Protocol Title: Maintenance Lenalidomide Therapy after Autologous Stem Cell Transplant in Patients with High Risk Relapsed/Refractory Lymphomas

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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1 Protocol Synopsis

PROTOCOL TITLE: Maintenance Lenalidomide Therapy after Autologous Stem Cell Transplant (ASCT) in Patients with High Risk Relapsed/Refractory Lymphomas	
DATE PROTOCOL FINAL:	September 27, 2016
INDICATION:	Relapsed/refractory lymphomas (diffuse large B-cell, mantle cell, follicular, marginal zone, peripheral T-cell, small lymphocytic with large cell transformation, and Hodgkin lymphomas)
STUDY PHASE:	Phase I/II

BACKGROUND AND RATIONALE:

Lenalidomide (Revlimid®, CC-5013) is an oral immunomodulatory drug which has activity in several hematologic malignancies. Patients with relapsed/refractory lymphomas who failed multiple cytotoxic chemotherapy regimens were found to have encouraging overall response rates (over 30%) and duration of response (over 10 months) when treated with lenalidomide as a single agent.

We have previously reported the outcome of patients with relapsed/refractory lymphomas who continued to have residual hypermetabolic lesions on positron emission tomography (PET) scans after salvage chemotherapy and prior to ASCT (Svoboda et al. 2006, 211-216). We concluded that these patients have an extremely poor chance of durable remission after ASCT and should be considered for novel therapeutic approaches. Using lenalidomide maintenance therapy after ASCT in this setting is a novel concept which might improve the historically poor outcomes in this population.

STUDY OBJECTIVES:

Primary:

Determine the safety of lenalidomide maintenance therapy implemented early after ASCT and the appropriate dose for further studies.

Secondary:

Determine the progression free survival (PFS) and overall survival (OS) after ASCT in this high risk group with relapsed/refractory lymphomas treated with lenalidomide maintenance. We will compare these findings to our historical controls with PET positive disease prior to ASCT.

STUDY DESIGN:

We propose a phase I/II trial of lenalidomide maintenance therapy after ASCT in high risk patients with relapsed/refractory lymphomas. We define this group of patients by the presence of residual hypermetabolic lesion(s) on PET scans (PET positive disease) after salvage chemotherapy and prior to ASCT. This will be a non-randomized, single institution study.

Patients will be identified and undergo screening activity to determine eligibility within 28-100 days after ASCT following positive PET scan. Patients will be registered if determined to be eligible. Eligible patients will proceed with lenalidomide maintenance therapy.

Patients will continue on lenalidomide maintenance for 24 months unless they develop progressive disease or unacceptable toxicity. The initial dose of maintenance therapy will be 10 mg of lenalidomide daily. We plan to adjust the dose according to specific dose modification criteria. To monitor response during lenalidomide maintenance, we will obtain post-ASCT imaging scan prior to starting lenalidomide and then every three months during the first year and every 4 months during the second year.

STUDY ENDPOINTS
Primary:
Dose limiting toxicity (DLT) as assessed by NCI CTCAE version 4.0
Secondary:
Progression free survival
Overall survival

STUDY DURATION: 60 months

DOSING REGIMEN: The initial dose of lenalidomide will be 10 mg daily. We will use a 3+3 design to determine tolerability of this dose in these heavily pretreated patients. We will allow decreasing lenalidomide to 5 mg daily according to specific dose modification criteria. We will stop the study if there are 2 subjects with DLTs at the 5 mg dose level.

TOTAL SAMPLE SIZE: We plan to enroll 24 evaluable patients with relapsed/refractory lymphoma who will initiate lenalidomide maintenance after ASCT during the initial 3 years of the study. It is likely that at least 28 patients may be enrolled to provide 24 evaluable patients.

DRUG SUPPLIES: Celgene Corporation will provide lenalidomide at no charge through the Revlimid REMS® program for study participants.

2 Schedule of Study Assessments

Procedure	Screening	Cycle 1			Cycles 2-24*	Discontinuation From Protocol Therapy	Follow-Up Phase
	On day 28-100 after ASCT at hematological recovery (<28 days before starting maintenance)	**Day 1^**	**Day 15**	**Day 22**	**Day 1**		**Every 3 months[8]**
Informed Consent	X						
Record lymphoma diagnosis, current medications	X						
Record prior anti-cancer therapies	X						
Physical examination, vital signs, weight	X	X[6]	X		X	X	
ECOG performance status	X	X[6]	X		X	X	
Imaging (PET/CT or CT scan)	X				X[4]		
ECG	X						
CBC	X	X[6]	X	X	X	X	
Serum chemistries[1]	X	X[6]	X		X		
Pregnancy testing[2,3]	X	X[6]			X	X	
Register patient into Revlimid REMS® program	X						
Baseline lesion assessment	X						
Prescribe lenalidomide via Revlimid REMS®[7]	X				X		
Response assessment[4]					X[4]	X[4]	
Record adverse events			X		X	X[5]	
Record concomitant therapies/procedures		X			X	X	
Assess drug compliance/patient's study calendar					X	X	
Follow-up anti-cancer treatments							X
Follow-up progression and survival information							X

* Variations of ± 7 days of scheduled visits are permitted; in rare circumstances, the study calendar may be recalculated to accommodate for a change in study visits out of this window (due to transportation issues, weather events, etc.) at the discretion of the treating physician.

^ To be performed within 7 days of day 1 of lenalidomide therapy. If Screening physical examination, vital signs, weight, labs and ECOG performance status were done within 7 days of Day 1, they do not need to be repeated at this timepoint.

An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.

