Official Title of Study:

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

The “RELEVANCE” trial

(Rituximab Lenalidomide Versus ANy ChEmotherapy)

NCT Number: NCT01476787

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

INVESTIGATIONAL PRODUCT (IP):	**Lenalidomide**
PROTOCOL NUMBER:	**RV-FOL-GELARC-0683C**
DATE FINAL:	**07 Jul 2011**
AMENDMENT 1.0	**08 Jun 2012**
AMENDMENT 2.0	**08 Feb 2016**
AMENDMENT 3.0	**21 Apr 2016**
AMENDMENT 4.0	**25 Feb 2019**
AMENDMENT 5.0	**08 Jan 2024**
EudraCT NUMBER:	**2011-002792-42**
IND NUMBER:	**60100**
SPONSOR NAME/ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

CONFIDENTIAL

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

See Electronic Signature and Date on File in Electronic Document Management System
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

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COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator and Title **Site Number:**_____ **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

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OVERALL RATIONALE FOR PROTOCOL AMENDMENT 5.0:

The rationale for this protocol amendment is to include an additional criterion, which is time driven, to the existing criterion, which is events driven, to trigger the final progression free survival (PFS; co-primary endpoint) analysis and therefore the end of the study.

Based on preliminary assumptions in the initial version of the protocol, a median PFS of 83 months (6.9 years) was expected with standard treatment (rituximab plus chemotherapy), and the objective was to increase the median PFS by 30% with the experimental treatment (rituximab plus lenolidomide), ie, an expected median PFS of 108 months (9 years). To detect this difference with a power of 80% and a bilateral alpha risk of 5%, 456 PFS events (assessed by an Independent Review Committee [IRC]) were required.

A decrease in the number of PFS events (progression/relapse), as assessed by the IRC, over the past 4 years has been noted, decreasing from 46 events in 2019 to 7 events in 2022, and it is anticipated that over time there will be almost no progression/relapse events to be detected. As follicular lymphoma is an indolent lymphoma and yearly computed tomography (CT) scans are not recommended, a significant number of patients who are followed for an extended period will not have CT scans at the discretion of the investigator. Of note, the recent PFS curve assessed by the IRC showed a trend toward a plateau.

Taking into account published data for this study (Morschhauser, 2022) and the uncertainty of reaching the expected 456 PFS events in 9 years, using a median follow-up period of 9.5 years to trigger the final PFS analysis (with an estimated study end date of 30 Apr 2024) is not anticipated to impact the overall results of the study.

Additional minor changes have been made related to administrative information. This protocol amendment represents cumulative changes to the original protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1: Synopsis	Added text to the second paragraph under the subheading "Interim analysis for efficacy" in the Statistical Analysis section. Previous: "The final PFS analysis will be performed based on a total of 456 PFS events." Revised: "The final PFS analysis will be performed based on a total of 456 PFS events or, at the latest, when 9.5 years of median	Based on the initial version of the protocol, the final analysis for the co-primary endpoint PFS was to be performed when the required 456 progression/relapse/death events had occurred for all randomized patients. Based on initial assumptions, it was expected that 456 events would be reached at 9 years of median follow-up.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	follow-up has been reached, whichever occurs first."	
	Added text to the second bullet under the subheading "Final analysis" in the Statistical Analysis section. Previous: • "for the co-primary endpoint PFS: when the required 456 progression/relapse/death events have occurred among all randomized patients." Revised: • "for the co-primary endpoint PFS: when the required 456 progression/relapse/death events have occurred among all randomized patients or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs first." The alpha level for the final analysis may be adjusted based on the total number of PFS events if the study is terminated prior to accumulating the originally planned 456 events.	The 9 years of median follow-up has been reached but not the 456 PFS events. This amendment is being initiated to update the study end definition in view of the uncertainty regarding the date for obtaining the number of events required to trigger the final analysis for the co-primary endpoint PFS.
Section 14.3: Sample Size and Power Considerations	Revised paragraph 6, last sentence. Previous: "The analysis of PFS will occur in about 142 months when the required 456 progression/relapse/death events are expected to be observed."	To update the study end date definition.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Revised: "The analysis of PFS will occur in about 142 months when the required 456 progression/relapse/death events are expected to be observed or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs first."	
Section 14.7.2: Interim Analysis for efficacy	Revised paragraph 2, sentence 3. Previous: "The final PFS analysis will be performed based on a total of 456 PFS events." Revised: "The final PFS analysis will be performed based on a total of 456 PFS events or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs first."	To update the study end date definition.
Section 14.8: Final Analysis	Revised the second bullet. Previous: • "for the co-primary endpoint PFS: when the required 456 progression/relapse/death events have occurred among all randomized patients." Revised: • "for the co-primary endpoint PFS: when the required 456 progression/relapse/death events have occurred among all randomized patients or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs	To update the study end date definition.

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Section Number & Title	**Description of Change**	**Brief Rationale**
	first." The alpha level for the final analysis may be adjusted based on the total number of PFS events if the study is terminated prior to accumulating the originally planned 456 events.	
Section 19: References	Added the following reference: Morschhauser F, Nastoupil L, Feugier P, et al. Six-year results from RELEVANCE: lenalidomide plus rituximab (R^2) versus rituximab-chemotherapy followed by rituximab maintenance in untreated advanced follicular lymphoma. *J Clin Oncol* 2022;40(28):3239-45.	Reference added as referred in the Overall Rationale for Protocol Amendment 5.0

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1 SYNOPSIS

This phase 3 study (RV-FOL-Gelarc-0683C) is a companion to the RV-FOL-Gelarc-0683 study with a combined enrollment target of 1000 patients and will enroll up to 250 patients. The data from both studies will be collected into one database and the statistical analyses as described in Section 14 will be performed on the combined total of patients enrolled into both studies. A single data safety monitoring committee (DSMC), central pathology, and central Independent Review Committee (IRC) will be utilized for these two studies.	
Title of the study	A phase 3 open label randomized study to compare the efficacy and safety of rituximab plus lenalidomide (CC-5013) versus rituximab plus chemotherapy followed by rituximab in subjects with previously untreated follicular lymphoma.
Protocol version	Amendment 5.0
Investigational Product	Lenalidomide
Sponsor	Celgene Corporation
Coordinating investigator	[redacted]
Co-coordinating investigator	[redacted]
Study Objectives	The primary objective of the study is to compare the efficacy of rituximab plus lenalidomide to rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma. Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG (Cheson, 1999) criteria. The secondary objectives of the study are: • To compare the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab using other parameters of efficacy: – Complete Response (CR) at 120 weeks by IWG 1999, Event Free Survival (EFS) by IWG 1999, Time to Next Anti-LymphomaTreatment (TTNLT), and Overall Survival (OS) • To compare the safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab.
Duration of the study	The duration of the entire study will be approximately 12-13 years. Patients receive up to four weeks of screening, approximately 2.5 years of treatment and up to 10 years of follow-up.
Number of patients	Up to 250
Inclusion criteria	Patients must satisfy all the following criteria to be enrolled in the study: 1. Histologically confirmed CD20+ follicular lymphoma grade 1, 2 or 3a as assessed by the investigators: • a formalin fixed paraffin embedded specimen taken within 18 months before signing informed consent must be available for central review, and • a formalin fixed paraffin embedded bone marrow biopsy taken within 18 months before patient signing informed consent must be available for central review. 2. Have no prior systemic treatment for lymphoma.

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	3. Must be in need of treatment as evidenced by at least one of the following criteria:
	• Bulky disease defined as:
	  • a nodal or extranodal (except spleen) mass >7cm in its greater diameter or,
	  • involvement of at least 3 nodal or extranodal sites (each with a diameter greater than >3 cm)
	• Presence of at least one of the following B symptoms:
	  • fever (>38C) of unclear etiology
	  • night sweats
	  • weight loss greater than 10% within the prior 6 months
	• Symptomatic splenomegaly
	• Compression syndrome (ureteral, orbital, gastrointestinal)
	• Any one of the following cytopenias due to lymphoma:
	  • hemoglobin < 10g/dL (6.25 mmol/L)
	  • platelets <100 x 10^9/L , or
	  • absolute neutrophil count (ANC) < 1.5 x 10^9/L
	• Pleural or peritoneal serous effusion (irrespective of cell content)
	• LDH > ULN or β2 microglobulin > ULN
	4. Bi-dimensionally measurable disease with at least one mass lesion > 2 cm that was not previously irradiated.
	5. Stage II, III or IV disease.
	6. Must be ≥ 18 years and sign an informed consent.
	7. Performance status ≤ 2 on the ECOG scale.
	8. Adequate hematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) within 28 days prior to signing informed consent, including:
	• Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
	• Platelet count ≥ 75 x 10^9/L
	• Hemoglobin ≥ 8.0 g/dl (5 mmol/L)
	9. Must be able to adhere to the study visit schedule and other protocol requirements.
	10. Females of childbearing potential (FCBP)† receiving lenalidomide must:
	Have two negative pregnancy tests as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the patient practices complete abstinence from heterosexual contact.
	Either commit to complete abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.
	11. Male patients receiving lenalidomide must†
	Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days

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	following study drug discontinuation, even if he has undergone a successful vasectomy. Agree to not donate semen during study drug therapy and for 28 days after discontinuation of study drug therapy. 12. All patients receiving lenalidomide must: Have an understanding that the study drug could have a potential teratogenic risk. Agree to abstain from donating blood while taking study drug therapy and for 28 days after discontinuation of study drug therapy. Agree not to share study medication with another person. Agree to be counseled about pregnancy precautions and risk of fetal exposure. Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation. 13. For all patients receiving Rituximab: Women must not breast feed and must use effective contraception must not be pregnant and agree not to become pregnant during participation in the trial and during the 6 months thereafter. Men must agree not to father a child during participation in the trial and during the 6 months thereafter.
Exclusion criteria	The presence of any of the following will exclude a patient from enrollment: 1. Clinical evidence of transformed lymphoma by investigator assessment. 2. Grade 3b follicular lymphoma. 3. Patients taking corticosteroids during the last 4 weeks, unless administered at a dose equivalent to ≤ 10 mg/day prednisone (over these 4 weeks). 4. Major surgery (excluding lymph node biopsy) within 28 days prior to signing informed consent. 5. Seropositive for or active viral infection with hepatitis B virus (HBV): • HBsAg positive • HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA Note: • Patients who are HBsAg negative, anti-HBs positive, and/or anti-HBc positive, but viral DNA negative are eligible • Patients who are seropositive due to a history of hepatitis B vaccine are eligible. 6. Known seropositive for, or active infection with hepatitis C virus (HCV). 7. Known seropositive for, or active viral infection with human immunodeficiency virus (HIV). 8. Life expectancy < 6 months. 9. Known sensitivity or allergy to murine products. 10. Prior history of malignancies, other than follicular lymphoma, unless the patient has been free of the disease for ≥ 10 years. Exceptions include a history of previously ***treated*:** a. Localized non-melanoma skin cancer b. Carcinoma in situ of the cervix 11. Prior use of lenalidomide.

† See APPENDIX H for details.

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	12. Neuropathy > Grade 1. 13. Presence or history of CNS involvement by lymphoma. 14. Patients who are at a high risk for a thromboembolic event and are not willing to take venous thromboembolic (VTE) prophylaxis. 15. Any of the following laboratory abnormalities: • serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) > 3x upper limit of normal (ULN), except in patients with documented liver or pancreatic involvement by lymphoma • total bilirubin > 2.0 mg/dl (34 μmol/L) except in cases of Gilberts Syndrome and documented liver involvement by lymphoma • creatinine clearance of < 30 mL/min 16. Uncontrolled intercurrent illness. 17. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form. 18. Pregnant or lactating females. 19. Any condition, including the presence of laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study, or which confounds the ability to interpret data from the study.
Design of the trial	This multi-center, open-label study is designed to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab. The study is divided into the Screening Period, Treatment Period, and Follow-up Period. Once a patient gives written consent, the patient may enter the Screening Period, which is permitted to last up to 4 weeks. During the Screening Period, the investigator will choose one standard-of-care regimen ("investigator's choice") for the patient from a list of permitted choices of rituximab-containing chemotherapy regimens. In addition, during the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either experimental arm (rituximab plus lenalidomide) versus control arm ("investigator's choice" of rituximab-chemotherapy). The patient will enter the Treatment Period once the patient has fulfilled the required assessment in the Screening Period and has been randomized. Treatment must start as soon as possible after randomization but no later than 2 weeks after randomization. Treatment Period for each patient starts with first intake of study drug, which is defined as Study Day 1 of Cycle 1. The patients will receive protocol-specified treatments until (1) inability to achieve a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment), (2) inability to achieve a response by 24 weeks (second CT assessment), (3) relapse or progression of disease, (4) withdrawal of consent or (5) unacceptable toxicity. All randomized patients will be followed for progression free survival and overall survival using the same schedule. This includes all patients who discontinue the study early for any reason without documented evidence of disease progression. Upon completion of the required treatments, the subject will enter the Follow- Up Period. In the follow-up period, the patients will be followed for disease progression and overall survival.
Study Treatments	Control arm : Patients randomized to receive investigators choice will receive ONE of the following: Rituximab-CHOP: with six cycles of R-CHOP in 21 day cycles followed by two 21 day cycles of 375 mg/m^2 rituximab; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles,

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R-CHOP	Route	Dose	Days
Rituximab	IV	375 mg/m^2	1
Cyclophosphamide	IV	750 mg/m^2	1
Doxorubicin	IV	50 mg/m^2	1
Vincristine	IV	1.4 mg/m^2 (2mg cap)	1
Prednisone	PO	100 mg/day	1 to 5

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

R-CVP	Route	Dose	Days
Rituximab	IV	375 mg/m^2	1
Cyclophosphamide	IV	750 mg/m^2	1
Vincristine	IV	1.4 mg/m^2 (2mg cap)	1
Prednisone	PO	40 mg/m^2	1 to 5

Rituximab-Bendamustine: with six cycles of R-B in 28 day cycles; and 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles,

R-Bendamustine	Route	Dose	Days
Rituximab	IV	375 mg/m^2	1
Bendamustine	IV	90 mg/m^2	1 & 2

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For patient ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) that lead to changes in BSA. For rituximab, no dosage adjustments should be performed.

Experimental arm: Patients randomized to receive rituximab-lenalidomide will receive six cycles of lenalidomide 20 mg daily on days 2-22 every 28 days.

Patients exhibiting a CR/CRu after six cycles then receive 12 cycles of 10 mg lenalidomide daily on days 2-22 every 28 days for a total of 18 cycles.

Patients exhibiting a PR after six cycles receive an additional 3 or 6 cycles of the 20 mg lenalidomide dose until they achieve a CR/CRu at which time they receive the 10 mg lenalidomide dosing for 9 or 6 cycles respectively for a total of 18 cycles. Patients who remain in PR after the additional 6 cycles will receive 10 mg lenalidomide dosing for a total of 18 cycles.

All patients randomized to receive rituximab-lenalidomide receive rituximab, 375 mg/m^2 on days 1, 8, 15 and 22 of cycle 1, day 1 of cycles 2 to 6; and 8 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles.

Lenalidomide treatment is continued for 18 cycles or until disease progression, unacceptable toxicity, or voluntary withdrawal.

The lenalidomide dose for each patient will be interrupted and modified following toxicity as described in Table 2, Table 3, and Table 4. If a dose is reduced, re-escalation is not permitted.

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	In addition, patients who do not achieve the threshold clinical activity of 1) a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment), or 2) a response of at least PR by 24 weeks (second CT assessment) will be withdrawn from the study treatment and followed for survival and PFS using the same schedule of assessments as patients continuing treatment as described in Table 1.
Screening and Randomization	Once a patient gives written consent, the patient may enter the Screening Period, which is permitted to last up to 4 weeks. During the Screening Period, the investigator will choose one standard-of-care regimen ("investigator's choice") for the patient from the list of permitted choices of rituximab- containing chemotherapy regimens. In addition, during the Screening Period, the patient will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either experimental arm (rituximab plus lenalidomide) versus control arm (Investigators Choice of R-CHOP, R-CVP, or R-B). Screening and randomization will be performed via IVRS/IWRS.
Statistical Analysis	Sample size: Sample size calculation is based on providing adequate power to evaluate treatment effect on the co-primary efficacy endpoints. The co-primary efficacy endpoints are complete response (CR/CRu) rate at 120 weeks and PFS. To fulfill the primary objective of the study, it must be shown that the experimental arm is superior to the control arm at $\alpha = 0.05$ level based on CR/CRu rate at 120 weeks which could be the basis for an early approval or based on PFS to obtain full approval (Shih, 2003). It is hypothesized that the complete response (CR/CRu) rate at 120 weeks is 60% in the control arm and 72% in the experimental arm. For 90% power to detect this difference with two-sided $\alpha = 0.05$, a total of 644 patients (322 in each arm) will be required. Considering the sample size requirements for both co-primary endpoints, it is planned to enroll a total of approximately 1000 patients into the study. With this sample size, the power to detect the difference of 12% of complete response (CR/CRu) rate between arms will be 98%. It is hypothesized that the median PFS is 83 months in the control arm, and there is a 30% increase in the median PFS in the experimental arm (corresponding hazard ratio of 0.7692). For 80% power to detect this difference with two-sided $\alpha = 0.05$, a total of 456 progression/relapse/death events will be required. It is planned to randomize a total of approximately 1000 patients in 1:1 ratio to the two treatment arms (about 500 in each arm).
	Analysis Plan: The co-primary efficacy endpoints are the complete response (CR/CRu) rate at 120 weeks and the PFS. The primary efficacy analysis will be based on the ITT population. Analysis based on the mITT population is supportive. The number and percent of patients with complete response (CR/CRu) at the 120 week assessment will be tabulated by treatment arm. The experimental arm will be declared superior if the two-sided p-value from a chi-square test is ≤ 0.05 in favor of the experimental arm. The primary analysis will be performed using a stratified Cochran-Mantel-Haenszel (CMH) test to adjust for possible confounding effects of the stratification factors: FLIPI score (0-1 vs 2 vs 3-5), Age (>60 vs $\leq$ 60), longest diameter of the largest node (> 6 v $\leq$ 6 cm). The un-stratified test will be a supportive analysis. The Kaplan-Meier estimates of PFS function will be provided. If a patient has a missing or incomplete CT scan, all other available CT scans or MRIs of the patient will still be used for the analysis. The experimental arm will be declared superior if the two-sided p-value from a stratified log-rank test is ≤ 0.05 in favor of the experimental arm. Conventionally, hazard ratio with two-sided 95% confidence interval (CI) will be

