treatment group.

By-subject listings will display medical history including all relevant data collected on the CRF.

8.4. Prior Anti-lymphoma Therapy

Prior anti-lymphoma drugs will be summarized using frequency tabulations by preferred name (World Health Organization [WHO] dictionary term, Version March 2018 or later). A summary of last prior anti-lymphoma drugs (i.e., drugs included in the anti-lymphoma regimen prior to study entry) will also be produced.

Number of prior radiation therapies, best response to prior radiation therapies, prior transplantation, and best responses to prior transplantation, number of prior systemic anticancer therapies, time from the last therapy, best response to last systemic anticancer therapies, best response to each line of prior systemic anticancer therapy will be summarized accordingly.

8.5. Prior Medications

Prior medications are defined as medications that were started before the start of the study treatment (regardless whether medications ended before the start of the study treatment or not). Prior medications that continue into study treatment period will also be reported as concomitant therapy.

All prior medications will be summarized in frequency tabulations. The Anatomical Therapeutic Chemical (ATC) coding scheme of the WHO dictionary term (Version March 2018 or later) will

be used to group medications into relevant categories for these tabulations. The frequencies will be summarized by ATC level 1 term and preferred name (PN) in descending order of frequency by ATC level 1 term, and then within each ATC level 1 term by descending order of PN by the rituximab plus lenalidomide treatment group.

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.

9.1. Treatment Duration

Treatment duration (months) of a drug is defined as:

[(end date of the study drug – (start date of the study drug) + 1] / 30.4375.

The start date of study drug is defined as the first dosing date of the study drug;

The end date of a study drug is the latter one of the last dose date of the study drug and the Day 28 of the last cycle for the study drug, or death date, whichever occurs first, i.e. Min (Max (the last dose date of the study drug, Day 28 of the last cycle for the study drug), death date).

Summary statistics will be provided for treatment duration for rituximab and lenalidomide/placebo separately. Total number of cycles in treatment phase will be tabulated by treatment arm.

9.2. Cumulative Dose

Cumulative dose will be calculated separately for rituximab and lenalidomide/placebo. Cumulative dose during the treatment is defined as the sum of all doses taken across the treatment period.

9.3. Dose Exposure

Dose exposure will be calculated separately for rituximab and lenalidomide/placebo. Dose exposure for lenalidomide/placebo is defined as the total number of actual days on drug during the treatment phase. Dose exposure for rituximab is defined as the total number of actual doses received during the treatment phase.

9.4. Average Dose

Average dose will be calculated separately for rituximab and lenalidomide/placebo. For lenalidomide/placebo, average dose will be calculated as the cumulative dose divided by dose exposure in days. For rituximab, average dose will be the total actual dose received divided by total number of actual doses received.

9.5. Dose Intensity

Dose intensity will be calculated separately for rituximab and lenalidomide/placebo. Dose intensity during the treatment period is defined as the cumulative dose divided by treatment duration for lenalidomide/placebo (mg/week) and for rituximab(mg/m2/week) separately.

9.6. Relative Dose Intensity

Relative dose intensity is dose intensity divided by planned dose intensity.

- For lenalidomide/placebo, the planned dose intensity is the first 21 days of 20 mg/day (10 mg/day if moderate renal impairment) every 28 days.
- For rituximab, the planned dose intensity is 375 mg/m^2 at Days 1, 8, 15 and 22 of Cycle 1, and then Day 1 of 375 mg/m^2 for the Cycles 2 through 5.

9.7. Dose Modification or Interruption or Reduction

Dose modification will be summarized by assigned treatment group and study medication. Time to first dose reduction/interruption for subjects with at least 1 dose reduction/interruption is the time in days elapsed from the date of first dose of treatment to the date that first dose reduction/interruption occurred.

Dose interruption is defined as the number and percent of subjects who interrupted treatment with study drug for 1 or more days at least once during the treatment period due to AE or any other reasons.

Dose reduction is defined as a subject is taking less than 95% of baseline assigned treatment for lenalidomide/placebo during the treatment period due to AE or any other reasons.

Summaries include subjects who have at least one dose reduction, time to first dose reduction, subjects who have at least one dose reduction due to AE, time to first dose reduction due to AE.