[1] To include Thyroid Stimulating Hormone (TSH) at Screening B, at treatment discontinuation, and whenever clinically indicated. T3 and T4 levels may be assessed as clinically indicated. If HIV and Hepatitis B status are unknown (unlikely since all patients undergoing ASCT are screened), then these tests will be sent at Screening B.

[2] Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

[3] Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide, and at Day 28 post the last dose of lenalidomide. If menstrual cycles are irregular, the pregnancy testing must occur weekly every 14 days throughout the duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

[4] Progression will be determined by the treating physician as based on clinical picture and radiographic findings. The initial imaging will be performed after ASCT, but prior to initiating maintenance lenalidomide therapy. During the maintenance phase, imaging (PET/CT or CT scan) will be performed every 3 months during the first year and every 4 months during the second year of maintenance. Imaging studies after the second year of maintenance will be at discretion of treating physician. During the first cycle of maintenance therapy, there will be two visits with physical exam. Then, participants will be seen on day 1 of each subsequent cycle. It will not be required to document progression by tissue biopsy (it will be at discretion of treating physician).

[5] An additional safety assessment will be done 28 days (+/- 7 days) following the last dose of protocol therapy.

[6] If screening assessments were done within 7 days of Day 1, they do not need to be repeated at Study Day 1.

[7] Lenalidomide must be prescribed through and in compliance with Celgene's Revlimid REMS® program. Prescriptions must be filled within 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the Revlimid REMS® program.

[8] Subjects will be followed every 3 months for the first 3 years after discontinuation of protocol therapy, and then annually thereafter; those patients who did not achieve hematological recovery by Day 100 after ASCT and never started on lenalidomide maintenance will also be followed every 3 months for the first year and then annually for anti-cancer treatment and progression/survival information.

3 Background and Rationale

3.1 Introduction

For majority of lymphoma patients who relapse after complete response or who are primary refractory to initial treatment, a combination of salvage chemotherapy followed by high dose chemotherapy and ASCT is considered the standard of care. Sensitivity to salvage chemotherapy affects the outcome after ASCT (Philip et al. 1987, 1493-1498). Traditionally, the response to salvage chemotherapy prior ASCT was determined by conventional computed tomography (CT) scans using size criteria. In the past several years, it has been shown that functional imaging with PET scans using fluorodeoxyglucose (FDG) provides additional information to anatomic imaging with CTs. Recently, PET scans have been incorporated into the response assessment as published by the Imaging Subcommittee of International Harmonization Project in Lymphoma (Juweid et al. 2007, 571-578). These days, most institutions use 'PET/CT scans' which incorporate functional imaging with PET scan fused with low dose non-contrast enhanced CT scan.

We have previously reported the outcome of patients with relapsed/refractory lymphomas who continued to have residual FDG avid PET ('positive') lesions after salvage chemotherapy and prior to ASCT (Svoboda et al. 2006, 211-216). This group of patients included those who had excellent anatomic response by size criteria, but continued to have persistent hypermetabolic FDG activity within the residual lesions. We found that PET positive patients have an extremely poor chance of durable remission after ASCT. In the PET negative group, the median PFS was 19 months with 54% of patients without progression at 12 months after ASCT. In the PET positive group, the median PFS was 5 months with only 7% of patients without progression at 12 months after ASCT. We concluded that, for patients with PET positive residual disease after salvage chemotherapy and prior to ASCT, novel therapeutic approaches and agents need to be investigated.

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against hematological malignancies. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF (Dredge et al. 2005, 56-63). In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production (Corral et al. 1999, 380-386). Up-regulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity (Schafer et al. 2003, 1222-1232). The increased levels of circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity (Davies et al. 2001, 210-216).

Clinical activity of lenalidomide in various lymphoma subtypes has been documented in several phase II trials (Wiernik et al. 2008, 4952-4957; Witzig et al. 2009, 5404-5409; Habermann et al. 2009, 344-349; Boll et al. 2010, 480-482). In patients with relapsed/refractory mantle cell lymphoma, the overall response rate (ORR) was 53% with PFS at 12 month 40% (Habermann et al. 2009, 344-349). In patients with aggressive lymphoma (mostly diffuse large B-cell subtype), the ORR was 35% with PFS at 12 months about 25% (Wiernik et al. 2008, 4952-4957). There

also have been many case reports of patients who achieved durable complete response to lenalidomide after failing multiple cytotoxic chemotherapy regimens (Musuraca et al. 2010; Ivanov et al. 2010, 1758-1760).

Most clinical studies of lenalidomide in patients with active lymphoma used dose of 25 mg daily on days 1-21 in 28 day cycle which is the dosing recommended for active multiple myeloma. While lenalidomide was well tolerated in the lymphoma studies, the dose of 25 mg is associated with high risk of developing cytopenias including grade 3 neutropenia in 25-40% of patients and thrombocytopenia in 12-20% (Habermann et al. 2009, 344-349; Wiernik et al. 2008, 4952-4957). Our group reported that low dose lenalidomide at 10 mg daily (continuous dosing) in combination with weekly dexamethasone can be effective in patients with active relapsed/refractory low grade and mantle cell lymphomas (Ahmadi et al. 2009, 1700). The continuous dose of 10 mg daily has also been used in treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (Andritsos et al. 2008, 2519-2525).

Lenalidomide has been used as maintenance therapy in multiple myeloma, but there is limited experience with maintenance lenalidomide in lymphoma patients. Two large clinical trials of maintenance lenalidomide in patients with multiple myeloma after ASCT have shown benefit in PFS over observation. These studies used daily dosing of lenalidomide at 10 mg or 15 mg which were well tolerated over long term administration (Attal et al. 2010; McCarthy et al. 2010).