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	estimated using the Cox proportional hazards model. But the treatment effect will be determined by the p-value, not by this 95% CI. The un-stratified log-rank test will be a supportive analysis. Subgroup analysis for PFS will be performed as appropriate The secondary efficacy endpoints are CR rate at 120 weeks , EFS, TTNLT, and OS. In order to control an overall two-sided 0.05 study-wise Type I error rate, a fixed- sequence gate-keeping procedure will be employed to interpret the analysis results of these secondary efficacy endpoints in the order of CR rate at 120 weeks, EFS, TTNLT, and OS.
	Time of analysis: *Interim analysis for futility* For the co-primary endpoint of the complete response (CR/CRu) rate at 120 weeks, two interim analyses for futility are pre-planned: • The first interim analysis will be performed when the first 200 patients have their response assessments done at 6 months of treatment, or have had disease progression or died prior to this timepoint. • The second interim analysis will be performed when the first 200 patients have their response assessments done at 120 weeks, or have had disease progression or died prior to this timepoint. The intention of these two interim futility analyses is to assess risk-benefit and ensure patient safety. The proposed futility boundaries are non-binding. The results of these two futility analyses will be reviewed by the independent DMC to make recommendation of go/no go. There is no plan to claim efficacy superiority based on these interim results, therefore, no Type I error rate adjustment is needed. *Interim analysis for efficacy* The co-primary endpoint PFS will be analyzed as an interim analysis at the timepoint when the co-primary endpoint CR/CRu rate at 120 weeks is reported, i.e., when all randomized patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment. In order to control the overall alpha for PFS, an alpha spending function of Gamma Family with parameter -2.5 will be applied. It is estimated that around 228 PFS events (ie, 0.50 information) would occur at the first interim PFS analysis, and 342 PFS events (ie, 0.75 information) are required at the second interim PFS analysis. The final PFS analysis will be performed based on a total of 456 PFS events or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs first. A statistically significant treatment effect on PFS will be reached if the two-sided p-value is ≤ 0.011 at the first interim PFS analysis, or ≤ 0.019 at the second interim PFS analysis, or ≤ 0.039 at the final PFS analysis.
	Final analysis The final analysis will be performed: • for the co-primary endpoint CR/CRu rate at 120 weeks: when all randomized patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120-week assessment, • for the co-primary endpoint PFS: when the required 456 progression/relapse/death events have occurred among all randomized patients or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs first. The alpha level for the final analysis may be adjusted based on the total number of PFS events if the study is terminated prior to accumulating the originally planned 456 events. The secondary endpoint CR rate at 120 weeks will be analysed when all randomized

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	patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120-week assessment. In order to control the alpha for the other secondary endpoints EFS, TTNLT and OS, the final analysis of these endpoints will be performed at the time of the final PFS analysis, and only descriptive statistics (Kaplan-Meier estimates, median, etc.) will be reported without formal statistical comparison at the time of the final CR/CRu rate at 120 weeks analysis.
Planned start/end of recruitment	December, 2011 – March, 2015

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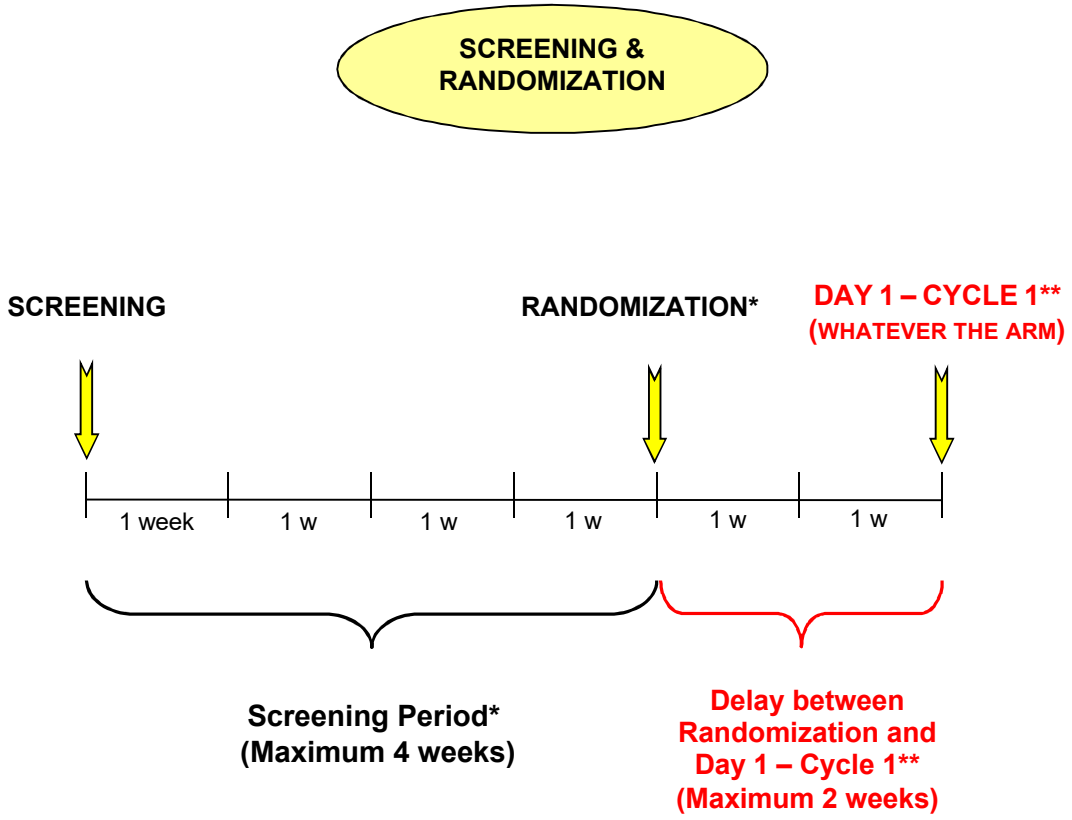
Figure 1: Study Flow Chart



* Randomization should occur anytime within 4 weeks window after screening date (ICF signature date)

** Treatment (Day 1 – Cycle 1) (whatever the arm) must begin as soon as possible after randomization but no later than 2 weeks after randomization

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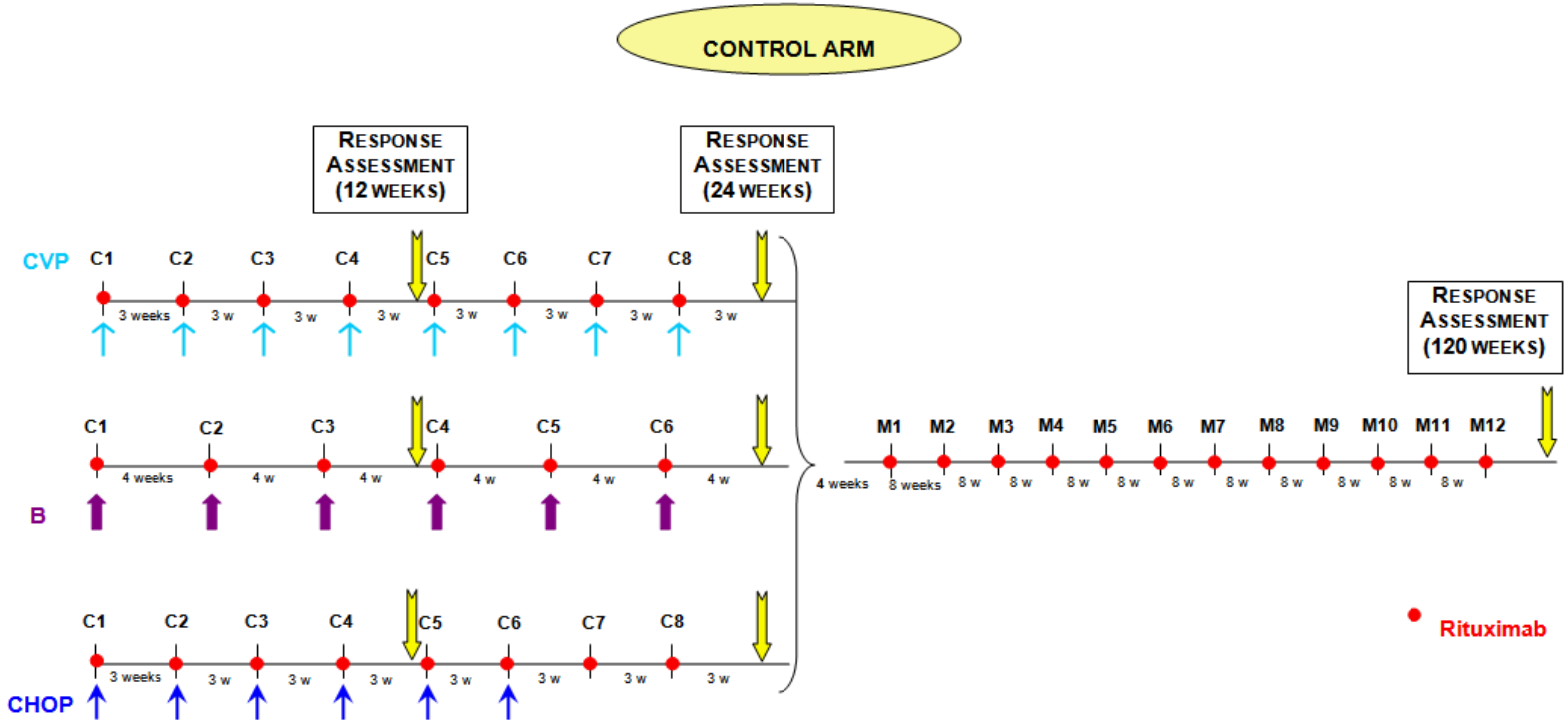

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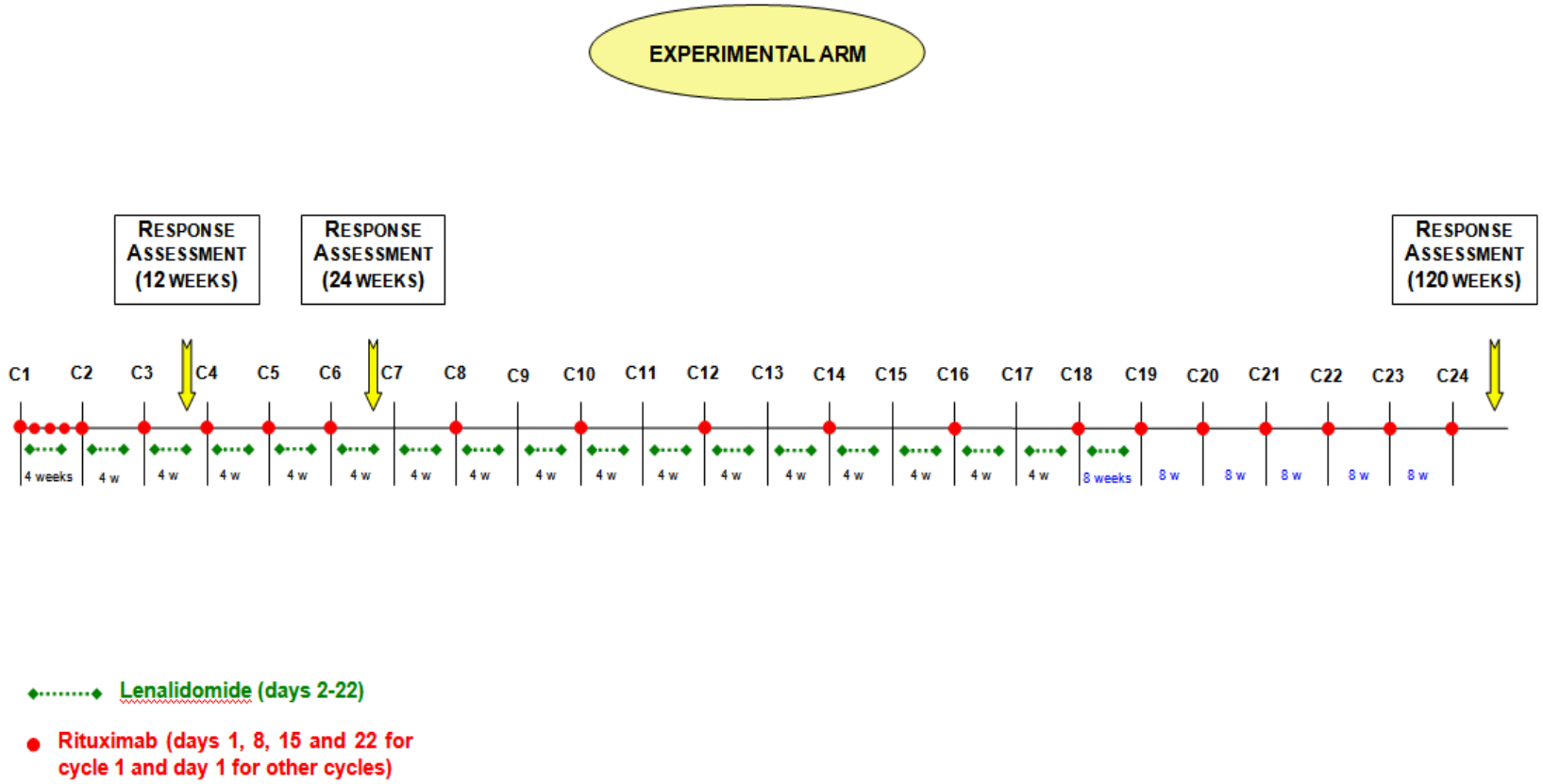

Approved v1100 930216136 2.0

Table 1: Schedule of Study Assessments

Table 1 indicates the study assessment to be performed and the general timing of these assessments. See Section 10 for details and the exact timing of assessments.

Procedure	Screening (see Section 10.2 for the window)	Every Cycle Day 1 (- 2 days)	Only Cycle 1 Day 8, 15 (± 1 Day)	Cycles 2–6 Day 15 (± 1 day)	Weeks 12, 24, 36, 52, 76, 100, 120 after Cycle 1 Day 1 (see Section 10.3 for windows)	At Treatment Discontinuation (± 4 Weeks)
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Complete Medical History	X					
CNS Lymphoma Evaluation[1]	X					
Creatinine Clearance (Cockcroft-Gault estimation)	X					
12-Lead ECG[2]	X					
HBV screening[3]	X					
Echocardiography (LVEF)[2]	X					
FFPE Tumor Specimen[4]	X					
FcgR polymorphism[5, 8]	X					
Select Potential Control Treatment and Randomize	X					
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X			X	X
Vital Signs[6]	X	X				X
B symptoms	X				X	X
CBC with Differential[7]	X	X	X	X		X
Serum Chemistry[7]	X	X	X	X		X
Thyroid stimulating hormone (TSH)[7]	X				X[7]	
Beta2-microglobulin	X					

Approved v1100 930216136 2.0

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Lactate dehydrogenase (LDH)	X				X	
Serum immunoglobulins[8]	X[8]				X[8]	X[8]
Peripheral blood immunophenotyping[8]	X[8]				X[8]	X[8]
Anti-tetanus toxoid antibody[8]	X[8]				X[8]	
Anti-pneumococcal antibody[8]	X[8]				X[8]	
Pregnancy Testing (FBCP only)[9]	X	X				X
Birth Control / Lenalidomide Counseling (Experimental arm)	X	X				X
Distribute Lenalidomide Counseling Sheet (Experimental arm)	X	X				X
Adverse Events	X	X	X	X	X	X[10]
Assessment of Second Primary Malignancy (SPM)[11]	X	X	X	X	X	X
Record Hospitalizations	X	X	X	X	X	X[10]
Tumor Flare / Tumor Lysis Assessment			X			
Concomitant Medications/Procedures	X	X	X	X	X	X
Physical Examination	X	X			X	X
CT/MRI of Neck, Chest, Abdomen and Pelvis[12]	X				X	
Response Assessment					X	
FDG-PET Scan[13]	X				X	
MRD Assessment[14, 8]	X				X	

Approved v1100 930216136 2.0

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EORTC QLQ-C30[15]	X				X	X
EQ-5D[15]	X				X	X
Bone Marrow Biopsy[16]	X				X	
Dispense Study Drugs		X				
Study Drug Return/Accountability		X				X
All subsequent anti-lymphoma Therapy		X				X

1. Central nervous system (CNS)
2. Electrocardiogram (ECG); left VEF (measured by ultrasound echocardiography or scintigraphy) to be performed according to physcian's decision if the patient is planned to recieve anthracycline.
3. Hepatitis B virus (HBV).
4. Formalin-fixed paraffin embedded (FFPE) See Section 10.2 for more details
5. Polymorphism at position 158 of either valine (V) or phenylalanine (F) in the Fc gamma IIIa receptor, FcγRIIIA (FcgR) will be assessed as part of exploratory analysis and will be performed only by selected sites and countries.
6. Vital signs include weight, height (only at screening), blood pressure, temperature, and pulse.
7. See Section 10.2 and 10.3 for more details about Complete blood count (CBC) and serum chemistry. Only hematology assessment will be performed on Day 15 of cycles 5 and 6. TSH assessment required at baseline and will follow the same schedule as the CT scans (see Section 10.3.2 for the CT scan schedule). However if the lab for Day 1 of the cycle are drawn within the given window as specified for CT scan, it need not be repeated again.
8. Serum immunoglobulins, peripheral blood immunophenotyping, anti-tetanus toxoid antibody, anti- pneumococcal antibody, MRD will be assessed as part of exploratory analysis and will be performed only by selected sites and countries. See Section 10.2 and 10.3 for more details
9. Females of childbearing potential (FCBP). For patients receiving lenalidomide see APPENDIX H, "Pregnancy Prevention Risk Management Plan" for details. For all patients receiving rituximab see inclusion criterion 13.
10. Until 28 days post-last dose of study drug(s). See Section 13 for details regarding AE and SAE collection during follow-up

Approved v1100 930216136 2.0

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

[12.] Computed tomography (CT); magnetic resonance imaging (MRI). See Section 10.3 for more details

[13.] Fluorine 18-fluoro-2-deoxy-glucose-positron emission tomography (FDG-PET) assessment will be optional and will be performed at 24 weeks after the first dose date (-1 week/+ 4 weeks), 76 weeks after the first dose date (-1 week/+ 3 weeks), 120 weeks after the first dose date (-1 week/+ 4 weeks). See Section 10.3 for more details

[14.] Minimal residual disease for the detection of t(14;18) by a polymerase chain reaction assay or other MRD assays are Optional and See Section 10.2 and 10.3 for more details

[15.] European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. See Sections 10.2.7 and 10.3.3 for more details.