10. CONCOMITANT MEDICATIONS/PROCEDURES AND NEXT ANTILYMPHOMA TREATMENT

10.1. Concomitant Medications

Concomitant mediations are defined as non-study medications that are started after the initiation but before the end of the study treatment + 28 days, or started before the initiation of the study treatment and ended or remain ongoing up to the end of the study treatment + 28 days.

All concomitant treatments documented during the treatment period will be summarized in frequency tabulations. The ATC coding scheme of the WHO dictionary term will be used to group medications into relevant categories for these tabulations. The frequencies will be summarized by ATC level 1 term and PN in descending order of frequency by ATC level 1 term, and then within each ATC level 1 term by descending order of PT by the rituximab plus lenalidomide treatment group.

By-subject listings will be provided for all prior and concomitant medications and therapies taken during the trial.

10.2. Concomitant Procedures

The CRF page records procedure, date, and indication. These procedures will be coded using MedDRA Version 20.0 or higher. A frequency summary of subjects by concomitant procedures summarized in frequency tabulations by high level term and preferred term by treatment arm for the ITT Population.

Concomitant procedures will be identified as procedures or surgeries that occurred after or on the date of first dose of any study drug until 28 days after the last dose of any study drug.

10.3. Next Antilymphoma Treatment

Subsequent antilymphoma treatment and next antilymphoma chemotherapy will be summarized by ATC level 1 term and preferred name for the safety population, respectively. Details of subsequent antilymphoma treatment will be presented in subject data listings.

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11. EFFICACY ANALYSES

All efficacy analyses will be performed on the ITT population. Key efficacy analyses will be performed on the mITT population as supportive evidence and to assess robustness of efficacy findings. Subjects will be analyzed according to randomized treatment group.

The primary endpoint PFS per 2007 IWGRC and ORR per 1999 IWGRC will also be analyzed by subgroups.

All stratified analyses will be based on CRF data

For time-to-event data, Kaplan-Meier (KM) survival analyses will be performed (unadjusted for the stratification variables). Number and percent of subjects censored will be provided. Kaplan-Meier product limit method will be used to estimate the survivorship function for all time-to-event endpoints (eg, PFS, OS, EFS, etc). Event rates at specific time points will be estimated from KM curves. Medians together with 2-sided 95% confidence intervals (CIs) will be provided. The confidence interval will be constructed using log-log transformation.

The resulting survival estimates will be presented graphically for selected endpoints.

The stratified (by stratification factors: previous rituximab treatment [yes, no]), time since last antilymphoma therapy [≤ 2, >2 years], histology [FL, MZL]))) Cox proportional hazard regression models will be used to estimate the HRs and associated 95% CIs for the HRs.

For categorical data, CMH test with the stratification factors as strata will be used. The p-values will be presented. The probability of rates will be estimated using the proportion of subjects with responses with exact 2-sided 95% CIs.

11.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is PFS assessed by the IRC using 2007 IWGRC but without PET imaging. In addition to CT/MRI scan to assess response and progression, subjects with gastric MALT lymphoma will also undergo endoscopy as part of response assessment.

Progression-free survival is defined as the time from date of randomization into the study to the first observation of documented disease progression or death due to any cause, whichever occurs first.

The primary endpoint will be compared between the 2 treatment arms when approximately 193 IRC assessed PFS events after applying appropriate censoring rules are achieved. KM estimates of PFS will be provided. Kaplan-Meier product limit method will be used to estimate the survivorship function for PFS. PFS rates at specific time points will be estimated from KM curves. Medians together with 2-sided 95% CIs will be provided. The resulting PFS estimates will be presented graphically.

The stratified (with all 3 stratification factors: previous rituximab treatment [yes, no], time since last anti-lymphoma therapy [≤ 2, >2 years], histology [FL,MZL]) log-rank test will be used to assess superiority of the experimental arm.

The experimental arm will be declared superior if the one-sided p-value from a stratified log-rank test is < 0.025 in favor of the experimental arm.

Conventionally, the hazard ratio with 2-sided 95% CI will be estimated using the Cox proportional hazards model with Efron method for handling a tie.

The primary PFS analysis will be performed for the ITT population following the censoring rules in Table 3 (based on FDA guidance [FDA, 2007]).