3.1.1 Indications and Usage:

Revlimid® (lenalidomide) is currently indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

3.2 Adverse Events

The most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

3.3 Rationale for Treatment in this Setting

Our previously reported data and similar studies from other institutions indicate that patients with PET positive lesions after salvage chemotherapy and prior ASCT do very poorly (Svoboda et al. 2006, 211-216; Spaepen et al. 2003, 53-59). In our study, patients with residual PET positive lesions before ASCT had median PFS of 5 months with only 7% of patients without progression at 12 months after ASCT. It can be speculated that patients with PET positive lesions prior ASCT harbor chemotherapy resistant lymphoma cells in their tumors. Since the mechanism of action of lenalidomide differs from traditional cytotoxic chemotherapy, the use of this novel agent in this group of patients is an attractive concept. The immunomodulary properties of lenalidomide over the maintenance period of 24 months could improve the overall outcome of patients following ASCT. Since there is a valid concern that lenalidomide could cause severe cytopenias when used early after ASCT, we proposed to administer dose 10 mg of lenalidomide daily with an option of dose modification to 5 mg daily according to previously defined toxicity criteria. The daily maintenance dosing of lenalidomide at 10 mg has been used in patients with multiple myeloma after ASCT and improved PFS in two large randomized trials (Attal et al. 2010; McCarthy et al. 2010).

4 Study Objectives and Endpoints

4.1 Objectives

4.1.1 Primary Objectives

- Determine the safety and dose-limiting toxicity of lenalidomide maintenance therapy implemented early after ASCT and the appropriate dose for further studies.

4.1.2 Secondary Objectives

- Determine the progression free survival and overall survival after ASCT in this high risk group with relapsed/refractory lymphomas treated with lenalidomide maintenance. We will compare these findings to our historical controls with PET positive disease prior to ASCT.

4.2 Endpoints (see Section 10.3 for definitions)

4.2.1 Primary Endpoints

- Dose limiting toxicity (DLT) as assessed by NCI version 4.0

4.2.2 Secondary Endpoints

- Progression free survival (PFS)
- Overall survival (OS)

5 Investigational Plan

5.1 Overall Design

Patients with relapsed/refractory lymphoma will undergo screening after ASCT following positive PET/CT scan. PET/CT scan results will be categorized as negative when no evidence of lymphoma is found by the radiologist at the time of the scan. PET/CT results will be categorized as positive when the intensity of any non-physiological signal is over 2.5 SUV, which is the measurement of FDG uptake often used to differentiate between benign and malignant lesions (Elstrom et al. 2003, 3875-3876; Al-Sugair and Coleman 1998, 303-319). Patients with diffuse bone marrow activity while on growth factors and with mild symmetric supraclavicular adipose tissue activity in the absence of focal lesions will be deemed as negative. All studies will be reviewed by a University of Pennsylvania nuclear medicine radiologist.

Patients with PET positive lesions who are candidates for ASCT as determined by their treating physician will undergo ASCT. The conditioning regimen will be at the discretion of the treating physician. Subsequent screening to determine eligibility will commence 28 to 100 days after ASCT at the time of count recovery defined as ANC $\geq$ 1,000 and platelets $\geq$ 60,000. Those patients who will undergo consolidative radiation after ASCT can proceed with maintenance treatment, but completion of their radiation and hematological recovery must occur by day 100 after ASCT.

To monitor response to lenalidomide, we will obtain post-ASCT imaging with PET/CT or CT scan prior to starting lenalidomide. During the lenalidomide maintenance, imaging (PET/CT or CT scan) will be performed at least every three months during the first year and at least every 4 months during the second year which reflects general frequency of imaging in this setting outside of this trial. Further imaging after 2 years of follow-up will be at discretion of the treating physician.

Patients will continue on lenalidomide for 24 cycles unless they develop progressive disease or unacceptable toxicity. One cycle is defined as 28 day period. We will initiate maintenance therapy with 10 mg of lenalidomide daily. We will dose adjust or hold lenalidomide for hematologic toxicity according to specific dose modification criteria.

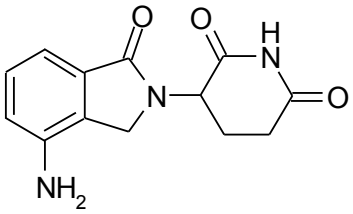
The 3+3 design will be conducted as follows (see details in Section 10.4). The first 3 patients enrolled on our study must each be followed for 28 days on lenalidomide before enrolling the second group of 3 patients. If there is zero or one episode of dose limiting toxicity (DLT) in the initial group of 3 patients, then the group will be expanded to 6 patients at the 10 mg dose. If there are 2 or more DLTs in the initial group of 3 patients, then we will decrease the dose of lenalidomide to 5 mg daily and repeat the 3+3 design. If there is a second DLT in the expanded group of 6 patients at the 10 mg dose, then we will also decrease the dose to 5 mg and repeat the 3+3 design. We will stop the study if there are 2 or more DLTs at the 5 mg dose.

5.1.1 Protocol Therapy

5.1.1.1 Lenalidomide Description

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

5.1.1.2 CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

5.1.1.3 Pharmacokinetics and Drug Metabolism:

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg (Wu A. 2004, 2056). Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters:

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

5.1.1.4 Supplier(s)

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the Revlimid REMS® program.

5.1.1.5 Dosage Form

Lenalidomide will be supplied as capsules for oral administration.

5.1.1.6 Packaging

Lenalidomide will be shipped directly to patients. Bottles will contain a sufficient number of capsules for one cycle of dosing**.**

5.1.1.7 Storage

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

5.1.1.8 Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle**.

5.2 Screening and Eligibility

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

Approximately 60 subjects with relapsed/refractory lymphoma undergoing ASCT in our institution will be screened for enrollment over a 36 month period. We anticipate that at least 28 patients will be categorized as having PET positive disease prior ASCT and be enrolled on study. Twenty four patients will proceed with the maintenance phase involving daily dosing with lenalidomide.