[16.] Paraffin fixed bone marrow biopsy taken within 18 months of ICF signature must be submitted to central pathology during screening but no later than 12 weeks after randomization. If biopsy was not collected within 18 months of ICF signature, a newly obtained biopsy is required. Patients with negative bone marrow at screening require no further bone marrow biopsy. Patients with positive bone marrow at screening must have a post-screening bone marrow biopsy to confirm CR/CRu within 28 days of first achieving radiological, clinical and biochemical CR/CRu. Post-screening bone marrow biopsies taken when the patient is not in CR/CRu that are negative also require no further bone marrow biopsy. At 120 weeks, patients with a positive bone marrow at screening who are in radiological, clinical and biochemical CR/CRu and who have not had a negative post-screening bone marrow biopsy must have a repeat bone marrow biopsy at this time to confirm CR/Cru

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Table 1: Schedule of Study Assessments (Continued)

		Follow-up period up to 10 years																						
Year					**1**				**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**
Months	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**	**102**	**108**	**114**	**120**
Week	**120**																								
CT/MRI of Neck, Chest, Abdomen and Pelvis[12]	**End of maintenance assessment**		X		X		X		X		X		X		X		X		X		X		X		X
LDH			X		X		X		X		X		X		X		X		X		X		X		X
Physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphoma Related Symptoms and ECOG PS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30[15]			X		X		X		X		X		X		X		X		X		X		X		X
EQ-5D[15]			X		X		X		X		X		X		X		X		X		X		X		X
Response Assessment			X		X		X		X	X	X	X	X	X	X		X		X		X		X		X
Adverse Events[10]		X																							
Assessment of Second Primary Malignancy (SPM)[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
All subsequent anti-lymphoma Therapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum immunoglobulins[8]			X		X																				
Pregnancy Testing (FBCP only)[9]		X[9]																							
Record Hospitalizations[10]		X[10]																							

Approved v1100 930216136 2.0

TABLE OF CONTENTS

Approved v1100 930216136 2.0

Approved v1100 930216136 2.0

Approved v1100 930216136 2.0

Approved v1100 930216136 2.0

LIST OF TABLES

Approved v1100 930216136 2.0

LIST OF FIGURES

Approved v1100 930216136 2.0

2 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
B	Bendamustine
BSA	Body Surface Area
CD20	antigen expressed on the surface of normal and malignant B lymphocytes
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CVP	Cyclophosphamide, vincristine, prednisone
CR	Complete Response
CRF	Case Report Form
CRu	Complete Response unconfirmed
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-Cell Lymphoma
DSMC	Data Safety Monitoring Committee
EC	Ethic Committee
ECOG	Eastern Cooperative Oncology Group
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
FL	Follicular Lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
IP	Investigational product

Approved v1100 930216136 2.0

ABBREVIATION	TERM
IRC	Independent Review Committee
IV	IntraVenous
LDH	Lactic DeHydrogenase
LYSARC	Lymphoma Academic Research Organisation
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	^{18}F-FDG Positron Emission Tomography
PFS	Progression Free Survival
PR	Partial Response
PS	Performance Status
R	Rituximab
SAE	Serious Adverse Event
SD	Stable Disease
SPM	Second Primary Malignancy
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUVmax	Maximum Standardized Uptake Value
TFR	Tumor Flare Reaction
TLS	Tumor Lysis Syndrome
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
VTE	Venous Thromboembolic Event
WHO	World Health Organization

Approved v1100 930216136 2.0

3 RESPONSIBILITIES

3.1 Title of the trial

A phase 3 open label randomized study to compare the efficacy and safety of rituximab plus lenalidomide (CC-5013) versus rituximab plus chemotherapy followed by rituximab in subjects with previously untreated follicular lymphoma.

3.2 Sponsor and coordination center

3.2.1 Sponsor

RV-FOL-GELARC-0683C Companion Study:

Celgene Corporation
✉ : 86 Morris Avenue
Summit, NJ 07901 USA

This phase 3 study (RV-FOL_Gelarc-0683C) is a companion to the RV-FOL-Gelarc-0683 study with a combined enrollment target of 1000 patients and will enroll up to 250 patients. The data from both studies will be collected into one database and the statistical analyses as described in Section 14 will be performed on the combined total of patients enrolled into both studies. A single data safety monitoring committee (DSMC), central pathology, and central Independent Review Committee (IRC) will be utilized for these two studies.

3.2.2 Coordination

Coordinating Principal Investigator: [redacted]

Co-Coordinating Principal Investigator: [redacted]

Head of Steering Committee: [redacted]

Pathological Coordinator: [redacted]

Biological Studies: [redacted]

3.2.3 Study Management

Celgene Corporation
✉ : 86 Morris Avenue
Summit, NJ 07901 USA

Lead Study Manager:
[redacted]

Approved v1100 930216136 2.0

Medical Monitor/Emergency Contact: [redacted]

Drug Safety Contact: Global Drug Safety
Phone : [redacted]
Fax : [redacted]
Email : [redacted]

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

Back-up 24 Hour Global Emergency Contact Call Center: [redacted]

Central Pathology : LYSA-P

[redacted]

Central Imaging :LYSA -IM

[redacted]

3.3 Laboratory sites

Laboratories of each study center must provide their normal ranges and an updated accreditation for quality control.

Approved v1100 930216136 2.0

4 RATIONALE

4.1 Follicular lymphoma

Non-Hodgkin's Lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment (Armitage, 1993). Most of the NHLs are of B-cell origin. The prognosis depends on the histologic type, stage, age, and treatment. Follicular lymphoma (FL) is the most frequent low grade NHL accounting for approximately 20% of all NHL. FL is typically indolent with a median overall survival of 7-10 years. Although FL responds well to treatment it is characterized by recurrent progressions with shorter intervals in between (Salles, 2007). Transformation to diffuse large B-cell lymphoma is relatively common in patients with FL occurring at a rate of approximately 2-3% per year for at least 15 years (Bastion, 1997). Eventually most FL patients die of lymphoma regardless of the treatment initiated.

Both clinical and biological (immune signature) prognostic factors have been reported (Solal-Celigny, 2004; Federico, 2009; Dave, 2004). The high incidence (~90%) of BCL-2 deregulation involving a t(14;18) translocation in FL forms the basis for PCR assessment of minimal residual disease (MRD) in FL (Rambaldi, 2002). The substantial spontaneous remission rate (Horning, 1984), prognostic value of the local immune response (Dave, 2004) and immune suppression (Ramsay, 2009) common in FL all point to the importance of the host immune response in this disease.

4.2 Standard of Care Therapy in Previously Untreated Follicular Lymphoma

Localized stages (Stage I and II) of FL are typically treated with loco-regional radiotherapy. Watch and wait is a strategy that has been employed by some clinicians for asymptomatic, low tumor burden FL and in some cases even for advanced stage disease FL patients. There is, however, consensus that previously untreated FL patients with advanced stage symptomatic or bulky disease (Stage II bulky disease, Stage III and IV) are in need of systemic therapy (Salles, 2007).

Historically FL lymphoma has been treated with single agent or combination chemotherapy (Van Hende, 2007). The addition of rituximab, a monoclonal antibody with specificity for the B-cell CD20 antigen, to combination chemotherapy has consistently demonstrated increased overall response rates, response durations and in some studies an overall survival benefit (Salles, 2007) establishing rituximab-chemotherapy regimens as standard therapy for previously untreated FL patients in need of treatment. The National LymphoCare study which studied treatments administered to 2,728 newly diagnosed FL patients in the US during 2004-2007 reported rituximab-CHOP and rituximab-CVP as the most often used rituximab-chemotherapy regimens (Friedberg, 2009). R-CVP is also approved as first line therapy for FL in the US.

In late 2009, the StiL group reported results from a Phase 3 study to compare the efficacy and safety of rituximab-bendamustine (R-B) versus R-CHOP as first line therapy for patients with FL, indolent and mantle cell lymphomas (Rummel, 2009). Five hundred forty nine patients in need of treatment were randomized to treatment with 2 doses of bendamustine (90 mg/m2) and 1 dose of rituximab (375 mg/m2) every 28 days, or to the standard R-CHOP regimen every 21 days, for a maximum of 6 cycles. Patient characteristics were well balanced and a median number of 6 cycles

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was given in both treatment arms. At the time of analysis the median observation time was 32 months. Overall response rate for patients treated with R-B was similar to the CHOP-R group (93,8% vs 93,5%, respectively). The CR rate was significantly higher with 40.1% for R-B compared to 30.8% for R-CHOP (p=0.0323). Median PFS was significantly longer after R-B compared to R-CHOP: 54.8 versus 34.8 months (p=0.0002), hazard ratio (HR) 0.5765 (95% confidence interval (CI) 0.4292 to 0.7683) for all patients and was not reached after R-B versus 47 months after R-CHOP for the FL patients. Further, R-B was better tolerated than R-CHOP demonstrating significantly less toxicity. Based upon these findings the authors concluded that the combination of bendamustine plus rituximab improves PFS and CR rates while showing a better tolerability profile compared to R-CHOP and that R-B has the potential to become a new standard first-line treatment option for patients with FL, MCL, and indolent lymphomas in some countries. The approval of rituximab by both the EMA and FDA for use as a maintenance agent in previously untreated FL patients responding to rituximab-chemotherapy further anticipates the apparent evolution of the rituximab-bendamustine combination.

In 2010 the GELA (Salles, 2010) reported results from the PRIMA Phase III study that investigated 2 years of rituximab (R) maintenance in follicular lymphoma (FL) patients responding to first-line immunochemotherapy consisting of either 8 cycles of R-CVP, or 6 cycles of R-CHOP or R-FCM (plus 2 additional rituximab infusions). 1,217 patients were enrolled and 75% received R-CHOP induction, 22% R-CVP and 3% R-FCM. 1,018 eligible patients responding to induction therapy were randomized (stratified by regimen and response to induction) to observation or R-maintenance, 375 mg/m2 i.v. every 8 weeks for 2 years. The primary endpoint of PFS was met at the planned interim analysis (ITT: 513 observation, 505 rituximab maintenance). Median follow-up was 25 months from randomization (31 months from study entry). There was a significant (stratified log-rank, P<.0001) improvement in the primary endpoint PFS, for R-maintenance (hazard ratio [HR]=0.50; 95% CI [0.39-0.64]; 2-year PFS 82%; 95% CI [78-86%] vs 66% [61-70%] for observation). Time to next anti-lymphoma treatment, as well as response rate at the end of maintenance or observation, were significantly improved in the R-maintenance arm. The most common AEs were infections (22% observation, 37% R-maintenance). Grade 3-4 AEs were reported in 16% (observation) and 22% (R-maintenance) of patients (neutropenia 1% vs 4%; infections 1% vs 4%, respectively). The authors concluded that the study demonstrates 2 years of R-maintenance therapy after induction immunochemotherapy in previously untreated FL significantly improves PFS with little additional toxicity and provides evidence for a new standard of care for FL patients in need of treatment. Based upon the results of the PRIMA study (Salles, 2011), both the European (October 2010) and United States (February 2011) regulatory agencies approved rituximab as a first-line maintenance treatment for patients with follicular lymphoma whose disease has responded to initial induction therapy.

Taken together, the above results indicate that rituximab-containing chemotherapy followed by rituximab maintenance therapy is a standard of care for patients with previously untreated follicular lymphoma in need of treatment. Median progression free survival (PFS) of 5-7 years or more can be expected with this treatment approach. Nevertheless, unlike other lymphoma histologies such as diffuse large cell lymphoma, cures are not expected. In addition, the existing treatments use

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cytotoxic agents, with associated safety concerns. Therefore, there is a need to develop more effective and safer treatments in follicular lymphoma patients who have a long natural disease course and thus are at risk to experience side effects related to first line treatments.

4.3 Lenalidomide

Lenalidomide (REVLIMID® Celgene Corp., NJ, USA) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiD®); and has potent immuno-modulatory, anti-angiogenic and pro-apoptotic activities *in vitro*.

It offers potential benefit over the first commercially available IMiD® compound, thalidomide, in terms of both safety and efficacy in human patients (Galustian, 2004). The key to its therapeutic potential lies in the fact that it has multiple mechanisms of action, which act to produce both anti-inflammatory and anti-tumor effects. These effects are thought to be contextual in that they depend on both the cell type and the triggering stimulus. To date, lenalidomide has been associated with TNF-α inhibitory, T-cell costimulatory, and antiangiogenic activities (Galustian, 2004).

Lenalidomide is marketed in the United States for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk Myelodysplastic Syndrome (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities and in combination with dexamethasone for patients with previously treated multiple myeloma. Lenalidomide is also approved and marketed in the US, EU, and Australia, in combination with dexamethasone, for the treatment of patients with multiple myeloma who had been treated with at least one prior therapy.

Lenalidomide is being investigated as treatment for various hematological and oncologic indications. Studies have also been conducted in non-oncologic conditions including complex regional pain syndrome.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational product (IP).

4.4 Preclinical Studies with Lenalidomide and Rituximab in Lymphoma

Lenalidomide is an immunomodulatory agent that has both direct tumoricidal and immunomodulatory activities which are critical for its clinical activity in the treatment of various hematologic malignancies. This activity is at least in part mediated by enhanced T-cell and NK-cell effector function to eliminate tumor B cells, attributed to restoration of impaired T-cell activity and formation of immunologic synapses. There are also direct effects on tumor cells, including up-regulation of tumor suppressor genes, leading to cell cycle arrest.

Preclinical studies have shown an enhancement of ADCC (Wu, 2008) and anti-tumor effects in vivo (Hernandez-Ilizaliturri, 2005; Zhang, 2009) when lenalidomide was combined with rituximab. In a murine NHL model, lenalidomide induced significant increase in the recruitment of NK cells to tumor sites resulting in enhanced anti-tumor activity of Rituximab (Reddy, 2008). When combined with rituximab, lenalidomide improved survival in a mouse NHL model and the anti-tumor activity was shown to be NK-mediated. (Hernandez-Ilizaliturri, 2005).

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Recent preclinical studies suggest that lenalidomide may promote restoration of anti-tumor immunological effects in patients with certain hematological malignancies. Ramsay, 2008 reported that impaired T cell immunological synapse formation was seen in both CD4 and CD8 T cells from follicular lymphoma (FL) patients compared to age-matched healthy donors. It was further demonstrated that the immune synapse defects were repaired in part by treatment of the cells with lenalidomide. Treatment of both FL B cells and autologous T cells with lenalidomide (1μM for 24h) was required to enhance formation of the F-actin synapse. Lenalidomide treatment induced actin cytoskeleton reorganization and polarization of MCL cells as early as 30 min, a process termed "capping," which is considered an important subcellular component of the immune synapse formation (Gaidarova, 2009). Additionally it has been shown that the combined use of lenalidomide and rituximab enhances NK cell-mediated immune synapse formation and the resultant cytotoxicity, versus each agent alone. It was recently demonstrated that lenalidomide induces CD20-localization within the "cap," and that the addition of rituximab can enhance immune synapse formation (Gaidarova, 2009). The capping of CD20 is accompanied by redistribution of proteins such as Vav1 and Rac1 that become part of the immune synapse complex. Therefore the capping process induced by lenalidomide appears integral to immune synapse formation and may coordinately enhance the clustering of both the CD20 antigen and the attached rituximab, potentially further enhancing its activity, which would support the clinical combination of these agents.

Gandhi, et al (2009) reported that in FL cell lines and primary cells the lenalidomide-rituximab combination produced synergistic anti-proliferative effects, cytotoxicity mediated via non-immune mechanisms, up regulated expression of the p21 gene, maintenance of elevated Egr1 expression and that lenalidomide can potentiate rituximab-induced cell death through a mechanism involving Bcl-2 phosphorylation. The authors concluded that these data were consistent with the clinical findings demonstrating the clinical benefit of combining lenalidomide with rituximab.

These laboratory observations of direct lenalidomide and rituximab effects on tumor cells, in inducing the expression of potential tumor suppressor genes and proteins potentially involved in tumor cell recognition by T cells, as well as cellular lenalidomide effects on the host immune cells potentially to improve tumor cell recognition, serve as the scientific basis for the use of rituximab-lenalidomide combination described in the clinical trial protocol.

4.5 Clinical Studies of Lenalidomide or Rituximab-Lenalidomide in FL

Single agent lenalidomide was studied in patients with relapsed/refractory indolent NHL, including FL (Witzig, 2009). The dose/regimen used in this study was 25 mg qd x 21 days q 28 days for maximum of 52 weeks. Forty-three (43) patients enrolled. Patients received a median of three prior systemic therapies (range, 1 to 17) and half were refractory to last therapy. ORR was 23% (10 of 43), including a 7% complete response (CR) or unconfirmed CR rate. Twenty-seven percent (six of 22) of patients with follicular lymphoma grade 1 or 2 responded to therapy. Median duration of response (DR) was not reached, but was longer than 16.5 months with seven of 10 responses ongoing at 15 to 28 months for the entire group including FL. Median PFS for the whole group was 4.4 months (95% CI, 2.5 to 10.4 months). The most common grade 3 or 4 adverse

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events were neutropenia (30% and 16%, respectively) and thrombocytopenia (14% and 5%, respectively).

Three recent clinical studies have reported that the combination of rituximab-lenalidomide yields high response rates and high complete response rates in patients with FL.

In 2011, Fowler et al reported the results of an ongoing Phase 2 study evaluating the efficacy and safety of rituximab-lenalidomide in patients with untreated, stage III/IV, indolent NHL. Patients with measurable (>1.5 cm) disease untreated indolent NHL received 20 mg/day of lenalidomide on days 1-21 and rituximab 375 mg/m^2 on day 1 of each 28 day cycle for up to 6 cycles. Response was assessed after every 3 cycles using the IWG (Cheson, 1999) criteria. At the time of this report, 75 patients had completed 6 cycles of treatment or were off-study. The median age was 57 (35-84) years, 55% of pts were male, and 70 pts were evaluable for response. Among all patients, the overall response rate was 90%. Complete responses (CR) were attained in 66% of patients, 17 pts (25%) had a partial response, and stable disease was seen in 6 (9%). Among the subset of patients with follicular lymphoma, 34/39 (87%) evaluable patients attained a CR. Following cycle 6, nearly all FL patients demonstrated molecular response without detectable BCL-2 by PCR. At a median follow up of 14.4 (7-32.5) months, 4 patients experienced progression of disease. Grade 3/4 adverse events were rash (7 pts), neutropenia (20 pts), muscle pain (7 pts), thrombocytopenia (4 patients) infection (3 pts), and thrombosis (3 pts). Five patients were removed from treatment due to adverse events but were eligible for toxicity assessment, including 1 with grade 3 rash, 1 arterial thrombosis, 2 infusion reactions and 1 transient episode of respiratory failure, all of which occurred during the first 2 cycles. The authors concluded that the biologic combination of lenalidomide and rituximab used as front line therapy produces excellent overall and complete response rates with manageable toxicity in patients with indolent B cell NHL.

Dutia et al (2009) reported the results of a clinical trial of the combination of rituximab and lenalidomide in 16 patients with relapsed/refractory indolent lymphoma. Patients received lenalidomide 20 mg daily for three weeks in 4-week cycles and also rituximab 375 mg/m2 weekly x 4 doses starting on day 15. Lenalidomide was continued to disease progression. The median age was 60 years old, median lines of prior therapy was 3, and 7 patients were refractory to rituximab. Of the 16 patients, 13 had FL. In this subset of FL patients, the response rate was 85%. A CR/CRu was achieved in 5 patients (38%).

Ahmadi et al (2009) are conducting a phase II trial of lenalidomide-dexamethasone-rituximab in patients with indolent B-cell or mantle cell lymphomas refractory to rituximab, defined as failure to respond to or progression within 6 months, of rituximab monotherapy, prior rituximab containing chemotherapy, or rituximab maintenance. Patients receive two 28-day treatment cycles of lenalidomide 10 mg daily and dexamethasone 8 mg once weekly (Part 1). After assessment of response, all patients receive rituximab 375 mg/m^2 weekly for 4 doses during cycle 3 (Part 2). Lenalidomide-dexamethasone therapy continues during and after rituximab. Of the first 9 patients with FL completing both parts of the treatment regimen, the response rate was 56% and the CR rate was 44%.