Table 3: Censoring Rules Used for the Primary Analysis of Progression-free Survival

Situation	Date of Event or Censoring	Outcome
Death before first PD assessment while on study	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Progression documented	Date of earliest assessment which revealed progression determined by IRC	Event
Death or progression after more than 1 consecutively missed scheduled visits	Date of last adequate assessment which revealed no progression	Censored
No baseline assessment	Randomization	Censored
No progression, nor death	Date of last adequate assessment with evidence of no progression by IRC	Censored
Study discontinuation for any reason other than death or disease progression	Date of last adequate assessment with evidence of no progression by IRC	Censored
Non-protocol new antilymphoma treatment started prior to progression/death	Date of last adequate assessment with evidence of no progression by IRC before the start of new antilymphoma treatment	Censored

IRC = Independent Review Committee; PD = progressive disease.
Source: FDA, 2007.

11.1.1. Sensitivity Analyses for PFS

In order to evaluate the robustness of the primary PFS analysis, several sensitivity analyses will be performed;

1. IRC assessed PFS is analyzed per European Medicines Agency (EMA) guideline (EMA, 2013). All progressions and deaths are considered as events, regardless of whether they occurred after initiating next anti-lymphoma treatment or after 2 or more missed scheduled assessments. Subjects alive and for whom an objective disease progression had not been observed are censored at last assessment date that the subject is known to be progression-free. Other censoring rules specified in Table 3 Table 3 are still followed.
2. PFS is analyzed based on investigator assessment using FDA censoring rule.
3. PFS is analyzed based on investigator's assessment using censoring rule following EMA guidance.
4. PFS is analyzed based on IRC's assessment per 1999 IWGRC (Cheson, 1999) using censoring rule following FDA guidance.

The primary analyses for PFS will also be performed on mITT population.

11.2. Analyses of Secondary Efficacy Endpoints

Secondary endpoints will be analyzed without controlling α as there are no key secondary endpoints declared. All secondary efficacy endpoints will be analyzed in the ITT population. Secondary endpoints will also be analyzed in the mITT population.

All secondary efficacy endpoints will be analyzed at the time when the final primary endpoint PFS is due for analysis.

11.2.1. Overall Survival

Overall survival is calculated as the time from randomization to death from any cause. Overall survival will be censored at the last date that the subject was known to be alive for subjects who were alive at the time of analysis and for subjects who were lost to follow-up before death was documented.

Kaplan-Meier estimates of OS will be provided. Survival rates at specific time points will be estimated from KM curves. Medians together with 2-sided 95% CIs will be provided. The resulting OS estimates will be presented graphically. In addition, this OS will also be summarized after 5 years from the last subject randomized date.

Censoring rules used for the OS analysis are shown in Table 4.

Table 4: Censoring Rules Used for the Primary Overall Survival Analysis

Situation	Date of Progression or Censoring	Outcome
Death prior to or on the cutoff date	Date of death	OS event
No death prior to or on the cutoff date	Date of last known alive	Censored

Last date known alive is defined as the last valid date of subject assessment prior to or on the data cutoff date in the clinical database. For subjects who have withdrawn consent during the study, the last date known alive will be the date of consent withdrawal from the study. For all other subjects, the last date known alive will be derived by searching through all valid assessment dates in all study datasets to identify the last valid subject assessment date available for each subject.

If the last valid subject assessment date available is on or prior to the data cutoff date, it is used as the last date known alive.

If the last valid subject assessment date available is after the data cutoff date, the data cut-off date is used as the last date known alive.

11.2.2. Objective Response Rate

Objective response rate is defined as the proportion of subjects with best response of at least PR during the trial without administration of new anti-lymphoma therapy.

The number and percent of subjects with CR/PR will be tabulated by treatment arm. A stratified CM test to adjust for the stratification factors will be performed and p-value will be provided for ORR.

11.2.3. Complete Response Rate

Complete response rate is defined as the proportion of subjects with best response of CR during the study by administration of new anti-lymphoma therapy.

The number and percent of subjects with CR will be tabulated by treatment arm. A stratified CMH test to adjust for the stratification factors will be performed and p-value will be provided for CR rate.

11.2.4. Durable Complete Response Rate

Durable complete response is defined as the proportion of subjects that stay in CR for at least 1 year, ie, have duration of CR no less than 1 year (>=48 weeks).