5.2.1 Inclusion Criteria

Subjects must meet the following inclusion/exclusion criteria to be registered to this study.

Inclusion criteria:

1. Able to understand and voluntarily sign the informed consent form.
2. Aged ≥18 years at the time of signing the informed consent form.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Biopsy-proven diagnosis of lymphoma (including diffuse large B-cell, mantle cell, follicular, marginal zone, peripheral T cell, small lymphocytic lymphoma with large cell transformation, and Hodgkin lymphomas).
5. Completion of at least 2 cycles of salvage chemotherapy, with pre-ASCT PET/CT imaging showing PET positive residual lesion(s) (SUV > 2.5).
6. Disease free of other malignancies for ≥ 2 years with exception of basal cell and squamous cell carcinomas of the skin, or carcinoma *in situ* of the cervix or breast.
7. Completion of high-dose chemotherapy with ASCT.
8. Hematologic recovery at 28-100 days after ASCT (defined as ANC ≥ 1,000 and platelet count ≥ 60,000).
9. All study participants must be registered into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of the Revlimid REMS® program
10. ECOG performance status of ≤ 2 at study entry (see Appendix B).
11. Patients undergoing planned consolidative radiation therapy must be finished with the therapy by day 100 after ASCT.
12. Laboratory test results within these ranges:
    - Absolute neutrophil count (ANC) > 1,000/uL
    - Platelet count > 60,000/uL
    - Serum creatinine ≤ 2.0 mg/dL
    - Total bilirubin ≤ 1.5 x ULN. Patients with known Gilbert's disease (as confirmed by study doctor) may participate with elevated bilirubin (serum bilirubin ≤ 2.0 x ULN) as long as their AST and ALT are within normal range.
    - AST (SGOT) and ALT (SGPT) ≤ 3 x ULN.

13. Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

14. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (warfarin or low molecular weight heparin may be used for patients intolerant of aspirin or at the discretion of the treating physician).

5.2.2 Exclusion criteria:

1. A PET/CT or CT scan post-ASCT which shows disease progression.
2. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
3. Pregnant or breast feeding females (lactating females must agree not to breast feed while taking lenalidomide).
4. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
5. Use of any other experimental drug or therapy within 28 days of initiating treatment with lenalidomide.
6. Known hypersensitivity to thalidomide.
7. The development of erythema nodosum, a blistering or desquamating rash, while taking thalidomide or similar drugs.
8. Any prior use of lenalidomide.
9. Concurrent use of other anti-cancer agents or therapies during study treatment.
10. Known seropositive for or active viral infection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV). Patients who are seropositive because of hepatitis B virus vaccine are eligible.

[†] A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

5.3 Visit Schedule and Assessments

5.3.1 Screening/Enrollment - to take place at the time of hematologic recovery, between Days 28-100 post ASCT and within 28 days of initiation of treatment with lenalidomide:

- Review and signing of the Informed Consent Form
- Complete medical history, including prior and current medications, treatments, and anti-cancer therapies.
- Physical Exam and evaluation of ECOG PS
- Vital signs, including blood pressure, heart rate, oral temperature and weight
- Imaging with PET/CT scan or CT scan
- Electrocardiogram
- Serum Chemistry panel including sodium, potassium, chloride, CO2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT and TSH
- For women of childbearing potential, a serum pregnancy test must be performed 10-14 days and then within 24 hours prior to initiating treatment with lenalidomide
- Registration into Revlimid REMS® program

5.3.3 Cycle 1 of lenalidomide therapy

Within 7 days of initiating lenalidomide therapy

- Physical Examination and evaluation of ECOG PS (does not need to be repeated if previously performed within 7 days of starting treatment with lenalidomide)
- Vital signs: blood pressure, heart rate, temperature and weight (does not need to be repeated if previously performed within 7 days of starting treatment with lenalidomide)
- CBC with differential and platelets (does not need to be repeated if previously performed within 7 days of starting treatment with lenalidomide)
- Serum Chemistry panel including sodium, potassium, chloride, CO2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT (does not need to be repeated if previously performed within 7 days of starting treatment with lenalidomide)
- For women of childbearing potential, a serum pregnancy test must be performed 10-14 days and then within 24 hours prior to initiating treatment with lenalidomide

Cycle 1, Day 15 (+/- 3 days)

- Physical Examination and evaluation of ECOG PS
- Vital signs: blood pressure, heart rate, temperature and weight
- CBC with differential and platelets
- Serum Chemistry panel including sodium, potassium, chloride, CO2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT
- Serum pregnancy test (for women with irregular menses)
- Review of interim adverse events and concomitant medications

Cycle 1, Day 22 (+/- 3 days)

- CBC with differential and platelets

5.3.4 Cycles 2-24, Day 1 (+/- 7 days)

- Physical Examination and evaluation of ECOG PS
- Vital signs: blood pressure, heart rate, temperature and weight
- CBC with differential and platelets
- Serum Chemistry panel including sodium, potassium, chloride, CO2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT
- Serum pregnancy test (for women of child-bearing potential)
- Review of interim adverse events and concomitant medications

5.3.5 Radiographic Evaluations

Subjects will undergo radiographic evaluations to assess disease status at the timepoints listed below. Timing of radiographic evaluations may be altered based on clinical indication or the discretion of the treating physician.