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4.6 Lenalidomide pharmacokinetics

Lenalidomide pharmacokinetics (PK) has been studied in healthy volunteers, patients with renal impairment, and patients with multiple myeloma (MM) or myelodysplastic syndromes (MDS) (Revlimid package insert, 2009). Please see the Investigator Brochure for further details.

Renal function is the most important intrinsic factor affecting pharmacokinetics of lenalidomide. With diminishing renal function, total and renal clearance of lenalidomide decreased while total drug exposure AUC and the $t_{1/2}$ increased. Dose adjustments are recommended for patients with CLcr <60 mL/min.

In patients with MM (baseline serum creatinine level ≤ 1.5 mg/dL), C_{max} occurred between 0.5 to 6 hours post-dose. Plasma exposure (AUC and C_{max}) increases proportionally with dose following single and multiple doses (up to 50 mg/day). In patients with MDS (baseline serum creatinine level ≤ upper limit of normal range), the drug was also absorbed rapidly (median t_{max} =1 h), with approximately 65% of the administered dose excreted unchanged in urine over 24 hours postdose. Lenalidomide half-life in plasma ranged from 3 to 5 hours in these MM or MDS patients. As a result, the drug did not accumulate in plasma upon multiple daily doses. However, exposure (AUC) in these patients was approximately 50-60% higher compared to healthy volunteers. This is consistent with their compromised renal function, possibly as a consequence of their age and their disease.

The pharmacokinetics of lenalidomide has not been studied in patients with lymphoma, including follicular lymphoma, except that PK data is available in adult T-cell leukemia/lymphoma (ATLL) patients.

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5 STUDY OBJECTIVES

5.1 Primary Objective

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

5.2 Secondary objectives

The secondary objectives of the study are:

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

5.3 Exploratory objectives

The exploratory objectives of the study are:

- CR rate at 120 weeks and PFS by 2007 Revised Response Criteria for Malignant Lymphoma incorporating FDG-PET (Cheson, 2007) (APPENDIX B)
- Time to Treatment Failure (TTF), Time to Next Chemotherapy Treatment (TTNCT)and Overall Response Rate (ORR) at 120 weeks by IWG 1999 criteria
- Histological transformation rate at first progression
- To explore the relationship between lenalidomide exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To compare the effects of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab on minimal residual disease using PCR detection of the t(14;18) translocation in peripheral blood or other MRD assays.
- To compare the effects of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab on immune competence
- Evaluate Fc-γ receptor polymorphisms in blood samples collected pre-treatment and correlate with clinical outcomes
- To investigate potential predictive biomarkers of clinical response or resistance to rituximab plus lenalidomide, including, but not limited to, gene expression, analysis of acquired chromosomal aberrations (translocations, gains, deletions, single nucleotide polymorphisms, mutations), microRNA and protein expression in archival diagnostic or fresh tumor samples
- Health related quality of life as measured by the EORTC QLQ-C30 (APPENDIX C)

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- To examine utility during the active, maintenance, and follow-up phases using the EQ-5D (APPENDIX C), for the purpose of collecting information on the treatment regimens to support cost-effectiveness analyses and modeling.

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6 OVERALL STUDY DESIGN

6.1 Study Design Rationale

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

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

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

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

Known toxicities of lenalidomide, given alone or in combination with rituximab have been reported. In addition, in the clinical database and safety database of the sponsor, tumor flare, tumor lysis and venous thromboembolus have been reported, as described further in Section 9.1.

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

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6.2 Study Design

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

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

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

The patient will enter the Treatment Period once the patient has fulfilled the required assessment in the Screening Period and has been randomized. Treatment must start as soon as possible after randomization but no later than 2 weeks after randomization. Treatment Period for each patient starts with first intake of study drug, which is defined as Study Day 1 of Cycle 1. The treatments will be given as described in detail in Section 8. The patients will receive protocol-specified treatments, until:

1) Inability to achieve a 25% reduction in the sum of the products of the diameters (SPD) by 12 weeks (first CT assessment),
2) Inability to achieve a response of at least PR by 24 weeks (second CT assessment),
3) Relapse or progression of disease,
4) Withdrawal of consent or
5) Unacceptable toxicity.

All randomized patients are followed for progression free survival and overall survival using the same schedule described in Table 1, Schedule of Assessments. This includes patients who discontinue the study early for any reason without documented evidence of disease progression.

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

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

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

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

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

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

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

DSMC will conduct two early futility analyses, the first, 6 months after the 200th patient has been randomized (whatever their disease status) and the second, 120 weeks after the 200th patient has been randomized (whatever their disease status). The first futility analysis is to evaluate the complete response (CR/CRu) rate at 24 weeks (6 months) of treatment for the first 200 patients. The second futility analysis is to evaluate the complete response (CR/CRu) rate at 120 weeks for the first 200 patients.

Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG (Cheson, 1999) criteria. The primary analysis of complete response (CR/CRu) rate at 120 weeks will be conditional upon statistical validation that this endpoint accurately predicts PFS and the study will continue to final PFS analysis. Because all protocol specified analyses including early futility analyses are based on IRC review, all CT scans must be sent for central review as soon as possible.

See Section 14 for a detailed description of Statistical Analyses.

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

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

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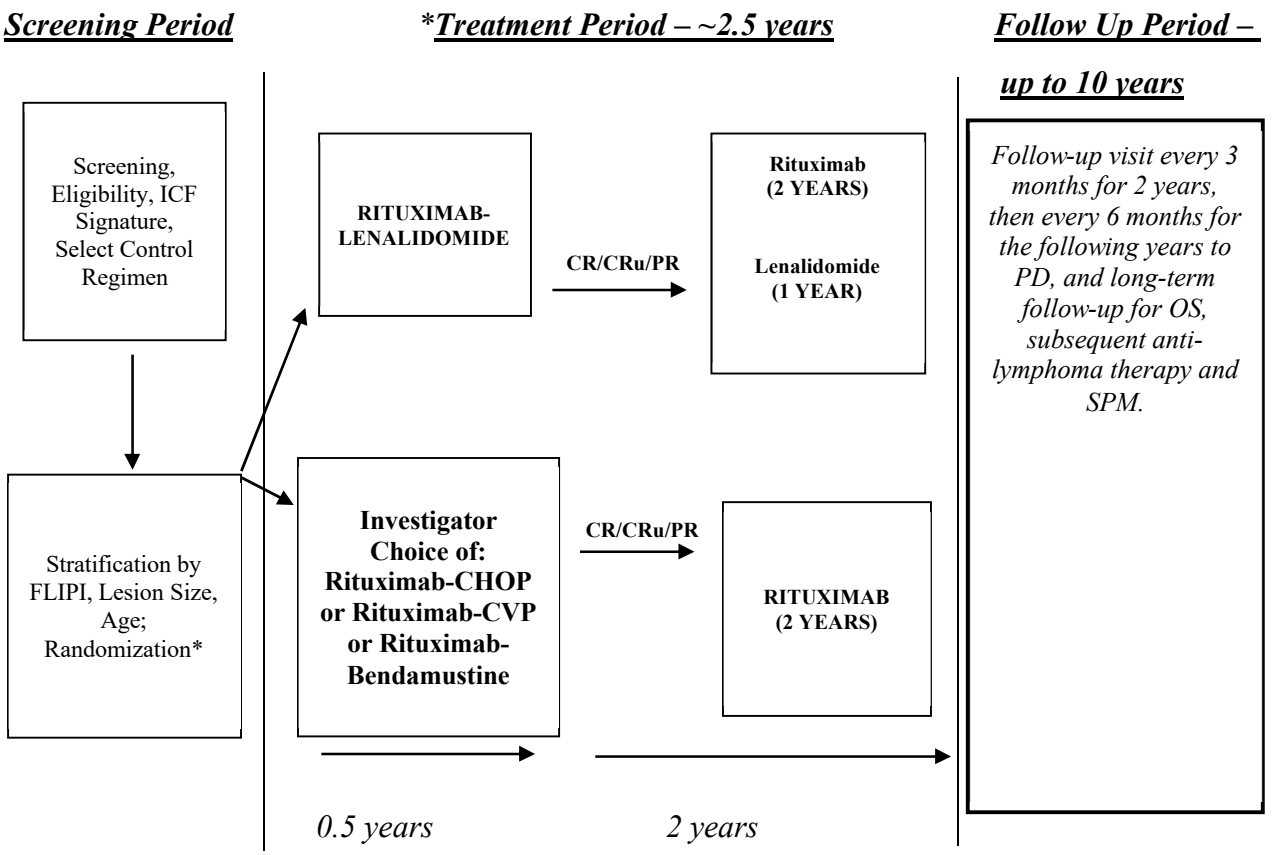
Figure 2: Overall Study Design



* *Treatment must begin as soon as possible after randomization but no later than 2 weeks after randomization.*

All randomized patients are followed for progression free survival TTNALT, TTCT and overall survival using the same schedule described in Table 1 Schedule of Assessments. This includes patients who discontinue the study early for any reason without documented evidence of disease progression.

6.3 Study Duration

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

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

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

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7 STUDY POPULATION

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

7.1 Inclusion criteria

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

1. Histologically confirmed CD20+ follicular lymphoma grade 1, 2 or 3a as assessed by the investigators:
   - a formalin fixed paraffin embedded specimen taken within 18 months before signing informed consent must be available for central review, and
   - a formalin fixed paraffin embedded bone marrow biopsy taken within 18 months before patient signing informed consent must be available for central review.
2. Have no prior systemic treatment for lymphoma.
3. Must be in need of treatment as evidenced by at least one of the following criteria:
   - Bulky disease defined as:
     - a nodal or extranodal (except spleen) mass >7cm in its greater diameter or,
     - involvement of at least 3 nodal or extranodal sites (each with a diameter greater than ≥3 cm)
   - Presence of at least one of the following B symptoms:
     - fever (>38C) of unclear etiology
     - night sweats
     - weight loss greater than 10% within the prior 6 months
   - Symptomatic splenomegaly
   - Compression syndrome (ureteral, orbital, gastrointestinal)
   - Any one of the following cytopenias due to lymphoma:
     - hemoglobin < 10g/dL (6.25 mmol/L)
     - platelets <100 x 10^9/L , or
     - absolute neutrophil count (ANC) < 1.5 x 10^9 /L
   - Pleural or peritoneal serous effusion (irrespective of cell content)
   - LDH > ULN or β2 microglobulin > ULN
4. Bi-dimensionally measurable disease with at least one mass lesion > 2 cm that was not previously irradiated.
5. Stage II, III or IV disease.
6. Must be > 18 years and sign an informed consent.
7. Performance status ≤ 2 on the ECOG scale. (APPENDIX F)
8. Adequate hematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) within 28 days prior to signing informed consent, including:

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- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 /L
- Platelet count ≥ 75 x 10^9 /L
- Hemoglobin ≥ 8.0 g/dl (5 mmol/L)

9. Must be able to adhere to the study visit schedule and other protocol requirements.
10. Females of childbearing potential (FCBP)† receiving lenalidomide must:

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

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

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

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

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

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

    Agree not to share study medication with another person.

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

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

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

7.2 Exclusion criteria

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

1. Clinical evidence of transformed lymphoma by investigator assessment.
2. Grade 3b follicular lymphoma.
3. Patients taking corticosteroids during the last 4 weeks, unless administered at a dose equivalent to < 10 mg/day prednisone (over these 4 weeks).

† See APPENDIX H for details

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4. Major surgery (excluding lymph node biopsy) within 28 days prior to signing informed consent.
5. Seropositive for or active viral infection with hepatitis B virus (HBV):
   - HBsAg positive
   - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA
   - Note:
   - Patients who are HBsAg negative, anti-HBs positive, and/or anti-HBc positive, but viral DNA negative are eligible
   - Patients who are seropositive due to a history of hepatitis B vaccine are eligible.
6. Known seropositive for, or active infection with hepatitis C virus (HCV).
7. Known seropositive for, or active viral infection with human immunodeficiency virus (HIV).
8. Life expectancy < 6 months.
9. Known sensitivity or allergy to murine products.
10. Prior history of malignancies, other than follicular lymphoma, unless the patient has been free of the disease for ≥ 10 years. Exceptions include a history of previously ***treated***:
    - Localized non-melanoma skin cancer
    - Carcinoma in situ of the cervix
11. Prior use of lenalidomide.
12. Neuropathy > Grade 1.
13. Presence or history of CNS involvement by lymphoma.
14. Patients who are at a high risk for a thromboembolic event and are not willing to take venous thromboembolic (VTE) prophylaxis.
15. Any of the following laboratory abnormalities:
    - serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) > 3x upper limit of normal (ULN), except in patients with documented liver involvement by lymphoma
    - total bilirubin > 2.0 mg/dl (34 µmol/L) except in cases of Gilberts Syndrome and documented liver or pancreatic involvement by lymphoma
    - creatinine clearance of < 30 mL/min
16. Uncontrolled intercurrent illness.
17. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form.
18. Pregnant or lactating females.
19. Any condition, including the presence of laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study, or which confounds the ability to interpret data from the study.

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8 STUDY TREATMENTS

8.1 Drugs description

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

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

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

8.2 Treatment schedule and design

Treatment must start as soon as possible after randomization but no later than 2 weeks after randomization. Treatment Period for each patient starts with first intake of study drug, which is defined as Study Day 1 of Cycle 1.

8.2.1 Experimental Arm : Rituximab - Lenalidomide

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

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

Lenalidomide dosing will be based on patients creatinine clearance calculated using the Cockcroft-Gault formula. Creatinine clearance should be calculated using actual body weight.

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

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

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

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

8.2.2 Control Arm : Investigators Choice

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

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

OR

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

OR

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

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

8.2.3 Rituximab background therapy

The planned dose of rituximab is 375 mg/m^2 in all regimens. Schedule is as described for individual regimens. Premedication should be administered (see package insert and protocol Section 9.3.2 package).

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

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

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In rare cases, for patients with high leukemic infiltration the very first dose of rituximab may be given as 2 parts on days 1 and 2, respectively, but the medical monitor or coordinating investigator must be contacted for prior authorization. The amounts administered on day 1 and day 2 will be at the discretion of the physician.

8.2.4 R-CHOP regimen

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

The doses of CHOP components are:

Cyclophosphamide, 750 mg/m2 IV on day 1

Doxorubicin, 50 mg/m2 IV on day 1

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

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

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

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For patient ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA but drugs other than vincristine should not be capped.

Rituximab is administered on day 1 for six cycles with CHOP in 21 day cycles followed by two 21 day cycles of 375 mg/m^2 rituximab; and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert and protocol Section 9.3.2).

8.2.5 R-CVP regimen

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

Cyclophosphamide 750 mg/m^2 day 1

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

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

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

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose may be capped at 2 mg. For patient ≥70 years old, the vincristine dose may be capped at 1.5 mg. For chemotherapy, dosages may be adjusted in

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case of are large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA but drugs other than vincristine should not be capped.

Rituximab is administered on day 1 for eight cycles with CVP in 21 day cycles: and 7 weeks later responding patients continue with 375 mg/m^2 rituximab every 8 weeks for 12 cycles. Premedication should be administered (see package insert and protocol Section 9.3.2).

8.2.6 R-Bendamustine regimen

Bendamustine is administered at 90 mg/m^2 on days 1 + 2 every 28 days for six cycles. Bendamustine will be administered according to the standard preparation and infusion procedures of each investigational site. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Rituximab is administered on day 1 for six cycles with bendamustine in 28 day cycles and 8 weeks later responding patients continue with 375 mg/m^2 rituximab on day 1 every 8 weeks for 12 cycles. Premedication should be administered (see package insert and protocol Section 9.3.2)

8.3 Dose Modifications

8.3.1 Lenalidomide Dose Modifications

The lenalidomide dose for each patient will be interrupted and/or modified by following the toxicity rules as described in Table 2, Table 3, and Table 4.

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

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

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

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

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

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

If dosing is interrupted for toxicity or cycle delayed, it can only be restarted if:

- The ANC is ≥ 1,000 cells/mm^3 (1.0 X 10^9/L);

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

These conditions must be met on Day 1 of each cycle to initiate dosing for the cycle. If these conditions are not met on Day 1 of a new cycle, the patient will be evaluated once every seven days and a new cycle of treatment with lenalidomide will not be initiated until the toxicity has resolved as described above. When a cycle is delayed, both drugs (rituximab and lenalidomide) should be delayed. If a new cycle is delayed for more than 28 days, the Medical Monitor must be notified.

Table 2: Lenalidomide Dose Modification Rules

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Grade 3 Neutrophil count decreased (neutropenia) (one time reading)	Follow CBC at least every seven days.
Neutrophil count decreased (Neutropenia) Sustained (≥ 7 days) Grade 3 OR ≥ Grade 3 associated with fever (temperature ≥ 38.5º C) OR Grade 4	• If neutropenia has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow CBC every seven days • If neutropenia occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • Use of G-CSF, is permitted if the ANC is below 500 during a cycle at the discretion of the Investigator as per ASCO and ESMO guidelines. • In both cases, restart subsequent cycle at next lower dose
Platelet count decreased (Thrombocytopenia) ≥ Grade 3 (platelet count < 50,000 cells/mm³ [50x10^9/L])	• If thrombocytopenia has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow CBC every seven days • If thrombocytopenia has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Allergic reaction or hypersensitivity **Grade 2** Grade 3-4	• If allergic reaction has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If allergic reaction has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose • Permanently discontinue lenalidomide study drug

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Table 2: Lenalidomide Dose Modification Rules

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

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Table 2: Lenalidomide Dose Modification Rules

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Tumor Lysis Syndrome (TLS)**	
Laboratory TLS or Grade 1 TLS	• Continue lenalidomide (maintain dose), or at the investigator's discretion, continue lenalidomide and reduce dose by one level at the start of the subsequent cycle • Provide vigorous intravenous hydration and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy is appropriate (if approved by the local Health Authority) as needed to reduce hyperuricemia • Hospitalization will be at investigator's discretion
Grade 2-4	• If TLS has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days
	• If TLS has occurred before day 15 and resolved to Grade 0 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose • If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following re-initiation of lenalidomide
Other lenalidomide related non- hematologic AEs ≥ Grade 3	• If AE has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If AE has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
<u>Hypothyroid</u>	
If the TSH is > ULN and patient is clinically euthyroid	• repeat TSH on Day 1 of next cycle. • No dose decrease or interruption
If TSH is > ULN for more than 2 cycles, or if patient has clinical symptoms of hypothyroidism;	• Endocrinology evaluation is recommended and thyroid hormone replacement is allowed if clinically indicated. • No dose decrease or interruption

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Table 2: Lenalidomide Dose Modification Rules

DLT, based on NCI CTCAE Toxicity Grade	Action Required
Hyperthyroid If TSH < ULN and patient is clinically euthyroid,.	• repeat TSH every 3 months. • No dose decrease or interruption
If TSH <ULN at repeat evaluation and patient is clinically euthyroid	• recommend endocrine evaluation. • No dose decrease or interruption
If TSH < ULN and patients have symptoms of hyperthyroid (tremor, tachycardia, unintentional weight loss, or *new onset* night sweats),	• Hold lenalidomide for remainder of cycle. • Obtain endocrine evaluation and workup for alternative etiologies. • Repeat TSH level on day 1 of next cycle and contact PI. • If endocrine evaluation rules out hyperthyroidism, restart lenalidomide at the same dose at next cycle • If hyperthyroidism confirmed and alternative etiologies eliminated, restart lenalidomide dosing at next lower dose in the next cycle.