The number and percent of subjects with durable complete response will be tabulated by treatment arm. A stratified CMH test to adjust for the stratification factors will be performed and p-value will be provided for DCRR.

11.2.5. Duration of Response

This analysis will be restricted to responding subjects.

Duration of response is defined as from the time from of initial response (at least PR) until documented disease progression or death. Subjects who do not progress at the time of analysis will be censored at the last assessment date that the subject is known to be progression-free.

Subjects who receive a new treatment without documented progression will be censored at the last assessment date that the subject is known to be progression-free prior to the start of the new treatment.

Kaplan-Meier estimates of DoR will be provided. Kaplan-Meier product limit method will be used to estimate the survivorship function for DoR. Durable response rates at specific time points will be estimated from KM curves. Medians together with 2-sided 95% CIs will be provided. A stratified log-rank test will be performed and p-value will be provided.

11.2.6. Duration of Complete Response

This analysis will be restricted to subjects with CR.

Duration of complete response is defined as from the time from of initial CR until documented disease progression or death. Subjects who do not progress at the time of analysis will be censored at the last assessment date that the subject is known to be progression-free. Subjects who receive a new treatment without documented progression will be censored at the last

assessment date that the subject is known to be progression-free prior to the start of the new treatment.

Kaplan-Meier estimates of DoCR will be provided. Kaplan-Meier product limit method will be used to estimate the survivorship function for DoCR. Complete response rates at specific time points will be estimated from KM curves. Medians together with 2-sided 95% CIs will be provided. A stratified log-rank test will be performed and p-value will be provided.

11.2.7. Event-free Survival

Event-free survival (EFS) is defined as the time from date of randomization to date of first documented progression, relapse, institution of new anti-lymphoma treatment (chemotherapy, radiotherapy or immunotherapy) or death from any cause. Responding subjects and subjects who are lost to follow up will be censored at the last date known alive. Censoring rules of for EFS are summarized in Table 5.

Kaplan-Meier estimates of EFS will be provided. Kaplan-Meier product limit method will be used to estimate the survivorship function for EFS. EFS rates at specific time points will be estimated from KM curves. Medians together with 2-sided 95% CIs will be provided. A stratified log-rank test will be performed and p-value will be provided.

Table 5 Censoring rules for EFS

Situation	Date of EFS	Outcome
Death	Date of death	Event
Progression	Date of progression	Event
Death or progression after more than one missed visit	Date of death or date of progression	Event
New antilymphoma therapy started after first progression	Date of progression	Event
New antilymphoma therapy started prior to first progression	Date of the first administration of the antilymphoma therapy	Event
New antilymphoma therapy started without prior or subsequent progression	Date of the first administration of the antilymphoma therapy	Event
No baseline tumor assessment	Randomization	Censored
No progression, no new antilymphoma therapy, nor death,	Last day known alive	Censored

11.2.8. Time to Next Anti-lymphoma Treatment

Time to next anti-lymphoma treatment (TTNLT) is defined as the time from date of randomization to date of first documented administration of a new anti-lymphoma treatment

(including chemotherapy, radiotherapy, radioimmunotherapy or immunotherapy). Censoring rules for TTNLT are provided in Table 6.

Table 6 Censoring rules for TTNLT

Situation	Date of TTNLT	Outcome
Death without any new anti-lymphoma treatment	Date of death	Censored
Administration of any new antilymphoma treatment (chemotherapy, radiotherapy, radio-immunotherapy, immunotherapy)	Date of first administration of the treatment	Event
No Death or new administration of any new antilymphoma treatment	Last day know alive	Censored

Kaplan-Meier estimates of TTNLT will be provided. Event rates at specific time points will be estimated from KM curves. Medians together with 2-sided 95% CIs will be provided. A stratified log-rank test will be performed and p-value will be provided.

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11.4. Subgroup Analysis of Efficacy Endpoints

In addition to analyses that include all evaluated subjects, selected analyses will be performed to compare treatments within the subgroups defined in Section 5.2.4. Forest plots for subgroup analyses will be provided for selected endpoints.

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12. SAFETY ANALYSIS

All subjects who receive at least one dose of study drug will be included in the safety analyses.