- PET/CT after at least 2 cycles of salvage chemotherapy, but prior ASCT (using separate PET scan and dedicated CT scan performed within one week is acceptable)
- Imaging (PET/CT or CT scan) after ASCT, but prior Cycle 1 of lenalidomide therapy
- Imaging (PET/CT or CT scan) every 3 cycles during the first year of lenalidomide maintenance therapy (near end of Cycles 3, 6, 9, 12)
- Imaging (PET/CT or CT scan) every 4 cycles during second year of lenalidomide maintenance therapy (near end of Cycles 16, 20, 24)

5.3.6 Study Discontinuation

The following will be performed at the time of study discontinuation, whether due to study completion or early withdrawal from study participation

- Physical Exam and evaluation of ECOG PS
- Vital signs (Blood pressure, heart rate, temperature, weight)
- CBC with differential and platelets
- Serum chemistry panel including sodium, potassium, chloride, CO2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT and TSH
- Assessment of adverse events and concomitant medications

5.3.7 Safety Assessment (to be performed 28 Days (+/- 7 days) after study discontinuation)

- Assessment of adverse events and concomitant medications

5.3.8 Follow-Up (to be performed every 3 months for the first 3 years after study discontinuation, and then yearly thereafter)

- Review of anti-cancer treatments
- Review of progression and survival information

Assessments to be performed at screening and during scheduled study visits are also outlined in Section 2 Table of Study Assessments.

At treatment discontinuation, subjects will undergo off study evaluations per the Schedule of Assessments, Section 2. In addition, a safety assessment will be done approximately 28 days after the last dose of protocol therapy. Follow-up contact with the subjects should occur at a minimum of 3 months during the first 3 years after finishing maintenance phase and annually after that.

5.4 Drug Administration

5.4.1 Dosing Regimen

Lenalidomide capsule will be given by mouth daily (on days 1-28 of each 28 day cycle). Lenalidomide starting dose will be determined as detailed below.

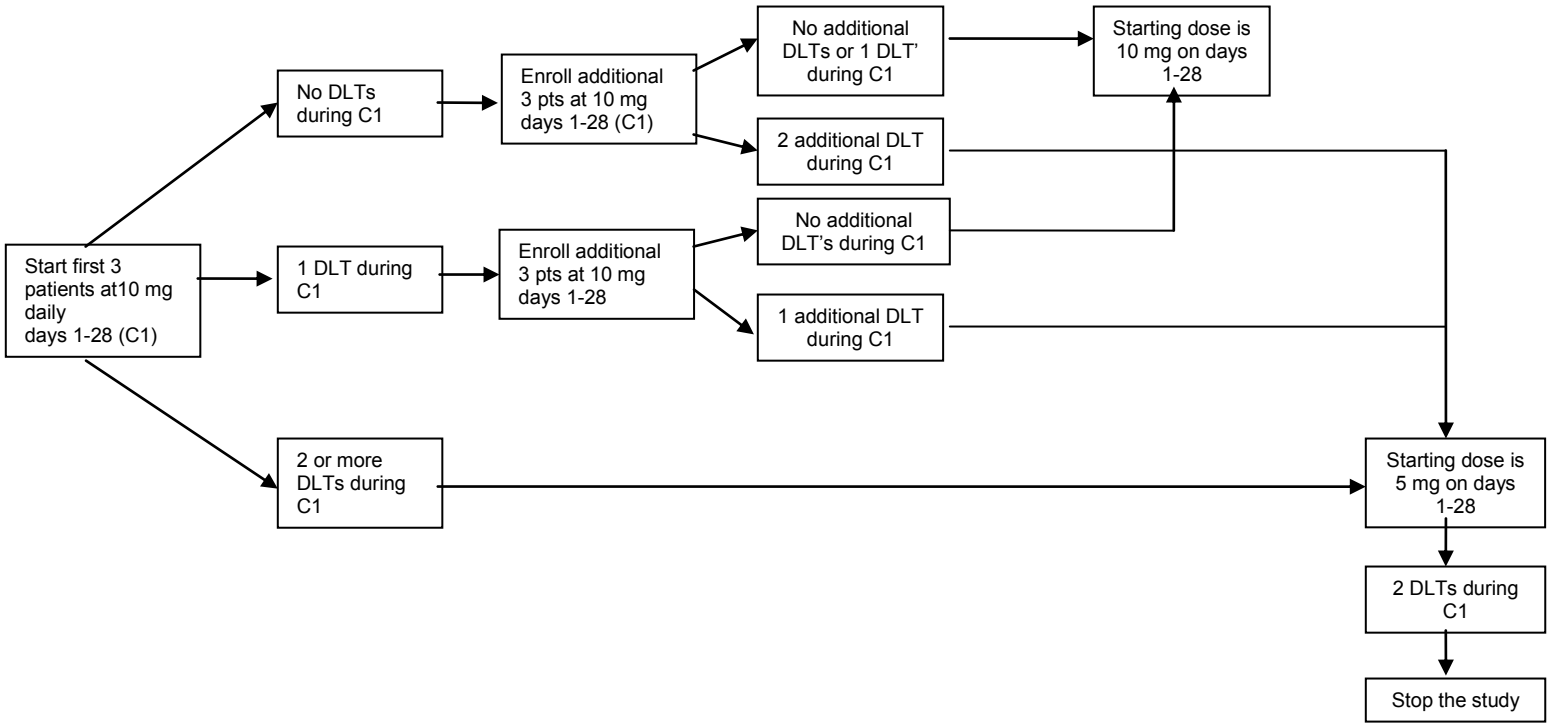
First 3 enrolled patients: The starting dose of lenalidomide for the first 3 subjects enrolled will be 10 mg daily. Three subjects must complete a full 28-day cycle before further study enrollment can proceed. The next cohort of 3 patients must also complete a full 28 day cycle before further enrollment can proceed. The lenalidomide starting dose for the remaining subjects will depend on the observance of dose limiting toxicities in this first cohort of 6 patients.