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

** AEs are graded using the Cairo-Bishop toxicity grade (APPENDIX G)

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

Table 3: Lenalidomide Dose Modification Rules for Rash

DLT, based on NCI CTCAE Toxicity Grade	Action Required < Day 15	Action Required ≥ Day 15
Rash[a] Grades 1-2	• Start supportive measures[b] if grade 2 • No dose adjustment	• Start supportive measures if grade 2 • No dose adjustment
Grade 3 (Non- desquamating or non- blistering)	• Hold (interrupt) dose. • Start supportive measures. • Evaluate weekly • If rash resolves to ≤ grade 1 prior to day 21 restart at the • same dose level and continue to • Day 21. • Restart subsequent cycle at next lower dose.	• Hold (interrupt) lenalidomide for remainder of cycle. • Start supportive measures. • Evaluate weekly until rash • ≤ grade 1. • Restart subsequent cycle at next lower dose.
Grade 4[c]	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures

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Table 3: Lenalidomide Dose Modification Rules for Rash

DLT, based on NCI CTCAE Toxicity Grade	Action Required < Day 15	Action Required ≥ Day 15
Desquamating (blistering) rash Any Grade[c]	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures

a AEs are graded using the NCI CTCAE v 4.03; however rash will be graded using NCI CTCAE v 3.0.

b Suggested supportive measures – 1) initiate daily oral antihistamines, for example, loratine 10 mg PO dialy, ceterizinge 10 mg PO dialy or diphenhydramine 25 mg PO daily; 2) Short courses of low-dose steroids for example, prednisone 10 mg PO x 3 days or hydrocortisone 20 mg PO QAM, 10 mg PO QPM x 3 days. It is recommended that the daily oral anti-histamines treatment be continued for the rest the of the lenalidomide treatment.

c In cases of severe (grade 4 or desquamating) rash, prompt dematologic evaluation with skin biopsy and workup for alternate causes is strongly recommended.

Table 4: Lenalidomide Dose Modification Rules For Abnormal Liver Function*

DLT, based on NCI CTCAE Toxicity Grade	Action Required
ALT grade 2 (>3 - 5 x UNL) **and** Total bilirubin grade 1 (> ULN - 1.5 x ULN)	• Continue study drug: re-test at next scheduled visit • No dose modification
ALT ≥ grade 3 (>5 x ULN) **or** Total bilirubin ≥ grade 2 (> 1.5 x ULN)	• hold (interrupt dose) for the rest of the cycle and follow weekly ALT and total bilirubin until return to baseline • Resume the same dose of study drug if recovery (return to baseline) from the event is ≤ 14 days. • If recovery is prolonged beyond 14 days, weekly testing of liver functions should occur during that cycle and then the study drug dose should be decreased by one level at the start of the next cycle.

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

8.3.2 Lenalidomide Dose Reductions Levels

The daily dose of lenalidomide may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction per cycle. Once a patient's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase. Refer to Table 5 for patients starting at the 20 mg dose, and to Table 6 for patients starting at the 10 mg dose.

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Table 5: Dose Reduction Levels from 20 mg Start Dose

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

Table 6: Dose Reduction Levels from 10 (or 15) mg Start Dose

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

* After completion of Cycle 2, if the patient remains free of Grade 3 or Grade 4 toxicity, the dose may be increased to a maximum of 15 mg once daily for 21 days (D2 – D22) starting on day 2 of cycle 3. The same dose reduction rules as in Table 5 would then apply.

Table 7: Dose Reduction Levels from the Cycle 13 - 10 mg Dose*

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

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

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

8.3.3 Dose Adjustment for Patients in the Control Arm

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

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8.4 Method of Treatment Assignment

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

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

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

8.5 Drug Dispensation and accountability

8.5.1 Packaging and labeling

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

8.5.2 Study Drug Receipt and Storage

The Investigator, or designee, is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug shipping order/packing slip.

The Investigator, or designee, will verify the accuracy of the information on the study drug shipping order/packing form and call the IVRS to register/activate the study drug received at the site.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored as directed on the respective package labels.

8.5.3 Drug Dispensing Requirements

In investigational studies, study drug will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of study patients. Once trained these healthcare staff will counsel study patients prior to study drug being dispensed to ensure that the study patient (FCBP & males) has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the study patient understands the risks associated with lenalidomide. This step will be documented by completing the Education and Counseling Guidance Document (APPENDIX H), and no study drug will be dispensed until this step occurs. Counseling includes verification with the study patient that required pregnancy testing was

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performed and results were negative. A Lenalidomide Information Sheet will be supplied as described in APPENDIX H.

8.5.4 Special Handling Instructions

Health care providers should consider wearing gloves when directly handling Revlimid (lenalidomide) capsules followed by standard hand washing. All patients should not handle or administer lenalidomide unless they are wearing gloves. All patients should not extensively handle or open lenalidomide capsules and should maintain storage of capsules in the packaging until ingestion.

8.5.5 Record of Administration

Accurate recording of all study drug administration will be made in the appropriate section of the patient's CRF and source documents.

8.5.6 Accountability and destruction

An accurate accounting of the dispensing/return of study drug for each study patient will be maintained in source documents on an ongoing basis by a member of the study site staff. Additionally, if any study drug is lost or damaged or if the study patient misses a dose, this information should be documented in the study patient's CRF and source documents.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

8.5.7 Compliance

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

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9 CONCOMITANT MEDICATIONS AND PROCEDURES

9.1 Permitted Concomitant Medications and Procedures

Therapies considered necessary for the patient's well being may be administered at the discretion of the Investigator. All medications (prescription and non-prescription), growth factors, transfusions, treatments and therapies taken from 28 days prior to start of study drug through the last dose of study drug, must be recorded on the appropriate page of the CRF.

9.1.1 TFR Treatment- Lenalidomide Arm

Treatment of TFR is up to the discretion of the investigator depending upon the severity and clinical situation. It is suggested that Grades 1 and 2 TFR be treated with non-steroidal anti-inflammatory drugs (NSAIDs) [i.e. ibuprofen 400-600 mg orally every 4-6 hours as needed], corticosteroids, and/or narcotic analgesics for pain management. Refer to Table 2 for further instructions and dose modifications for Grade 3 and 4 TFR.

In mild to moderate cases, it is suggested that lenalidomide be continued along with symptomatic treatment as above. In more severe cases, lenalidomide should be interrupted, as indicated Table 2.

During the Treatment Phase, emergency use of corticosteroids at any dose to treat TFR symptoms for a patient in the lenalidomide arm is allowed at the Investigator's discretion.

9.1.2 Thromboembolism Prophylaxis- Lenalidomide Arm

It is recommended that patients in the lenalidomide arm who are at high risk for a thromboembolic event (high risk includes but not limited to bulky disease, history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history) receive prophylactic aspirin (70 – 325 mg) daily unless contraindicated. If aspirin is contraindicated, use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the international normalized ratio (INR) in the range of 2-3, or use of other anti-thrombotic therapy according to hospital guidelines, or physician preference, is acceptable. However, the choice of anticoagulant for prophylaxis for VTE relies upon the investigator's discretion and should be tailored to the patient's individual risk/benefit profile by taking into account the individual thrombotic risk (e.g., history of venous thrombosis), bleeding risk, and the quality of compliance with antithrombotic treatment.

9.1.3 Growth Factors

Growth factors (e.g. G-CSF, erythropoietin, etc.) may be prescribed by the Investigator for rescue from severe hematologic events and should be used in accordance with the American Society of Clinical Oncology's (ASCO) guidelines or the European Society for Medical Oncology (ESMO) guidelines.

Growth factors or platelet transfusions are not to be administered prophylactically, except for high risk patients in accordance with the American Society of Clinical Oncology's (ASCO) guidelines or the European Society for Medical Oncology (ESMO) guidelines.

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9.2 Prohibited Concomitant Medications and Procedures

Systemic corticosteroid use at doses above 10 mg / day (prednisone or equivalent) is prohibited during the Treatment Phase. For patients receiving systemic corticosteroids at doses above 10 mg/ day (prednisone or equivalent), a 28 day washout period prior to Cycle 1 Day 1 study drug dosing is required. Systemic doses above 10 mg / day (prednisone or equivalent) are allowed for the exceptions of TFR treatment at any time, for rituximab cytokine release syndrome prophylaxis on C1D1, and treatment of infusion related reactions at any time.

In addition, short courses of steroids are permitted at high doses for short-term use if necessary for the well being of the subject. Examples of such short-term use include the treatment of exacerbation of rash not controlled by the suggested supportive measures specified in footnote b of Table 3, chronic obstructive pulmonary disease, and other conditions for which short-term steroid treatment is considered standard of care.

9.3 Required Concomitant Medications and Procedures

9.3.1 TLS Prophylaxis- Lenalidomide Arm

Patients in the lenalidomide arm should receive TLS prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of lenalidomide administration in the first cycle and as clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for TLS and cytopenia(s), the patients will have a complete blood count (CBC) and chemistry drawn on Days 1, 8 and 15 of the first cycle and additionally as clinically indicated. It is recommended that the patient be monitored for TLS during the first week of cycle 1. The site should make every effort to contact the patient on Day 5 (± 1 day) of the first cycle to inquire about the patient's condition and to make sure that he/she is continuing with TLS prophylaxis measures by keeping hydrated and taking the TLS prophylaxis as instructed. Any patient contact that is made on Day 5 (± 1 day) should be documented in patient's medical record and any AEs that are discovered should be captured on the CRF. TLS will be assessed by Cairo-Bishop Grading system (See APPENDIX G).

9.3.2 Rituximab premedication

Premedication consisting of acetaminophen or ibuprofen and an antihistamine should be administered before each rituximab infusion. Steroids used in CVP or CHOP should be administered before the start of the rituximab infusion.

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10 STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS

10.1 Study flow chart

See Figure 1.

10.2 Screening Examination and Procedures

See Table 1 – Schedule of Assessments.

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

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

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

10.2.1 Demographic Information

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

10.2.2 Histological diagnosis

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

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

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

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

10.2.3 Tumor and disease staging

- CT/MRI of neck, chest, abdomen and pelvis is required to locally confirm measurable disease of at least 2 cm. CT is to be performed with contrast unless it is medically contraindicated. This scan may be used as the baseline CT scan if it is obtained within 6 weeks prior to randomization.

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

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

  If bone marrow biopsy was not collected within 18 months of signing the informed consent, a newly obtained bone marrow biopsy is required. Bone marrow aspirate will not be acceptable.
- B-symptoms
- FLIPI and FLIPI 2 (See APPENDIX D)
- Ann Arbor staging (See APPENDIX E)
- ECOG performance status (See APPENDIX F)

10.2.4 Laboratory assessments

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

Cockcroft-Gault estimation of creatinine clearance (CrCl):

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

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

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

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

Creatinine clearance should be determined utilizing actual body weight (Cockcroft, 1976; Luke, 1990).

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

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

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

10.2.5 Cardiac function evaluation

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

10.2.6 Serologies and specific laboratory assessments

- Hepatitis B screening includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs)
- Two pregnancy tests for females of childbearing potential (FCBP) – 1) one during screening period (all FCBP) and 2) one within 24 hours prior the start of lenalidomide (only for FCBP randomized in experimental arm).

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

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

10.2.7 Quality of life assessments

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

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

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

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

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

After randomization, study drug is dispensed on Day 1 for lenalidomide patients or Investigator's Choice patients assigned to oral prednisone (R-CHOP or R-CVP). For Cycle 1 only, a 2 weeks window between randomization and Cycle1 Day 1 is allowed; however, the Screening period must remain within 28 days of Cycle 1 Day 1 dosing.

10.3 Evaluation during treatment and follow-up

Serial assessments of safety and efficacy will be performed as outlined in the Schedule of Study Assessments (Table 1). Patients in both arms will follow comparable assessment schedules. Note that for the first year of maintenance rituximab cycles are administered every 56 days and lenalidomide cycles every 28 days. To balance patient contacts during this time, patients in the rituximab arm will call the site/or call center for a phone call interview every 28 days after each rituximab treatment (for months without rituximab administration) during the first year of maintenance. Laboratories used for hematological and biochemical tests and assays including ongoing pregnancy tests during the study are individual centre laboratories.

10.3.1 Evaluation during each cycle of treatment

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

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

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

Note that the Cycle 1 Day 8 (±1 day) and 15 (±1 day) and Cycle 2-4 Day 15 (±1day) hematology labs are required only for patients in the experimental arm and suggested for patients in the control arm to monitor for cytopenias. The cycles 5-6 Day 15 hematology labs are required for all patients.

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

- TSH to be performed until week 76 and will follow the same schedule as the CT scans. See Section 10.3.2 for more details on the CT scan schedule. However if the lab for Day 1 of the cycle are drawn within the given window as specified for CT scan, it need not be repeated again.
  - It is recommended that the patient be monitored for TLS during the first week of cycle 1. The site should make every effort to contact the patient on Day 5 (± 1 day) of the first cycle to inquire about the patient's condition and to make sure that he/she is continuing with TLS prophylaxis measures by keeping hydrated and taking the TLS prophylaxis as instructed. Any patient contact that is made on Day 5 (± 1 day) should be documented in patient's medical record and any AEs that are discovered should be captured on the CRF.
  - Pregnancy tests for females of childbearing potential (FCBP) will be performed weekly during the first cycle, every 28 days (Day 1 of every cycle) during treatment and at Day 28 following study drug discontinuation as described in APPENDIX H.

10.3.2 Evaluation of response

- All response assessments will be determined from first dose date and will follow the counting of calendar days and not the dosing cycles.
- Patients with negative bone marrow at screening require no further bone marrow biopsy. Patients with positive bone marrow at screening must have a post-screening bone marrow biopsy to confirm CR/CRu within 28 days of first achieving radiological, clinical and biochemical CR/CRu. Post-screening bone marrow biopsies taken when the patient is not in CR/CRu that are negative also require no further bone marrow biopsy. At 120 weeks, patients with a positive bone marrow at screening who are in radiological, clinical and biochemical CR/CRu and who have not had a negative post-screening bone marrow biopsy must have a repeat bone marrow biopsy at this time to confirm CR/CRu.
- CT scans using contrast media are the preferred radiology method (MRI is allowed in case of contraindications to the use of CT scans):
  - 12 weeks after the first dose date (-1 week/+2 weeks),
  - 24 weeks after the first dose date (-1 week/+4 weeks),
  - 36 weeks after the first dose date (-1 week/+ 2 weeks),
  - 52 weeks after the first dose date (-1 week/+ 2 weeks),
  - 76 weeks after the first dose date (-1 week/+ 3 weeks),
  - 100 weeks after the first dose date (-1 week/+ 3 weeks),
  - 120 weeks after the first dose date (-1 week/+ 4 weeks),
  - and then every 6 months (± 4 weeks) for 2 years and then every year (± 4 weeks) until disease progression or relapse.
- FDG-PET scan (will be optional). FDG-PET is to be submitted in addition to CT/MRI data, not in lieu of it:
  - 24 weeks after the first dose date (-1 week/+4 weeks),
  - 76 weeks after the first dose date (-1 week/+ 3 weeks),

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  - 120 weeks after the first dose date (-1 week/+ 4 weeks).
- Physical examination (including ECOG PS and B symptoms) during each response assessment by CT scans. However if the physical examination for Day 1 of the cycle is drawn within the given window as specified for CT scan it need not be repeated again.
- Serum chemistry (LDH) during each response assessment by CT scans. However if the lab for Day 1 of the cycle are drawn within the given window as specified for CT scan, it need not be repeated again

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

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

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

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

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

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

10.3.3 Quality of Life Assessments

- EORTC QLQ-C30: Follow the same schedule as described for CT scans in Section 10.3.2.
- EQ-5D: Follow the same schedule as described for CT scans in Section 10.3.2 with the exception that EQ-5D assessments continue beyond disease progression/relapse until the end of follow-up period.

10.3.4 Specific laboratory assessments

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

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- Blood MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation in peripheral blood or other MRD assays at the following time points : 24 weeks (-1 week/+4 weeks), 76 weeks (-1 week/+ 3 weeks), 120 weeks (-1 week/+4 weeks).
- Bone marrow MRD assessment will be a sub-study performed in a subset of patients using PCR detection of the t(14;18) translocation or other MRD assays at the following time points : 24 weeks (-1 week/+4 weeks), 120 weeks (-1 week/+4 weeks) and only for patients with bone marrow involved by lymphoma at screening.
- Serum immunoglobulin levels are measured at the following time points: 24 weeks (-1 week/+4 weeks), 52 weeks (- 1 week/+2 weeks), 76 weeks (- 1 week/+3 weeks), 100 weeks (- 1 week /+3 weeks), 120 weeks (-1 week /+4 weeks).
- Peripheral blood immunophenotyping (Total T cells and B cells, as well as CD4/CD8 and NK cells) are at the following time points: 24 weeks (-1 week/+4 weeks), 76 weeks (-1 week/+3 weeks), 120 weeks (-1 week/+4 weeks).
- Tetanus (T-cell dependent) and pneumococcal (Pure B cell) response specific serum IgG is measured at 24 weeks (-1 week/+ 4 weeks) and 120 weeks (-1 week/+ 4 weeks) after the first dose date in patients with documentation of prior vaccination who consent to this additional assessment.

10.3.5 Assessments for tumor flare

Tumor flare assessments are conducted in Cycle 1: Days 1, 8, and 15, and when clinically indicated thereafter for patients in the experimental arm and suggested for patients in the control arm.

Tumor flare reaction (TFR) is defined in the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3 as a constellation of signs and symptoms of tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances in direct relation to initiation of therapy (National Cancer Institute, 2003).

TFR is an adverse effect of lenalidomide previously reported in patients with CLL (Chanan- Khan, 2008a). TFR has also been reported at a lower rate in clinical studies of lenalidomide in patients with non-Hodgkin lymphoma (NHL) (Witzig, 2009). The characteristic finding of TFR seen in lymphoma patients treated with lenalidomide, is consistent with findings in patients with CLL; a sudden and tender increase in the size of the disease bearing sites, including the lymph nodes, spleen and/or the liver, typically accompanied by pain and sometimes accompanied by low-grade fever and non-pruritic diffuse rash, typically occurring in the first cycle (Chanan-Khan, 2008a; Witzig 2009). The increase in lymphadenopathy may be localized or generalized. The onset of TFR has been as early as within a few hours after the first dose with the vast majority of TFR having occurred within the first 2 weeks. When it occurs, TFR usually occurs within the first cycle of treatment but can recur to a lesser extent if the dose is increased (Celgene Corporation, 2009a). Based on experience in Celgene-sponsored clinical studies, TFR subsides over time and usually resolves in 1-2 weeks with or without intervention (Celgene Corporation, 2009a).