12.1. Adverse Events

Adverse events will be coded according to the MedDRA Version 20.0 or higher. The intensity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, except for tumor flare reaction (TFR) which will be graded using the NCI-CTCAE Version 3.0.

The following preferred terms under system organ class 'Investigations' are reclassified into the new System Organ Class 'Blood and lymphatic system disorders' and are collapsed into different preferred terms respectively: 'Granulocyte count decreased','Granulocytopenia' and 'Neutrophil count decreased' are collapsed to 'Neutropenia'; 'Hyperchromic anaemia', 'Hypochromic anaemia', 'Hypoplastic anaemia', 'Haemoglobin decreased', 'Red blood cell count decreased', 'Anaemia macrocytic', 'Anaemia megaloblastic','Microcytic anaemia','Normochromic normocytic anaemia', 'Anaemia of chronic disease' and 'Anaemia of malignant disease' are collapsed to 'Anemia'; 'Platelet count decreased' is collapsed to 'Thrombocytopenia'.

A treatment-emergent adverse events (TEAEs) are is defined as any AE occurring or worsening on or after the first treatment of the study medication and within 28 days after the last dose date of any study drug.

The frequency of TEAEs will be summarized by MedDRA SOC and PT in descending order of frequency by SOC, and then within each SOC by descending order of PT by the rituximab plus lenalidomide treatment group. If a subject experienced the same PT multiple times then the subject will be counted only once within the particular PT and by greatest severity. All TEAEs will be summarized by SOC, PT and Cycle of Onset will be summarized.

The following TEAEs will be summarized by SOC and PT for each treatment group: TEAEs leading to study medication discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose interruption, TEAEs related to study medication, serious TEAEs, serious TEAEs related to study medication, serious TEAEs leading to study medication discontinuation, NCI-CTCAE Grade 3 or and 4 TEAEs, Grade 3 orand 4 TEAEs leading to study medication discontinuation, Grade 5 TEAEs and AEs of special interest.

Adverse events of special interest (except for SPMs) will be defined using standardized MedDRA Queries (SMQs), sub-SMQ, SOC, HLT or list of preferred terms that are selected by internal expertise based on the drug and the disease.

Adverse events of special interest include:

- Neutropenia
- Infection
- Thrombocytopenia
- Bleeding
- Cardiac arrhythmias

- Cardiac failure
- Ischemic heart disease (including myocardial infarction)
- Arterial thromboembolism (ATE) events
- Venous thromboembolism (VTE) events
- Mixed thromboembolism
- Renal failure
- Peripheral neuropathy
- Diarrhea
- Constipation
- Cutaneous reactions
- Hypersensitivity
- Angioedema
- Hepatic disorders
- Tumor lysis syndrome
- Tumor flare reaction
- Teratogenicity
- Interstitial lung disease (interstitial pneumonitis)

For each AESI, the incidence rate per 100 person-years along with 95% confidence interval will be provided. Total person-year of an AESI is defined as the total time to onset for subjects with any AE in the AESI category plus the total follow-up time for all other subjects. The confidence interval will be constructed using exact method with F distribution (Ulm, 1990).

Treatment-emergent adverse events, TEAEs with NCI-CTCAE Grade 3 or 4, and serious TEAEs will be descriptively summarized within subgroups defined by the following variables:

- Sex (Male, Female)
- Age group (<65, ≥ 65 years)
- Number of prior anti-lymphoma regimens (≤ 1,> 1)
- CrCl at baseline (< 60 mL/min, ≥ 60 mL/min)
- Race (White, Other Races)
- Ann Arbor stage at enrollment (I-II, III-IV)
- Region (US, EU and Other).

Deaths during treatment period (ie, after the first treatment of the study medication and within 28 days after last dose date of any study drug) and during the follow up stage (after the treatment period) will be tabulated by treatment arm for the safety population.

The number and percentage of subjects with SPMs will be tabulated by treatment group 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)

Hematologic malignancies will be subcategorized into B-cell malignancies, acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), MDS to AML and other hematologic malignancies.

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.

The number and percentage of subjects with SPMs who died and those who did not die will be tabulated by SPM category. Follow up time for all surviving subjects in the safety population will be summarized.