No DLTs observed: If the first 3 patients complete the first full cycle of study treatment without experiencing a DLT, then 3 additional patients will be enrolled. If 0 or 1 of 6 patients experience DLT, then 10 mg will be considered the appropriate dose and the remainder of enrolled subjects will also use a lenalidomide starting dose of 10 mg daily (on days 1-28 of each 28 day cycle). If 2 patients from the second 3-person cohort experience a DLT during the first cycle of study treatment, then 3 patients will be treated with lenalidomide at a dose of 5 mg daily (days 1-28 of each 28 day cycle). 3+3 assessment will be conducted at 5 mg.

One DLT observed: If 1 out of the first 3 patients experiences a dose limiting toxicity during the first cycle of study treatment, an additional 3 patients will be treated with a starting dose of 10 mg daily and must complete a full cycle of study treatment before study enrollment can resume. If no additional patients experience a DLT after the first cycle of treatment, then 10 mg will be considered the appropriate dose and the remainder of study patients will begin treatment using a lenalidomide dose of 10 mg daily. If 1 patient in the second 3-person cohort experiences a DLT, then 3 patients will be treated with lenalidomide at a dose of 5 mg by mouth daily. The 3+3 assessment will be conducted at 5 mg.

Two DLT's: If 2 patients from the first 3-person cohort experience a DLT during the first cycle of study treatment, then 3 patients will be treated with lenalidomide at a dose of 5 mg daily (days 1-28 of each 28 day cycle). 3+3 assessment will be conducted at 5 mg.

Two DLT's at 5 mg dose level: If the starting dose level is determined to be 5 mg daily and 2 or more patients experience DLT's at this dose level, the study will be stopped.



Dosing will be at approximately the same time each day. Prescriptions must be filled within 7 days.

See section 5.6.1.2 for concomitant anti-coagulation.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Subjects experiencing adverse events may need study treatment modifications (See section 5.5).

5.4.2 Special Handling Instructions

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

5.4.3 Record of Administration

Accurate records will be kept in the source documents of all drug administration (including prescribing and dosing). Subjects should also record lenalidomide dosing on the study calendar during each cycle.

5.5 Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit using the NCI CTCAE v4.0 as a guide for the grading of severity. Sections below describe dose reduction steps, instructions for initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

5.5.1 Dose Reduction Steps

Table 1: Lenalidomide Dose Modification Steps	
Current Lenalidomide Dose	**One Level Dose Reduction**
10 mg daily (on days 1-28 of each 28 day cycle)	5 mg daily (on days 1-28 of each 28 day cycle)*
5 mg daily (on days 1-28 of each 28 day cycle)*	See * below

* Lenalidomide 5 mg daily (on days 1-28 of each 28 day cycle) is the minimum lenalidomide dose. Lenalidomide will be discontinued in patients who cannot tolerate this dose. However, patients who experience toxicity requiring dose reduction while receiving lenalidomide 5 mg daily may, at the discretion of their physician, have their dose held until toxicity resolves as described in Sections 5.5.2 and 5.5.3, and then restart lenalidomide 5 mg daily. If the same toxicity recurs at lenalidomide 5 mg daily, consideration should be given to discontinuing lenalidomide.

5.5.2 Instructions for Initiation of a New Cycle

A new course of treatment may begin on the scheduled day 1 of a new cycle if:

- The ANC is $\geq$ 1,000/uL
- The platelet count is $\geq$ 50,000/uL
- Any drug-related rash or neuropathy that may have occurred has resolved to $\leq$ grade 1 severity.
- Any other drug-related adverse events that may have occurred have resolved to $\leq$ grade 2 severity.

If these conditions are not met on day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above.

5.5.3 Instructions for Dose Modifications or Interruption During a Cycle

Dose delay and dose reduction rules are as follows and in the table below.

- Lenalidomide dose reduction steps are outlined in Section 5.5.1.
- For treatment interruptions during a cycle, the 28-day schedule of each cycle will continue to be followed. Missed doses of lenalidomide are not made up.
- For treatment interruptions that delay the scheduled start of a new cycle, when toxicity has resolved as required to allow the start of a new cycle (Section 5.5.2), the restart day of therapy becomes day 1 of the next cycle.

Table 2: Dose Modifications :	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Grade 3 neutropenia associated with fever (T ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 28 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 28 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 28 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 28 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count is ≥ 50,000/mm³.
Non-blistering rash **Grade 3**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 28 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 28 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Grade 4	• If Grade 4, discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.
Lenalidomide-related neuropathy **Grade 3**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 28 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 28 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Grade 4	• If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate. • Restart lenalidomide at investigator's discretion (maintain dose level). • See Anticoagulation Consideration (Section 5.6.1.2)
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.

Table 2: Dose Modifications :	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Creatinine ≥ Grade 2 (>1.5 - 3.0 x baseline)	• Hold lenalidomide dose until resolved to grade < 2. When re-starting, reduce lenalidomide by 1 dose level. Omitted doses are not made up.
Other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 28 of the current cycle, restart lenalidomide and continue through the scheduled Day 28 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

5.5.4 Treatment Adherence

Study personnel will review the dosing compliance with subjects at each clinic visit, and make record of treatment adherence in the patient's medical record. In addition, study diaries will be provided to subjects at the beginning of each cycle of lenalidomide therapy. Subjects will be asked to record days on which lenalidomide is taken, and return the study diary at the end of each cycle. These diaries will not be mandatory, but will serve as supplemental documentation to dosing information collected during each study visit.

Any unused Revlimid® (lenalidomide) should be returned by the patient for disposition in accordance with the Revlimid REMS® program.