The experience with tumor flare in Celgene-sponsored studies of single agent lenalidomide in NHL is now summarized. Over 300 patients with relapsed or refractory aggressive or indolent non-Hodgkin's lymphoma have received lenalidomide in three Phase 2 clinical studies. Three studies

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(NHL-001, NHL-002, and NHL-003) were phase 2 multicenter, single-arm, open-label studies which evaluated lenalidomide 25 mg/day for 21 days of a 28-day cycle in 43 previously treated patients with indolent non-Hodgkin lymphoma, 49 patients with relapsed/refractory aggressive NHL, and 217 patients with relapsed/refractory aggressive NHL, respectively. These protocols suggested that any patient who experienced TFR during the first 1 to 2 weeks of Cycle 1 may be treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDS). TFR occurred in 4 patients (grade 1 (n=1) and grade 2 (n=3)) in the NHL-001 study, none in the NHL-002 study; and 7 of 217 patients in the NHL-003 study (Grade 1 (n=2), Grade 2 (n=2) and Grade 3 (n=3).

In an investigator initiated study, Ahmadi et al in a single-center, open-label Phase II study evaluated the use of lenalidomide, dexamethasone and rituximab in patients with relapsed or refractory indolent B-cell or MCL resistant to rituximab (Ahmadi et al., 2009). Among 24 patients, Grade 1 TFR occurred in 1 patient with follicular lymphoma.

It is important to note that the increased lymphadenopathy seen in TFR may mimic disease progression (PD). Therefore, careful monitoring and evaluation to differentiate TFR from PD is necessary for addressing treatment of individual patients including making decisions to discontinue treatment (Chanan-Khan et al. 2008b). There are currently no laboratory or radiological tests that distinguish TFR from PD. The distinction may be made on clinical grounds, incorporating observations such as timing of the event relative to the start of lenalidomide, associated physical findings, laboratory findings, and pace of disease before and after institution of lenalidomide treatment. Also, in case of TFR, inflammation and edema may reduce or disappear after short term treatment with NSAID and/or corticosteroids.

Management of TFR is described in Section 9.1.1.

10.3.6 Assessments for tumor lysis

Tumor lysis syndrome assessments are conducted in Cycle 1: Days 1, 8, and 15, and when clinically indicated thereafter for patients in the experimental arm and suggested for patients in the control arm. It is recommended that the patient be monitored for TLS during the first week of cycle 1. Also, the site should make every effort to contact the patient on Day 5 (± 1 day) of the first cycle to inquire about the patient's condition and to make sure that he/she is continuing with TLS prophylaxis measures by keeping hydrated and taking the TLS prophylaxis as instructed. Any patient contact that is made on Day 5 (± 1 day) should be documented in patient's medical record and any AEs that are discovered should be captured on the CRF.

Tumor lysis syndrome (TLS) is a well-known constellation of metabolic abnormalities resulting from spontaneous or treatment-related tumor necrosis or fulminant apoptosis. The metabolic abnormalities include: hyperkalemia, hyperuricemia and hyperphosphatemia with secondary hypocalcaemia with risk of renal failure. TLS has been reported in patients receiving rituximab plus lenalidomide and rituximab plus chemotherapy followed by rituximab.

The presence of known risk factors such as bulky disease, preexisting (moderate) renal insufficiency, high ALC and high uric acid levels (> 8 mg/dL) prior to therapy are known to increase the likelihood of TLS. Early identification of patients at risk and the prevention of TLS development with the initiation of preventive measures, as well as the careful monitoring for early

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signs of laboratory TLS and the prompt initiation of supportive care are critical to prevent potentially life-threatening metabolic derangements (Cairo, 2009).

The experience with tumor lysis syndrome in Celgene-sponsored studies of single agent lenalidomide in NHL is summarized below. Three phase 2 multicenter, single-arm, open-label studies evaluated lenalidomide 25 mg/day for 21 days of a 28-day cycle in 43 previously treated patients with indolent non-Hodgkin lymphoma (NHL-001), 49 patients with relapsed/refractory aggressive NHL (NHL-002), and 217 patients with relapsed/refractory aggressive NHL (NHL-003). All three studies suggested that patients receive tumor lysis prophylaxis (allopurinol or equivalent) and be well hydrated during the first 7 days of lenalidomide administration in the first cycle or as clinically indicated. Grade 1 TLS occurred in 1 of the 309 (0.3%) patients receiving lenalidomide.

In an investigator initiated study, Dutia et al., in a single-center, open-label Phase II study evaluated the use of lenalidomide and rituximab in patients with relapsed or refractory indolent B-cell NHL (Dutia, 2009). 2 of the first 4 patients treated using the lenalidomide dose of 25 mg developed tumor lysis. Thus, the lenalidomide dose was reduced to 20 mg and allopurinol prophylaxis was used in all subsequent patients with no further TLS events recorded. In the current study, it is recommended that patients randomized to the rituximab-lenalidomide receive allopurinol prophylaxis (see Section 9.3.1 for more information).

10.3.7 Assessments for Venous Thromboembolic events (VTE)

VTE including Deep vein thrombosis and pulmonary embolism will be assessed.

Deep vein thrombosis in Multiple Myeloma

In a number of randomized studies lenalidomide has demonstrated a significantly increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma who were treated with REVLIMID® (lenalidomide) combination therapy (Revlimid® Prescribing Information, January 2009). In the pivotal trials for REVLIMID (lenalidomide) in patients with multiple myeloma receiving lenalidomide plus dexamethasone, deep venous thrombosis and pulmonary embolism were reported in 7.8% and 3.2% of patients, respectively compared to 3.2% and 0.9% of patients receiving placebo and dexamethasone. The Eastern Cooperative Oncology Group (ECOG) trial (E4A03) evaluated lenalidomide 25 mg on Days 1-21 plus high-dose dexamethasone 40 mg on Days 1-4, 9-12 and 17-20 of a 28 day cycle (RD) versus lenalidomide plus low-dose dexamethasone 40 mg on Days 1, 8, 15 and 22 (Rd) in patients with newly-diagnosed MM. Overall venous thromboembolism (VTE) including DVT and PE occurred in 25% in the RD arm and 9% in the Rd arm (Rajkumar, 2007). DVT prophylaxis was to be used in both arms. In two Phase III studies (MM-009) and (MM-010) of lenalidomide plus dexamethasone in patients with relapsed or refractory MM, the number of patients experiencing a thrombotic event in the lenalidomide/dexamethasone arm was 12% versus 4% in the dexamethasone alone arm (Revlimid Prescribing Information, January 2009). An analysis of pooled data from the MM-009 and MM-010 studies demonstrated thromboembolic events were significantly higher in patients treated with lenalidomide/dexamethasone in absence of prophylactic use of an anticoagulant (P<0.001) (Dimopoulos et al., 2009) The effect of adding

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erythropoietin to lenalidomide/dexamethasone demonstrated a higher, but not statistically significant rate of thrombosis in the erythropoietin group 18% versus 10% for the lenalidomide/dexamethasone group without the addition of erythropoietin (*P*=0.14) (Weber et al., 2007).

Deep vein thrombosis in Non-Hodgkin's Lymphoma

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

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

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

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

10.3.8 Assessment for Treatment Discontinuation

- Physical examination including vital signs and ECOG PS
- Hematology and serum chemistry laboratory evaluations
- Adverse events including SPM
- Hospitalization
- Concomitant medication
- Study drug return/accountability
- Subsequent anti-lymphoma therapy
- EORTC QLQ-C30 and EQ-5D questionnaires
- Pregnancy Test for FCBP

10.4 Follow-up assessments

Follow-up period will start at the end of treatment (120 weeks) or at treatment discontinuation (if applicable). Adverse events and hospitalization will be recorded up to 28 days after the last dose of study drug (s).

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Patient will be followed every 3 months (± 2 weeks) for the first two years and every 6 months (± 4 weeks) up to end of follow-up period.

For patients who have completed treatment or discontinued treatment due to reasons other than progressive disease or relapse follow-up assessments include:

- Physical examination including ECOG PS
- Hematology laboratory evaluations (RBC count, hemoglobin, hematocrit, WBC count and differential, ANC, and platelet count) every 3 months (± 2 weeks) for the first two years and every 6 months (± 4 weeks)
- LDH will follow the CT scan assessment schedule as described in Section 10.3.2
- CT scans will follow the assessment schedule as described in Section 10.3.2
- Optional Serum immunoglobulin levels every 6 months/24 weeks (± 4 weeks) for 1 year of follow-up will only be performed by selected sites and countries.
- Overall survival
- SPM
- EORTC QLQ-C30 and EQ-5D questionnaires will follow the CT scan assessment schedule as described in Section 10.3.2

For patients who discontinue treatment due to progressive disease or relapse, follow-up assessments include:

- Overall survival,
- Subsequent anti-lymphoma therapy (including the time of and best response to the first anti-lymphoma treatment regimen utilized after discontinuation from the treatment)
- Subsequent anti-lymphoma chemotherapy (including the time of and best response to the first anti-lymphoma chemotherapy utilized after discontinuation from the treatment)
- EQ-5D questionnaire
- SPM and relevant information

10.5 Progression/Relapse

Relapse/progression will be determined as per Cheson1999 criteria (see APPENDIX A). Progressive disease should be based on CT scan.

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

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11 STUDY PROCEDURES

11.1 Informed consent

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

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

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

11.2 Pathological diagnosis

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

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

All the requested tumor paraffin embedded blocks from the formalin fixed sample (that was used for diagnosis), or 10 unstained slides, and bone marrow biopsy (or 5 unstained slides with H&E) will be sent to the LYSA-P, [redacted] France according to the process described in APPENDIX I.

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

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

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

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11.3 CT scan Review

CT scans must be performed according to the quality requirements detailed in the imaging manual. Specifically, all CT scans must be performed using IV contrast, a slice thickness of $\leq$5mm and must include thoracic, abdominal, neck and pelvic anatomical regions.

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

- screening (See Section 10.2.3 for details),
- 12 weeks after the first dose date (-1 week/+2 weeks),
- 24 weeks after the first dose date (-1 week/+ 4 weeks),
- 36 weeks after the first dose date (-1 week/+ 2 weeks),
- 52 weeks after the first dose date (-1 week/+ 2 weeks),
- 76 weeks after the first dose date (-1 week/+ 3 weeks),
- 100 weeks after the first dose date (-1 week/+ 3 weeks),
- 120 weeks after the first dose date (-1 week/+ 4 weeks). Scans at 120 weeks which are not performed as specified or are otherwise unevaluable must be repeated,
- Every 6 months (± 4 weeks) for 2 years and then every year (± 4 weeks) until disease progression or relapse,
- to document progression/relapse.

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

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

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

11.4 PET scan Review

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

- screening
- 24 weeks after the first dose date (-1 week/+ 4 weeks),
- 76 weeks after the first dose date (-1 week/+ 3 weeks),
- 120 weeks after the first dose date (-1 week/+ 4 weeks).

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

- 2 reviewers will analyze the PET scans independently.

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

11.5 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/CRO Medical Monitor, who will then contact you promptly.

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

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12 CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

12.1 Premature withdrawal from trial intervention

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

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

- Death,
- Toxicity (adverse event),
- Disease progression/relapse,
- Concomitant disease,
- Non compliance (including loss of patient to follow-up),
- Voluntary withdrawal,
- Major protocol violation, including initiation of alternate anti-neoplasic therapy.

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

12.2 Withdrawal of Consent

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

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

12.3 Patients Lost to Follow up

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

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13 ADVERSE EVENTS

13.1 Monitoring, Recording and Reporting of Adverse Events

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

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

Signs, symptoms or physical findings indicative of lymphoma or progression of lymphoma should not be reported as an adverse event or serious adverse event. However, if a finding cannot be attributed with certainty to lymphoma or progression of lymphoma, this finding must be reported as an adverse event or serious adverse event, as applicable. For examples, 1) a finding of dyspnea or pleural effusion in a patient experiencing disease progression outside of the mediastinum or lung must be collected as an AE or SAE as applicable while dyspnea or pleural effusion in a patient experiencing disease progression in the mediastinum or lung may be judged to be results of disease progression and therefore not reported as an AE or SAE; 2) a finding of bowel obstruction in a patient experiencing disease progression outside of the bowel must be collected as an AE or SAE as applicable while bowel obstruction in a patient experiencing disease progression in the bowel may be judged to be results of disease progression.

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

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

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13.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

13.2.1 Seriousness

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

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

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

SPM will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the patient is in (see Section 13.5). This includes any SPM, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the ICD up to and including the follow-up period of up to 10 years. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and patient's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X- rays, CT scans, etc.).

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

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.

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- A procedure or hospitalization for progression/relapse investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling).
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to study drug(s), action taken regarding study drug(s), and outcome.

13.2.2 Severity

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

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

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

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

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

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

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

Grade 5 = Death - the event results in death]

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

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based

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on patient/event *outcome* or *action* criteria associated with events that pose a threat to a patient's life or functioning.

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

13.2.3 Causality

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

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

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

13.2.4 Duration

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

13.2.5 Action Taken

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

13.2.6 Outcome

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

13.3 Abnormal laboratory Values

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

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

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The investigator has to notify in the patient's medical file all the abnormal laboratory values considered as clinically significant (write next to each abnormal laboratory value assessed as clinically significant "CS", or precise in the medical report).

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

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

13.4 Pregnancy

The Lenalidomide Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. See APPENDIX H. Refer to approved product/prescribing information for further information on rituximab pregnancy restrictions.

13.4.1 Females of Childbearing Potential

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

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

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

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

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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13.4.2 Male Patients

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The event must also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form.

13.5 Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page of the CRF. Signs, symptoms or physical findings indicative of lymphoma or progression of lymphoma should not be reported as serious adverse event. However, if a finding cannot be attributed with certainty to lymphoma or progression of lymphoma, this finding must be reported as an adverse event or serious adverse event, as applicable. All SAEs must be reported to Celgene Drug Safety (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

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

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

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

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC. (See Section 18.3 for record retention information)

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Safety Queries

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

13.6 Expedited Reporting of Adverse Events

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

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

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

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

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

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 18.3 for record retention information).

13.7 Follow up of Serious Adverse events

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

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14 STATISTICAL CONSIDERATIONS

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

14.1 Overview

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

Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG (Cheson, 1999) criteria. The primary analysis of complete response (CR/CRu) rate at 120 weeks will be accompanied by statistical validation that this endpoint is predictive of PFS, and the study will continue to final PFS analysis.

The evaluation of potential surrogate endpoint to PFS will be detailed in a separate statistical analysis plan. This protocol might be amended according to the surrogacy validation results.

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

14.2 Study Population Definitions

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

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

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

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

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

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

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14.3 Sample Size and Power Considerations

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

The co-primary efficacy endpoints are complete response (CR/CRu) rate at 120 weeks and PFS. To fulfill the primary objective of the study, it must be shown that the experimental arm is superior to the control arm at $\alpha = 0.05$ level based on CR/CRu rate at 120 weeks which could be the basis for an early approval or based on PFS to obtain full approval (Shih, 2003).

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

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

Considering the sample size requirements for both co-primary endpoints, it is planned to enroll a total of approximately 1000 patients into the study. With this sample size, the power to detect the difference of 12% of complete response (CR/CRu) rate between arms will be 98%.

Therefore, for an enrollment rate of 10 patients per month in the first six months, 25 patients per month in the next 11 months, and 30 patients per months thereafter with 6% dropout rate per year, a total of 1000 patients in 1:1 ratio to the two treatment arms (500 in each arm) will be needed, with a 40-month accrual period and up to 10 years follow-up. The analysis of PFS will occur in about 142 months when the required 456 progression/relapse/death events are expected to be observed or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs first.

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

A recent meta- analysis has demonstrated that the CR rate at 30 months is well correlated with PFS. The point estimate and corresponding 95% confidence intervals for the trial-level surrogacy measures R^2_{WLS} and R^2_{Copula} were 0.88 [0.77 to 0.96] and 0.86 [0.72 to 1.00], respectively. The

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relationship between odds ratio of CR rate at 30 months and hazard ratio (HR) of PFS based on weighted least square method is:

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

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

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

14.4 Background and Demographic Characteristics

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

Patient's demographics and baseline characteristics will be summarized for the ITT population. Patient disposition (analysis population allocation, randomized, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment arms. Protocol deviations will be summarized using frequency tabulations.

14.5 Efficacy Analysis

14.5.1 Co-Primary Efficacy Endpoints

Complete Response (CR/CRu) Rate at 120 weeks

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

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

Progression Free Survival (PFS)

PFS is an accepted endpoint of clinical benefit for previously untreated FL patient and was the basis for the recent approval of rituximab maintenance in this population (Salles, 2011). The disease progression status will be assessed by IRC using the IWG (Cheson, 1999) criteria. PFS is defined as the time from randomization into the study to the first observation of documented

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

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

14.5.2 Secondary Efficacy Endpoints

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

- Complete Response (CR) Rate at 120 weeks by IWG 1999
- Event Free Survival (EFS) by IWG 1999
- Time to Next Anti-Lymphoma Treatment (TTNLT)
- Overall Survival (OS)

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

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

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

14.5.3 Exploratory Endpoints

The following exploratory efficacy endpoints will be summarized using appropriate statistical methods.

- CR rate at 120 weeks and PFS by 2007 Revised Response Criteria for Malignant Lymphoma incorporating FDG-PET (Cheson, 2007)
- ORR at 120 weeks by IWG 1999 criteria

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- Time to Treatment Failure (TTF)
  TTF will be measured from the date of randomization to the date of first documented treatment discontinuation for any reason, including disease progression, treatment toxicity, and deaths.
- Time to Next Chemotherapy Treatment (TTNCT)
  TTNCT will be measured from the date of randomization to the date of first documented administration of new chemotherapy or new cytotoxic agent. For any given patient, the TTNCT may be the same as TTNLT. Patients continuing in response or who are lost to follow-up will be censored on their last visit date. Patients who died (due to any cause) before having received a new chemotherapy treatment will be included in the statistical analysis with death being counted as an event.
- Histological transformation rate at first progression.
  Histological transformation rate at first progression is defined by the appearance of diffuse areas of large lymphoma cells within a tumor site. For this purpose, a biopsy or a cytological examination should be obtained at progression, if possible. This material should be available for central pathological review. This analysis will be restricted to patients with a biopsy at first progression.
- Assessment of minimal residual disease
- Assessments of immune competence
- Fcγ receptor polymorphisms
- Predictive biomarkers of response or resistance to therapy
- Health related quality of life as measured by the EORTC QLQ-C30
- EQ-5D standardized measure of health status

14.5.4 Analysis Method

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

For the co-primary endpoint CR/CRu rate at 120 weeks, the number and percent of patients with CR/CRu at 120 weeks will be tabulated by treatment arm. The experimental arm will be declared superior if the two-sided p- value from a chi-square test is ≤ 0.05 in favor of the experimental arm. The primary analysis will be performed using a stratified Cochran-Mantel-Haenszel (CMH) test to adjust for possible confounding effects of the stratification factors: FLIPI score (0-1 vs 2 vs 3-5), Age (>60 vs $\leq$ 60), longest diameter of the largest node (> 6 v $\leq$ 6 cm). The un-stratified test will be a supportive analysis.