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 1 new malignancy within an SPM category, the onset of the earliest SPM will be used. Time to onset will be summarized descriptively by treatment group 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 were defined as the total time to onset for subjects with any SPM in the SPM category plus the total follow-up time for all other subjects.

Incidence rate per 100 person-years will be calculated for each treatment arm and SPM category. Confidence intervals will be provided.

12.2. Clinical Laboratory Evaluations

Clinical laboratory values will be graded according to NCI CTCAE Version 4.0 for applicable tests. Shift from baseline to worst severity grade observed during the treatment will be displayed by treatment. Normal ranges will be used to determine the categories if High, Low, and Normal for lab tests that have no severity grade.

Listings of clinical laboratory data with abnormal flags will be provided by subject and test.

12.3. Vital Sign Measurements

Vital signs will be presented in a listing, within and above the normal ranges, will be displayed in the listing for each treatment. Normal ranges are defined as follows:

- Systolic BP Normal (90 through 119 mmHg, inclusive)
- Diastolic BP Normal (60 through 79 mmHg, inclusive)
- Body Temperature Normal (36.1 through 37.8°C, inclusive)
- Pulse Normal (60 through 100 bpm, inclusive)

12.4. Physical Examination, Pregnancy Testing and B symptoms

The physical examinations will be summarized by each visit.

Pregnancy testing results for female subjects of childbearing potential will be summarized by visit.

For B symptoms, shift from Baseline to post baseline assessment will be tabulated.

12.5. ECOG Performance Status

Shift from baseline during study in ECOG performance status will be displayed for each treatment.

Scores for ECOG performance status are: 0 = fully active; 1 = restricted activity but ambulatory; 2 = ambulatory but unable to carry out work activities; 3 = capable of only limited self-care; 4 = completely disabled; 5 = death.

CCI [redacted]

CCI [redacted]

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CCI [redacted]

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14. INTERIM ANALYSIS

One interim analysis is planned at 50% of information (96 events) for futility only. An external IRC will review all the disease progression events at the time of interim and final analyses. For the interim analysis, the date of the approximate 96th event, as determined by the IRC, will be used as the data cutoff date. The results of the interim analysis will be reviewed by the independent external DMC.

A conditional power approach is used for futility analysis; if the interim analysis shows less than 25% conditional power for success, the trial may stop for futility.

A stratified log-rank test of IRC reviewed PFS data with censoring rule listed as primary analysis will be performed on the ITT population at the Interim analysis, and its p-value will be compared with the futility boundary.

The 25% conditional power is equivalent to a one-sided p-value of 0.579 under the design hazard ratio without binding. If the one-sided p-value is ≤ 0.579 at the interim analysis, the trial should continue until the required 193 PFS events in the ITT population are observed.

If the one-sided p-value is > 0.579 at the interim analysis, the 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.

15. REFERENCES

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Salles G et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* , 2011; 377: 42 – 51.

CCI [redacted]

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16. APPENDICES

16.1. Date Imputation Guideline

16.1.1. 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 TEAE.

16.1.2. 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.

16.1.3. Impute Missing Disease Diagnosis Dates

- For partial diagnosis dates, January will be assigned to the missing month; and the first day of the month will be assigned to the missing day.

16.1.4. Impute Missing Dates in Prior Anti-lymphoma Regimen

- For each prior anti-lymphoma regimen, the regimen start/stop date, will be collected. If the day of any date is missing, then the first day of the non-missing month will be assigned to the missing day; if month or year of the date is missing, then the date will not be imputed and treated as missing.

16.1.5. Impute Missing Dates in Subsequent Antilymphoma Therapy:

- Patients will be allowed to take other anti-lymphoma therapy after discontinuation from the study. The anti-lymphoma therapy start/stop date will be collected. If the day of any date is missing, then the last day of the non-missing month will be assigned to the missing day; if day and month are both missing, then 31 December of the non-missing year will be assigned to the missing day. If the imputed date is later than the last date known alive, the last date known alive will be used.

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: PPD
Title: PPD
Date: Monday, 25 June 2018, 11:32 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName: PPD
Title: PPD
Date: Monday, 25 June 2018, 11:33 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName: PPD
Title: PPD
Date: Monday, 25 June 2018, 11:42 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName: PPD
Title: PPD
Date: Monday, 25 June 2018, 12:49 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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