5.6 Concomitant Therapy

5.6.1 Recommended Concomitant Therapy

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, analgesics, and antiemetics when appropriate.

5.6.1.2 Anticoagulation

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased. For information on the risk of venous thromboembolism with combined oral contraception see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Study subjects will use aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate while taking lenalidomide. Low molecular weight heparin may be utilized in patients who are intolerant of aspirin. Coumadin should be used with caution and close monitoring of INR. Patients who are intolerant of anti-coagulants due to

bleeding disorders or for whom anti-coagulation is contraindicated may participate in this study and receive daily dosing with lenalidomide with approval from the principal investigator.

If prophylactic anti-coagulation is used, it should be held for platelet counts < 50,000/uL, and then restarted when platelet counts are at or above this level.

5.6.2 Prohibited Concomitant Therapy

Concomitant use of sargramostim (GM-CSF), anti-cancer therapies, including radiation, thalidomide, or other investigational agents is not permitted while subjects are receiving lenalidomide therapy during the maintenance treatment phase of the study.

5.7 Discontinuation of Study Treatment

Study treatment will continue until the completion of 24 cycles of lenalidomide maintenance therapy, or the occurrence of any of the following events:

- Disease progression (See Appendix D)
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Discontinuation or interruption in lenalidomide therapy for $\geq$ 28 consecutive days.
- Withdrawal of consent
- Lost to follow up
- Death
- Pregnancy or a positive pregnancy test

5.8 Follow-Up

Subjects who discontinue treatment for any reason will be followed for resolution of treatment-related adverse events and survival. At treatment discontinuation, subjects will undergo a safety assessment approximately 28 days post the last dose of protocol therapy. In addition, off study evaluations per the Schedule of Assessments, Section 2, will be performed. Subjects will be followed for additional chemotherapy and progression/survival data every three months for the first three years after study discontinuation, and then yearly until death or withdrawal from study participation.

6 Adverse Events

6.1 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Pregnancy

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

6.2 Adverse Event Reporting

The adverse event recording and reporting period will begin with each subject's first dose of lenalidomide and will end twenty-eight days after each patient's last dose of lenalidomide, or upon resolution of any treatment-related adverse events, should their duration extend beyond the 28-day reporting period. Pre-existing conditions (those events existing prior to each patient's first dose of lenalidomide) will not be reported as adverse events unless they worsen in grade or severity.

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome on the adverse event CRF. Lab abnormalities graded $\leq$ grade 2 in severity will not be reported as adverse events, unless deemed to be clinically significant by the treating physician.

Lymphopenia of any grade will not be considered an adverse event.

6.2.1 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject 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 Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE 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.

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.

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

6.2.2 Celgene Drug Safety Contact Information:

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, N.J. 07922

Fax: **(908) 673-9115**
E-mail: drugsafety@celgene.com

6.3 Investigator Reporting Responsibilities

6.3.1 Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500 form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-NHL-PI-0623) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

6.3.2 Report of Adverse Events to the Institutional Review Board/Data Safety Monitoring Committee

Institutional Review Board:
Serious adverse events which in the opinion of the principal investigator are **both** unexpected **and** related to research procedures should be reported to the IRB within 10 working days of investigator notification. An event is considered "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, applicable package insert information, and/or the current IRB-approved informed consent document. An event is considered "related to the research procedures" if the event is deemed probably or definitely related.

Deaths occurring for patients on-study and within 30 days of study drug administration that are considered unforeseen and indicates participants or others are at increased risk of harm (i.e. unexpected and probably/definitely related), must be reported to the IRB within 24 hours of notification.

In addition, if other information becomes available that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency, this should be reported within 3 days. Examples of this include:

- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
- Safety monitoring indicates that a particular side effect is more sever, or more frequent than initially expected.
- A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Any adverse event that represents a serious, unexpected problem that is rare in absence of drug exposure.
- Withdrawal from marketing for safety of a drug, device, or biologic used in a research protocol.
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Violation, meaning an accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk, or has potential to occur again.
- Breach of confidentiality.

The IRB will accept other reports when the investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold for an unanticipated event presenting risk to the participant.

Office of Regulatory Affairs, Institutional Review Board
3624 Market Street, Suite 301S, Philadelphia, PA 19104-6006
Phone: 215-573-2540
Fax: 215-573-9438

Abramson Cancer Center Data Safety Monitoring Committee (DSMC):

Grade 3 or higher AEs for Penn Subjects, determined to be related to the study drug regardless of expectedness, must be submitted to the Abramson Cancer Center's DSMC within 10 days of notification. Other events should be submitted if they may affect subject safety, if they are determined to be clinically significant, or if a relationship to the study drug cannot be ruled out. All unexpected deaths or deaths related to the study drug should be reported within 24 hours of notification. All other deaths should be reported within 30 days. Onsite SAE reports should be sent to the DSMC for 90 days following the last date the last subject received study drug, and will not be accepted or processed after that time. The AE recording period for this protocol is defined above in Section 6.2.

The following events do not require reporting to the ACC DSMC. The treating investigator must clearly document the relationship of these events.

- Grade 3 or 4 events that are probably or definitely related to the subjects' underlying disease and/or other co-morbidity.
- Grade 3 or 4 events that are probably or definitely related to an FDA approved drug based on the current labeling. However if the toxicity is more severe or is occurring more frequently than the current labeling, the event would be reportable. If the drug is not being used in accordance with the current FDA approval (i.e. dose, disease, route) then standard reporting is required.
- Grade 3 or 4 events that are obviously unrelated to the study drug (i.e. events related to a standard of care test/procedure).

AEs will be submitted to the DSMC through the Velos Clinical Trial Management System.