For the co-primary endpoint PFS, the Kaplan-Meier estimates of PFS function will be provided. If a patient has a missing or incomplete CT scan, all other available CT scans or MRIs of the patient will still be used for the analysis. The experimental arm will be declared superior if the two-sided p-value from a stratified log-rank test is ≤ 0.05 in favor of the experimental arm. Conventionally, hazard ratio with two-sided 95% confidence interval (CI) will be estimated using the Cox

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proportional hazards model. But the treatment effect will be determined by the p-value, not by this 95% CI. The un-stratified log-rank test will be a supportive analysis. Subgroup analysis for PFS will be performed as appropriate.

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

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

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

Step 3: If the result of TTNLT analysis fails to reach the 2-sided 0.05 significance level, no efficacy claims will be made for the remaining two secondary endpoints. If the p-value from the TTNLT analysis ≤ 0.05, the efficacy claim for TTNLT will be made, and further testing will be performed in the Step 4.

Step 4: If the result of OS analysis fails to reach the 2-sided 0.05 significance level, no efficacy claim will be made for the OS endpoints. If the p-value from the OS analysis ≤ 0.05, the efficacy claim for the OS be made.

14.6 Safety Analysis

Safety analysis will include all patients in the Safety population.

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

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

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

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treatment-related events, and serious adverse events will also be displayed in separate by-patient listings.

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

14.7 Interim Analysis

14.7.1 Interim Analysis for futility

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

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

The intention of these two interim futility analyses is to assess risk-benefit and ensure patient safety. The proposed futility boundaries are non-binding. The results of these two futility analyses will be reviewed by the independent DMC to make recommendation of go/no go.

There is no plan to claim efficacy superiority based on these interim results, therefore, no Type I error rate adjustment is needed.

As similarly defined for the primary efficacy endpoint, any assessments in a time window of 24 weeks ± 4 weeks are qualified as the 6 months assessments. If two or more assessments are performed in this time window, the assessment with the least favorable response will be used.

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

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

Based on the PRIMA study results, the following assumptions are made for simulations:

1. For the first 100 patients in the control arm when their response data at 6 months are observed, their observed CR/CRu rate at 6 months is estimated approximately 58% to 62%, and their observed ORR is approximately 88% to 92%.
2. In the control arm, among the patients who have CR/CRu observed at 6 months there will be a 0.75 probability for them to remain in CR/CRu at 120 weeks, and among the patients who have PR observed at 6 months there will be a 0.50 probability for them to convert to CR/CRu at 120 weeks.

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

The Table 8 below shows the likelihood of achieving a superiority result based on the observed CR/CRu rates at 6 months for the first 200 patients. The futility boundary of the first futility analysis is that if the observed CR/CRu ratio (experimental arm/control arm) at 6 months is 0.80 or lower, the trial should be recommended to stop considering both the efficacy and safety outcome.

Table 8: 1st Futility Analysis Simulation Results

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

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

1. For the first 100 patients in the control arm when their response data at 120 weeks are observed, their observed CR/CRu rate at 120 weeks is estimated approximately 60% to 66%.
2. For the next 400 patients in the control arm whose response data at 120 weeks have not been observed yet at the second futility analysis, the probability that they will have CR/CRu at 120 weeks is estimated to be equal to the observed CR/CRu rate at 120 weeks from the first 100 patient.

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

The Table 9 below shows the likelihood of achieving a superiority result based on the observed CR/CRu rates at 120 weeks for the first 200 patients. The futility boundary of the second futility analysis is that if the observed CR/CRu ratio (experimental arm/control arm) at 120 weeks is 0.98 or lower, the trial should be recommended to stop based on this efficacy and safety outcome.

Table 9: 2nd Futility Analysis Simulation Results

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

14.7.2 Interim Analysis for efficacy

The co-primary endpoint PFS will be analyzed as an interim analysis at the timepoint when the co-primary endpoint CR/CRu rate at 120 weeks is reported, i.e., when all randomized patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment.

In order to control the overall alpha for PFS, an alpha spending function of Gamma Family with parameter -2.5 will be applied. It is estimated that around 228 PFS events (ie, 0.50 information) would occur at the first interim PFS analysis, and 342 PFS events (ie, 0.75 information) are required at the second interim PFS analysis. The final PFS analysis will be performed based on a total of 456 PFS events or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs first. A statistically significant treatment effect on PFS will be reached if the two-sided p-value is ≤ 0.011 at the first interim PFS analysis, or ≤ 0.019 at the second interim PFS analysis, or ≤ 0.039 at the final PFS analysis.

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14.8 Final Analysis

The final analysis will be performed:

- for the co-primary endpoint CR/CRu rate at 120 weeks: when all randomized patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120-week assessment,
- for the co-primary endpoint PFS: when the required 456 progression/relapse/death events have occurred among all randomized patients or, at the latest, when 9.5 years of median follow-up has been reached, whichever occurs first.

The alpha level for the final analysis may be adjusted based on the total number of PFS events if the study is terminated prior to accumulating the originally planned 456 events. The secondary endpoint CR rate at 120 weeks will be analyzed when all randomized patients have their response assessments done at 120 weeks, or have had disease progression or died prior to the 120 week assessment.

In order to control the alpha for the other secondary endpoints EFS, TTNLT and OS, the final analysis of these endpoints will be performed at the time of the final PFS analysis, and only descriptive statistics (Kaplan-Meier estimates, median, etc.) will be reported without formal statistical comparison at the time of the final CR/CRu rate at 120 weeks analysis.

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15 STUDY COMMITTEES

15.1 Independent Data Safety Monitoring Committee (DSMC)

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

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

15.2 Independent Review Committee (IRC)

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

Bone marrow re-examinations will be conducted at the clinical sites.

Patients with negative bone marrow at screening require no further bone marrow biopsy. Patients with positive bone marrow at screening must have a post-screening bone marrow biopsy to confirm CR/CRu within 28 days of first achieving radiological, clinical and biochemical CR/CRu. Post-screening bone marrow biopsies taken when the patient is not in CR/CRu that are negative also require no further bone marrow biopsy. At 120 weeks, patients with a positive bone marrow at screening who are in radiological, clinical and biochemical CR/CRu and who have not had a negative post-screening bone marrow biopsy must have a repeat bone marrow biopsy at this time to confirm CR/Cru.

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16 STUDY MONITORING

16.1 Investigators Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. The sponsor staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all patients who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to patient records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

16.2 Sponsor Responsibilities

The sponsor or an authorized representative of this study has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, study adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the project leader and of his clinical research support team is to help the investigator maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, by a representative of the monitoring team to review study progress, investigator and patient adherence to study requirements and any emergent problems.

During monitoring visits, the following points will be scrutinized with the investigator: patient informed consent, inclusion and exclusion criteria, patient recruitment and follow-up, patient compliance to the study treatment, study treatment accountability (if applicable), concomitant therapy use, evaluations of response, serious/non serious adverse event documentation and reporting, and quality of data. Sections of Case Report Forms may be collected on a visit per visit basis.

16.3 Source Document Requirements

The sponsor ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the Investigator and the staff. Prior to enrolling patients into the study, a sponsor's representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by

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mail, email, fax, or telephone. At each monitoring visit, the facilities, investigational product storage area, CRFs, patient's source documents, and all other study documentation will be inspected / reviewed by the sponsor's representative for accuracy, adherence to the protocol and Good Clinical Practice.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.4 Case Report Form (CRF)

A Case report form will be completed for each study patient. It is the responsibility of the investigator(s) to ensure the accuracy, completeness, legibility and timeliness of the data reported in the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events and patient status.

The investigator, or designated representative, should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The investigator, or designated representative, should complete the CRF using a black ball point pen. Erroneous values and/ or text must not be obliterated. Instead the error must be crossed out with a single line, the correct value/ text added, and the correction signed, initialized and dated by the investigator(s).

16.5 Study Drug Monitoring

Accountability for the study drug at the clinical site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual.

Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, or disposal of the drug will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol. The sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

All unused study drug will be retained at the site until they are inventoried by the monitor. All used, unused or expired study drug and all material containing Lenalidomide will be treated and disposed of as hazardous waste in accordance with governing regulations.

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17 ETHICAL AND REGULATORY STANDARDS

17.1 Laws and regulations

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the sponsor, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

17.2 Informed consent

The Investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study patient's entry into the study and of the informed consent process should be recorded in the study patient's source documents including the date. The original informed consent document signed and dated by the study patient and by the person consenting the study patient prior to the study patient's entry into the study, must be maintained in the Investigator's study files and a copy given to the study patient. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study patients participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study patient and by the person consenting the study patient must be maintained in the Investigator's study files and a copy given to the study patient.

17.3 Ethics Review Committee and competent authorities submission

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by the sponsor or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by the sponsor or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed

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by a committee member. Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit patients for the study must be reviewed by the sponsor and the IRB/EC prior to use.

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to patients.

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18 ADMINISTRATIVE PROCEDURES

18.1 Secrecy agreement

The sponsor affirms the patient's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). The sponsor requires the Investigator to permit the sponsor's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the patient's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this study, the patient case report forms are the exclusive property of the Sponsor.

They may not be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of the Sponsor.

It is specified that the submission of this study and other necessary documentation to the Ethics Review Committee or a like body is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

18.2 Data Handling

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

Data will be collected via CRF and entered into the clinical database per the sponsor SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

18.3 Record keeping in investigating center(s)

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or

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contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer.

Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all patients;
- Patient identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, the sponsor, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all patients;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (patient records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify the sponsor if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from the sponsor prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

Any center will notify the sponsor before destroying any data or records.

18.4 Ownership of data and use of the study results

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

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18.5 Publication

The results of the trial will be published after complete data collection and evaluation. Publication is to be initiated by the two coordinating investigators in charge of the study with approval of coordinators.

Any publication in the form of a lecture, poster or article must be basically approved by the Scientific Committee.

The authors will be proposed by the coordinating investigator in charge of the study, approved by co-coordinator and finally decided by the Steering Committee.

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

All study data and publications are the property of the Sponsor.

18.6 Company audits and inspections by regulatory agencies

All aspects of the study will be carefully monitored by the sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within the sponsor. Representatives of this unit will conduct audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study patient participation for audits and inspections by IRB/IECs, regulatory authorities (e.g. FDA, EMA, Health Canada) and Pharmaceutical and Medical Device Agency [PMDA]) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact the sponsor immediately.

Sponsor will in all cases help the investigator prepare for an inspection by any regulatory agency.

18.7 Clinical study report

The sponsor will inform of the end of the trial the Competent Authorities and Ethics Committees during the 3 months following the end of the study. A publication, as a study report will be prepared under the responsibility of the sponsor, less than one year after the end of the study and forwarded to the Competent Authorities and Ethics Committees.

18.8 Study amendments

Any amendment to this protocol must be approved by the sponsor's Clinical Research Physician/Medical Monitor.

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Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable.

Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

18.9 Closure of the Study

The sponsor reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc...).

In addition, the Investigator or the sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

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Wu L, Adams M, Carter T, Chen R, Muller G, Stirling D, Schafer P, Bartlett JB. Lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. *Clin Cancer Res*. 2008 Jul 15;14(14):4650-7.

Zhang L, Qian Z, Cai Z, Sun L, Wang H, Bartlett JB, et al. Synergistic antitumor effects of lenalidomide and rituximab on mantle cell lymphoma in vitro and in vivo *Am J Hematol* 2009;84(9):553-9.

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20 APPENDICES

APPENDIX A IWG RESPONSE CRITERIA FOR NHL (CHESON, 1999)

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	**Normal**	**Normal**	**Normal**	**Normal**
Cru	**Normal**	**Normal**	**Normal**	**Indeterminate**
	Normal	**Normal**	**>75% decrease**	**Normal or indeterminate**
PR	**Normal**	**Normal**	**Normal**	**Positive**
	Normal	**≥50% decrease**	**≥50% decrease**	**Irrelevant**
	Decrease in liver/spleen	**≥50% decrease**	**≥50% decrease**	**Irrelevant**
SD	**Less than PR but is not PD nor relapsed disease**			
Relapse/PD	**Enlarging liver/spleen; new sites**	**New or increased**	**New or increased**	**Reappearance**

CR = complete remission; CRu = complete remission unconfirmed; PR = partial remission; SD = stable disease; PD = progressive disease

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APPENDIX B IWG RESPONSE CRITERIA FOR NHL (CHESON, 2007) WITH FDG-PET

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variable FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, IHC should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variable FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR = complete remission; FDG = [18F] fluorodeoxyglucose; PET = positron emission tomography; CT = computed tomography; PR = partial remission; SPD = sum of the product of the diameters; SD = stable disease; PD = progressive disease

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APPENDIX C EQ-5D AND EORTC QLQ-C30 HEALTH QUESTIONNAIRES

EuroQol Group. EuroQol - A new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199-208.

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76

EQ-5D

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group, 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and produces a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

EQ-5D essentially consists of 2 pages - the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS) (page 3). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. A total of 243 possible health states are defined in this way. Each state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 11223 indicates no problems with mobility and self care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety or depression. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.

The EQ VAS records the respondent's self-rated health on a vertical, 0-100 visual analogue scale where 100 = "Best imaginable health state" and 0 = "Worst imaginable health state". This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

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Health Questionnaire

(English version for the UK)

(validated for use in Eire)

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By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities***)**

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

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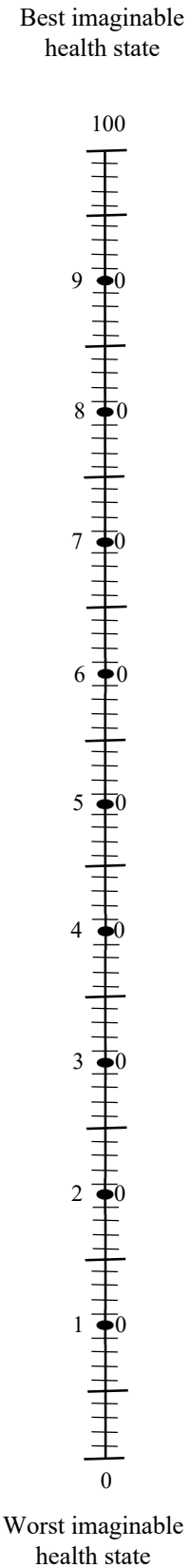
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire will be used as a measure of health-related quality of life. The QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/QOL scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

The QLQ-C30 employs a week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories "Not at all, ""A little," "Quite a bit" and "Very much." The two items assessing global health status/QOL utilize a 7-point scale ranging from 1 (“Very Poor”) to 7 (“Excellent”).

All of the scales and single item measures range in score from 0-100. A high score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QOL represents a high/good QOL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. (Aaronson et al., 1993)

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

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During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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APPENDIX D FLIPI FOR FOLLICULAR LYMPHOMA

FLIPI (Solal-Celigny, 2004)

Score 1 point for each of the following risk factors:

Hemoglobin, g/dL	< 12 g/L
Number of nodal areas	>4

(The spleen is considered as an extranodal site and not a nodal area)

Age, years	> 60
LDH level	> normal
Ann Arbor Stage	III/IV

RISK GROUPS	Number of Factors
Low	0-1
Intermediate	2
High	3-5

FLIPI 2 (Federico, 2009)

Score 1 point for each of the following risk factors:

Beta 2 – microglobulin	>UNL (upper normal limit)
Bone marrow involvement	yes
Hemoglobin, g/dL	< 12 g/L
LoDLIN, cm	> 6

(Longest diameter of largest involved lymph node)

Age, years	> 60

RISK GROUPS	Number of Factors
Low	0
Intermediate	1-2
High	3-5

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APPENDIX E ANN ARBOR STAGING

- **Stage I:**
  - I: Involvement of a single lymph node region
  - IE: Localized involvement of a single extralymphatic organ or site.
- **Stage II:**
  - II: Involvement of 2 or more lymph node regions on the same side of the diaphragm
  - IIE: Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm
- **Stage III:**
  - III: Involvement of lymph node regions on both sides of the diaphragm
  - IIIE: Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site
  - IIIS: Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen
  - IIIS+E: Both IIIS+IIIE
- **Stage IV:**
  - IV: Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non regional) nodal involvement

    IVE: Extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

Source: American Joint Committee on Cancer. Non Hodgkin's lymphoma. In: AJCC Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven;1997:289-294.

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APPENDIX F PERFORMANCE STATUS CRITERIA (OKEN, 1982)

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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APPENDIX G CAIRO - BISHOP DEFINITION OF TUMOR LYSIS SYNDROME

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Uric Acid	≥ 476 µmol/l (≥ 8.0 mg/dl) or 25% increase from baseline
Potassium	≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous	≥1.45 mmol/l (≥ 4.5 mg/dl) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s) (Cairo, 2004).

Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted)
2. Cardiac arrhythmia / sudden death
3. Seizure[a]

ULN = Upper limit of normal.

a Not directly attributable to a therapeutic agent.

Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrythmia	Seizure
0	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death[a]	Death[a]

LTLS = laboratory tumor lysis syndrome; ULN = upper limit of normal; ADL = activities of daily living.

a Probably or definitely attributable to clinical TLS.

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APPENDIX H LENALIDOMIDE PREGNANCY PREVENTION RISK MANAGEMENT PLAN

1 LENALIDOMIDE PREGNANCY PREVENTION PLAN FOR SUBJECTS IN CLINICAL TRIALS

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
   - Potential risks to the fetus associated with lenalidomide exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
   - Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP
2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Lenalidomide Information Sheet (Section 5) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

2 LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1 Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1 Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

2.1.2 Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

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2.2 Counseling

2.2.1 Females of Childbearing Potential

For a FCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4) and in the Informed Consent
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2 Females Not of Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

2.2.3 Males

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

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2.3 Contraception

2.3.1 Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

2.3.2 Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

2.4 Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

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Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

2.5 Pregnancy Precautions for Lenalidomide Use

2.5.1 Before Starting Lenalidomide

2.5.1.1 Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

2.5.1.2 Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

2.5.2 During and After Study Participation

2.5.2.1 Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

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- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

2.5.2.2 Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

2.5.3 Additional Precautions

- Subjects should be instructed to never give lenalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

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3 LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

3.1 Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).

     One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

     – Examples of highly effective methods:
       - ♦ Intrauterine device (IUD)
       - ♦ Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
       - ♦ Tubal ligation
       - ♦ Partner's vasectomy

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- Examples of additional effective methods:
  - ♦ Male condom
  - ♦ Diaphragm
  - ♦ Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.
- If the subject missed a period or has unusual menstrual bleeding.
- When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

3.2 Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:

☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.

☐ The subject has not and will never share lenalidomide with anyone else.

- ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

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4 LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

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Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

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5 LENALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

   If you are a female who is able to become pregnant:

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during breaks (dose interruptions) of lenalidomide
     - for at least 28 days after the last dose of lenalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of lenalidomide
     - 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking lenalidomide if you become pregnant while taking lenalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide**
   - The study doctor will be able to advise you where to get additional advice on contraception.

   If you are a female not able to become pregnant:

   In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

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If you are a male:

A small amount of lenalidomide is found in human semen. The risk to an unborn baby in females whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - During breaks (dose interruptions) of lenalidomide
  - For at least 28 days after the last dose of lenalidomide
- **Male subjects should not donate sperm or semen** while taking lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**
   - **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
   - **Do not break, chew, or open lenalidomide capsules at any point.**
   - You will get no more than a 28-day supply of lenalidomide at one time.
   - Return unused lenalidomide capsules to your study doctor.

   Additional information is provided in the informed consent form and you can ask your study doctor for more information.

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APPENDIX I PATHOLOGICAL SAMPLES AND REVIEW

General principles:

The RELEVANCE study requires a histological review of all patients included in the trial at diagnosis. The aims of the centralized histopathology study will be to **confirm the diagnosis of follicular lymphoma**, according to the criteria of the updated WHO classification 2008 (S. Swerdlow et al.) for each included patient. Histological criteria of inclusion and exclusion have been detailed in the protocol.

The review process will be co-ordinated by [redacted] and will be performed by an international board of expert pathologists including LYSA pathologists as well as any willing pathologist coordinator. Expert pathologists will meet in LYSA-P, [redacted], on a regular basis depending on the number of samples received and analyzed.

Therefore for each randomized patient, tumor tissue blocks and bone marrow biopsy- or only when not possible - unstained slides will have to be sent for analysis and confirmation of diagnosis to LYSA-P, [redacted], France following the process described below. To optimize the number of samples reviewed, it is advised to designate a coordinator pathologist per country who will be in charge of the sample request in his country.

Practical aspects of the LYSA-P review:

1. Information on patient randomization

For France and Belgium, at patient randomization, the investigator will be requested to fax [redacted] or email [redacted] to LYSA-P a copy of the histopathological report where the name and address of the pathologist having diagnosed the lymphoma will be easily identified as well as the bone marrow report when possible. However, in the case where no histopathological report is available, the name and address of the initial pathologist as well as the report number will have to be indicated on the CRF form. This procedure is set up to optimize tracing of the samples.

For other countries, the investigator will be requested to send a copy of the histopathological report (as described above) to the designated pathological coordinator.

2. Sample request

At reception of the pathological report and inclusion form, the LYSA-P or the designated pathological coordinator will contact the initial pathologist and send:

- The Pathology Initial Diagnosis form
- A letter requesting
  - the paraffin block from the formalin fixed sample that was used to set the diagnosis and/ or 10 unstained Superfrost+ slides
  - the paraffin block of the bone marrow biopsy (if available) or 5 unstained sections with the HES slide.
  - the completed Pathology Initial Diagnosis Form filled by the initial pathologist
  - A copy of the initial histopathological report of the diagnosis if in English

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3. Sample centralization at LYSA-P

Depending on the country of inclusion and its regulation, the initial pathologist will return the material and the completed pathology diagnosis form :

- to the designated pathological coordinator of its own country. This way, when sufficient materials are centralized, the pathological coordinator will centralize the tumor tissue material and send the collected material to LYSA-P on a regular basis (6 months depending on the inclusion rate).
- to LYSA-P

LYSA_P–RELEVANCE study,

[redacted]

4. Sample review

At sample reception, routinely stained sections will be performed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a local international pathological review involving the pathological coordinator will be organized at the LYSA-P. All the cases will be reviewed and the consensus diagnosis will be registered in LYSA-P data base and written on the LYSA-Pathology review form. This LYSA-Pathology review form will then be sent to the clinical coordinator and to the pathologist coordinator. The block will be returned to the pathologist with the consensus diagnosis.

5. Sample analysis

Tissue microarray will be performed for each patient and analysis of biological prognostic factors will be performed on each paraffin embedded tissue block received, to assess the expression of markers identified to influence the prognosis of follicular lymphoma. Tissue core will also be taken from the initial tumor block to extract the DNA and study follicular lymphoma prognostic biomarkers.

At the end of the inclusion, frozen tumor tissue will be requested for all French and Belgium randomized patients. The collection of the frozen tumor specimen will be organized and centralized at the LYSA-P. On frozen tissue, gene and protein expression analysis will be performed to assess the level of expression of genes/proteins known to influence the outcome of follicular lymphoma patients.

The LYSA-P Institute will make a commitment to stock the frozen samples in a tumor library or a biological centre insuring the respect of a convention which declines commitments of LYSARC relating to collection, conservation and use of frozen biological samples

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All the samples will be stored in:

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

This protocol amendment 4 is written to reduce the frequency of computed tomography (CT) scans during follow up (FU) visits. This modification in study procedure is implemented to decrease radiation exposure of study subjects. The schedule of CT scans during the FU period has been modified: after 2 years of FU, patients will have yearly scans until disease progression/relapse (previously: follow up is required every 6 months for 5 years, then yearly until progressive disease [PD] or relapse). This change is made in Table 1 Schedule of Study Assessments, Follow-up Period up to 10 Years and in Section 10.3.2 Evaluation of Response.

The schedule of Quality of Life assessment (EORTC QLQ-C30 and EQ-5D) and Lactate Dehydrogenase (LDH) have been changed following the new CT scan assessment schedule in Table 1.

Updated Progression Free Survival (PFS) analysis details were added in Statistical Analysis section of the Synopsis and in section 14.7.2 Interim Analysis for Efficacy to be aligned with the final Statistical Analysis Plan (SAP).

This amendment also includes a few administrative updates including study contact information update and spelling corrections.

Approved v1.0
EDMS Doc. Number: 23583420 - 17383993

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Re-insertion of Sections 13.4.1 and 13.4.2

  In drafting Amendment #2, Sections 13.4.1 and 13.4.2 from Amendment #1 were inadvertently removed. They are added back into Amendment #3.

- Added language to refer to the product/prescribing information regarding rituximab pregnancy restrictions

This language was added to alert investigators to refer to the current prescribing information for rituximab pregnancy restrictions.

This change is made in Section 13.4.

The amendment also includes a few minor clarifications and corrections.

Approved v5.0
EDMS Doc. Number: 20932387 - 17383993

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Change the timing of CR/CRu at 120 weeks from N = 644 to all randomized subjects.

Complete Response (CR/CRu) rate at 120 weeks from randomization and PFS are the co-primary endpoints. Both will be assessed by IRC according to IWG (Cheson, 1999) criteria. In the current protocol, the analysis of CR/CRu rate at 120 weeks will be based on the first 644 subjects randomized. It is important and logical to utilize full information on all patients randomized. This will also mean that at the time of analysis of the coprimary endpoint, all patients will have completed treatment which means that the study integrity will not be compromised if the results are released. This also provides increased power for various proposed subgroup analyses with more subjects in each subgroup. After consultation with the study scientific committee, it was recommended to amend the study protocol to conduct the primary analysis of CR/CRu rate at 120 weeks based on all randomized subjects.

This change is made in the following Sections:
Statistical Analysis Sample Size
Synopsis Interim analysis for efficacy
Synopsis final analysis
Section 14.3
Section 14.72
Section 14.8
Table 9

- Add an interim analysis for PFS

The co-primary endpoint PFS will be also analyzed as an interim analysis when the primary analysis of CR/CRu rate at 120 weeks based on all randomized subjects is performed. In order to control the overall alpha for PFS, an alpha-spending function of Gamma Family with parameter -2.5 will be applied. It is estimated that around 270 PFS events (or 0.60 information) would occur at the interim PFS analysis. A statistically significant treatment effect on PFS will be reached if the two-sided p-value ≤ 0.016 at the interim PFS analysis, and ≤ 0.043 at the final PFS analysis. If the actual number of PFS events greatly deviates from 270 at the time of the interim PFS analysis, the interim alpha spending will be adjusted accordingly using the same alpha spending function based on the actual number of PFS events and information level.

This change is made in the following Sections:
Synopsis Interim analysis for efficacy
Section 14.7.2

- Add CR at 120 weeks as the first secondary endpoint.

CR rate as a component of CR/CRu is of particular scientific and clinical importance (for example, a recently completed meta-analysis indicate an improvement in CR rate at 30 months predicts PFS very well (Sargent, DJ, et.al., J Clin Oncol 33, 2015 (suppl; abstr 8504)). Therefore, CR rate at 120 weeks is being upgraded as the first secondary efficacy endpoint. This

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change also allows adequate power for testing the CR rate at 120 weeks. In order to control an overall two-sided 0.05 study-wise type I error rate due to multiple testing, a sequential gate keeping approach will be used, that is testing on CR rate at 120 weeks will be conducted only if superiority of CR/CRu at 120 weeks is demonstrated.

This change is made in the following Sections:

Synopsis Study Objectives
Synopsis Analysis Plan
Synopsis Final analysis
Section 5.2
Section 14.3
Section 14.5.2
Section 14.5.4
Section 14.8

The amendment also includes several other minor clarifications and corrections, including

- Change in Medical Monitor
- Change in Lead Study Manager
- Clarification in Table 1
- Clarification of necessity and timing of post screening bone marrow biopsies
- Specified actual body weight should be used in creatinine clearance calculation
- Clarification on the use of steroids needed for the well being of the patient
- Ibuprofen was cited as an alternative to acetaminophen for rituximab premedication
- Provide guidance to investigators that abnormal lab values considered clinically significant must be notated as such.
- Clarification that bone marrow reexamination will be conducted at the clinical sites.

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. The secondary efficacy objectives in the protocol are updated to allow adjustment for multiplicity. The number of secondary efficacy endpoints is reduced to three: EFS, TTNLT, and OS. The other secondary objectives (TTF, TTNCT, ORR and health related quality of life questionnaire EORTC QLQ C30) are moved to the exploratory endpoints.

   Justification: The secondary endpoints are revised in accordance with [redacted] regarding multiplicity. In addition, TTF is not an efficacy endpoints clearly stated in the [redacted]; TTNCT is very similar to TTNLT and it will not add value but consume alpha; Similarly, ORR is also moved to exploratory since CR rate is being assessed as co-primary endpoint.

2. The overall survival (OS) will be calculated from the time of randomization.

   Justification: [redacted] the statistical plan was updated for calculation of OS from the time of randomization.

3. Lenalidomide dose adaptation rules are amended. In addition, dose adaption for thyroid stimulating hormone (TSH) abnormality and guidance on management of rash have been added.

   Justification: To improve patient compliance with dosing and study visit schedule, mid-cycle dose reductions are not allowed. During a cycle, only dose interruption and restart at the same dose level are allowed depending upon when the AE occurred and at the discretion of the treating physician. Based upon the two coordinating investigators recommendation dose adaptation for TSH and guidance on management of rash have been added.

4. The PK substudy is removed from the protocol.

   Justification: The sparse PK is removed from the study for the following reasons:

   a. A preliminary analysis with PK data from multiple disease indications indicate that type of cancer does not affect PK of lenalidomide.

   b. Drug-drug interactions between lenalidomide and rituximab is not anticipated, as they do not share the same clearance pathway.

   c. Sparse PK data without intensive PK data are difficult to analyze.

   d The drug exposure at one dose level of lenalidomide plus high exposure variability with the sparse PK is not wide enough for a meaningful exposure-response analysis in this study.

   e. An integrated PK/PD report utilizing historical data in MM/MDS and newly collected data in MCL/CLL is planned to be generated. This report will show that PK of lenalidomide is not sensitive to the type of cancer, and thus it may be used to support the future filling for FL.

5. Modified visit schedule to reduce the number of visits in Cycle 1; Day 2 and Day 4 visits have been removed from first cycle of treatment, with a recommended monitoring for TLS during first week of cycle 1 and telephone contact added at Day 5 of the first cycle.

Justification: Tumor lysis syndrome (TLS) is characterized by metabolic abnormalities that can occur during rapid tumor breakdown in response to anti-cancer treatment. TLS is common in patients with NHL or acute leukemia (Howard et al, 2011, NEJM 364: 1844), but it is uncommon among the patients with follicular lymphoma unless the patient has high WBC counts or receives anti-CD20 treatment.

Although rare, TLS has been reported in NHL patients treated with lenalidomide, either as monotherapy or in combination with rituximab. One case of grade 1 TLS was reported in the 309 relapsed/refractory NHL patients receiving lenalidomide monotherapy in three Celgene sponsored phase 2 studies. In a single-center, open-label Phase II investigator study, Dutia et al. (2009), evaluating the use of lenalidomide plus rituximab in patients with relapsed or refractory indolent B-cell NHL, two of the first four patients (with no TLS prophylaxis) receiving lenalidomide dose of 25 mg developed tumor lysis. After initiating TLS prophylaxis with allopurinol, no further TLS events were recorded in 12 additional patients receiving 20 mg lenalidomide dose (Total N=16) (Dutia et al., 2009, ASH abstract #1679).

TLS and tumor flare reaction (TFR) have commonly been observed in patients with CLL, who were treated with lenalidomide. In some CLL patients, tumor flare and tumor lysis have been life-threatening and fatal. Based on early CLL results from CC-5013-CLL-001, frequent monitoring visits were included during the first cycle in protocols evaluating lenalidomide in CLL and lymphoma patients, including the current study. Since then, more experience with lenalidomide in CLL populations has been gained with the current CLL-008 data that support the reduced monitoring visit frequency to ease the burden on subjects without compromising their safety. Celgene reviewed safety data from the first 55 subjects (26 received lenalidomide) enrolled into the CLL-008 study. No clinical TLS was reported. One case of laboratory TLS was reported however it could not be confirmed according to the Cairo-Bishop definition and didn't result in any dose modification.

Results to date, demonstrate that with implementation of TLS prophylaxis, TLS risk (which was the basis for the very frequent visits) could be mitigated.

In the current FL study, the patients randomized to the rituximab-lenalidomide:

- receive allopurinol prophylaxis and are strongly recommended to be well hydrated especially during the first week of lenalidomide administration.
- have 6 visits during the 28 days of Cycle 1 on Days 1, 2, 4, 8, 15, 22 with blood draws on Days 1, 2, 4, 8, 15

The amendment proposes to reduce the cycle 1 monitoring visits from 6 to 4 as follows:

- have 4 visits during the 28 days of Cycle 1 on Day 1, Day 8, Day 15, Day 22 of Cycle 1 with blood draws on Days 1, 8, 15

- Strong recommendation to monitor the patient during the first week of Cycle 1 and telephone contact for Day 5 of the first cycle

The amendment also includes several other clarifications and corrections

1. Change of name and contact info of 2nd /back-up medical monitor and Celgene study manager, new personnel added for biological studies and change name for GELA to LYSA.
2. Clarification of total number of patients enrolled in the US will be up to a maximum of 250 patients
3. Updated the inclusion criterion #3 regarding 'need for treatment' to include the choice of 'LDH >ULN or β2 microglobuline >ULN'
4. Clarified the exception for exclusion criterion #5 regarding patients who are seropositive for HBV, that the patient who are HBsAg negative, anti-HBs positive and/or anti-HBc positive but viral DNA negative are eligible.
5. Updated the definition of high risk patients for VTE prophylaxis to include ' Bulky disease'
6. Clarification of the window (2 weeks) allowed after randomization but prior to start of the treatment
7. Clarification that the first rituximab dose (C1D1) for patients with high leukemic infiltration in rare cases may be given as 2 parts - on day 1 and day 2, respectively upon prior authorization from the medical monitor or coordinating PI.
8. Clarification of the window (6 weeks) allowed for the baseline/screening CT scan prior to the randomization.
9. Updated the windows for the CT scans and FDG-PET assessments during the study to accommodate the 2 week window provided for the treatment start post randomization
10. AE terms in the lenalidomide dose modification rule table updated to be consistent with the CTCAE v 4.0
11. Clarification for consistency that the immunophenotyping, MRD, anti-tetanus, anti pneumococcal tests are optional in the table of assessment and also in section 10.3.5. Clarification of the optional lymphoma cells collection.
12. Clarification of the repeat bone marrow biopsy requirements for patients in the study who have achieved CR at 6 months and 120 weeks.
13. Updated the Response assessment section to include LDH assessment with the caveat that it need not be repeated if the Day 1 blood draw falls within the given windows as specified for the CT scan.
14. Updated the AE section to clarify that signs and symptoms related to PD will not be collected as AE or SAE.
15. Updated the follow-up section to be consistent with the figure and section 6.3 in regards to the assessment for the patients with PD/relapse.
16. For consistency, throughout the protocol 'subject' was replaced with 'patient'.

17. Clarification of the assessments for treatment discontinuations (section 10.3.8) to be consistent with table for schedule of assessments.
18. Clarification of the follow-up assessment based on the patients disease status and also to be consistent with figure 2 and section 6.3.
19. Added name lenalidomide prior to (CC-5013) to the header
20. Updated the window for Day 1 assessments and clarified windows for Day 8 (cycle 1) and Day 15 (Cycles 1 - 6) assessments.
21. Figure 1 updated to include the window for treatment start after randomization and clarification regarding follow-up visits.
22. Clarification regarding capping of vincristine dose in the control arm R-CHOP or R-CVP regimens.
23. Clarification regarding use of growth factors according to ASCO or ESMO guidelines and also the examples of growth factors that may be prescribed for rescue from severe hematologic events.
24. Updated section on drug dispensation and accountability to clarify about study drug receipt and storage, drug dispensing requirement, handling and recording drug administration.
25. Updated Apendix A to include definition of stable disease (SD).
26. Following clarification and correction in Table for schedule of assessments –
    a. Updated windows for Day 1 of each cycle from 3 to 2 days to be consistent with that in section 10.3.1
    b. Added Day 15 hematology assessment for cycles 5 and 6
    c. Added TSH, B symptoms, LDH, and β2 microglobuline assessments to the table
    d. Added window (±1 day) for Day 8 and Day 15 assessments of Cycle 1, window (± 1 day) for Day 15 assessment during cycle 2-6 and window (+/- 4 weeks) to the treatment discontinuation column
    e. Deleted sparse PK assessment
    f. Added footnote for the optional sub studies (immunophenotyping, MRD, anti-tetanus, anti pneumococcal) for clarification
    g. Deleted serum chemistry row and added LDH to the follow-up assessment table
    h. Deleted CT/MRI, FDG-PET scan, PFS/TTF/EFS, Response Assessments, and Bone marrow biopsy for the End of Treatment column as these assessment will be as per protocol specified schedule.
    Justification: CT schedule should be independent of treatment until disease progression and equally applied to both treatment arms. There is no need to do an additional CT if treatment discontinued due to toxicity at some arbitrary time point.