Medical Monitor:

The medical monitor for this study will be Dr. Amy Clark from the University of Pennsylvania. Dr. Clark is an Assistant Professor in the Department of Hematology-Oncology at Penn, with extensive oncology and research experience. Dr. Clark has served as the Principal Investigator and as a Sub-Investigator on various other Oncology Studies at Penn. Dr. Clark is not directly involved in the trial and is not collaborating with the sponsor-investigator on any other trials.

In the role, Dr. Clark will review all AEs including grading, toxicity assignments, all other safety data and activity data observed in the ongoing clinical trial. This will include a real-time review of safety data in the event of any unexpected/related SAE regardless of grade, and any on-study deaths. The Medical Monitor will also be consulted in the case of exception requests or the evaluation of deviations that may compromise subject safety or disrupt the design of the study. This information will be communicated to the Medical Monitor via email and filed in the Regulatory Binder/Subject Chart appropriately. As applicable, copies of this correspondence will be included in the corresponding IRB/ACC DSMC submission of these events.

The Medical Monitor will also be asked to review study data and comprehensive adverse event data at least bi-annually (every 6 months) or more frequently depending on enrollment. This meeting will take place in person, and all study/safety information will be presented appropriately. This meeting will be clearly documented on a Medical Monitor Review Sheet, signed off on by the Medical Monitor. At any point during the course of the study, the Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial.

6.4 Adverse Event Updates/IND Safety Reports

Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE that is possibly, probably or definitely associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify the University of Pennsylvania IRB promptly of any new serious and unexpected AE(s) or significant risks to subjects that meet the local reporting policy.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB on file (see Section 11.4 for records retention information).

7 Response Assessment

Baseline lesion assessments must occur within ≤ 28 days of protocol therapy initiation or as indicated in Section 2, Schedule of Study Assessments.

Efficacy assessments are scheduled to occur within 28 days prior to starting lenalidomide therapy, every three cycles during the first year, and every four cycles during the second year of study participation. Clinical assessments, including laboratory studies and physical exams, will occur monthly throughout study participation. Follow-up contact with the subjects should occur at a minimum of 3 months during the three years after finishing maintenance phase and annually after that. The frequency of follow-up imaging after completing 24 cycles of lenalidomide maintenance will be at discretion of the treating physician.

8 Protocol Amendments and Deviations

8.1 Protocol Amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Celgene. Amendments should only be submitted to IRB/CTSRMC after consideration of Celgene review. Written verification of IRB/CTSRMC approval will be obtained before any amendment is implemented.

8.2 Protocol Deviations

Reportable Events:
An one-time accidental or unintentional deviation from the approved protocol, identified retrospectively, that in the opinion of the investigator or as defined by the protocol, placed one or more participants at increased risk, compromises the rights or welfare of subjects, and/or disrupts the study design, is considered a reportable event and must be reported to the Study Principal Investigator, Study Medical Monitor, IRB, and ACC DSMC within 10 working days of notification. Principal Investigator and Medical Monitor approval/acknowledgement must be received first and included in with the IRB/DSMC submission.

Deviations to protect subjects from immediate harm/danger should be reported immediately following the event to the entities outlined above.

Exceptions:
An exception is defined as a one-time, unintentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. AND this action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects (i.e. requests to enroll and/or treat subjects outside of the current protocol criteria). Exceptions that meet this criteria will not be allowed unless reviewed and approved first by the Study Medical Monitor and the Study Principal Investigator, and then subsequently by the ACC DSMC, and IRB prior to this subject being enrolled/treated. Principal Investigator and Medical Monitor approval must be received first and included in with the IRB/DSMC submission. All entities should be given sufficient time to evaluate this request.

Examples of Exceptions/Deviations that require submission include:

- Violations of eligibility
- Dose adjustments/stopping rules that were not completed per protocol
- Other dosing errors

Events not deemed reportable as outlined above will require a PI assessment regarding study and/or safety impact.

9 Data Management

9.1 Analyses and Reporting

Data will be initially analyzed and reported on the 24 patients after the period of 12 months from starting lenalidomide maintenance. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

9.2 Data Monitoring Committee

Interim analyses of toxicity are to be performed after the first three patients finish one month of lenalidomide maintenance therapy, and then quarterly thereafter.

This investigator initiated protocol is considered high risk as per the Abramson Cancer Center Data and Safety Monitoring Plan (DSMC). As such, high risk protocols are audited approximately three-six months from their first subject accrual and approximately every six month thereafter for the duration of the study by the ACC Department of Compliance and Monitoring (DOCM). However, this schedule may be changed at the discretion of the DSMC. High or quick enrolling studies may be audited more frequently as necessary.

The PI will be notified in advance of the selection of their protocol for review and cases are randomly selected. Three randomly selected subjects or 10% of the total accrual (up to 10 subjects), whichever is higher, are audited. A formal report is written to the PI within about 5 business days of the audit. The committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies.

Upon review of inspection findings, the Committee designates the audit outcome as Minor, Moderate, or Major deficiencies. The deficiency assigned by the Committee initiates specific follow-up actions.

If an audit is unacceptable due to major deficiencies, representatives from the Department of Monitoring and Compliance (DOCM) meet with the PI to discuss the findings of the audit and review necessary corrective actions mandated by the DSMC. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DSMC Administrative Director will meet to discuss necessary actions concerning study status.

The PI is given five business days to respond to these finding. An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response. At this time, if the DSMC Chair and the Administrative Director do not find the response satisfactory, the IRB and OHR will be alerted of the actions taken by the ACC. The DSMC Director will update the IRB and OHR of the corrective actions being taken and progress being made.

Quarterly team meetings will also be held throughout the course of this study in order to discuss the protocol, ongoing patients, toxicity data, and applicable recruitment issues.

9.3 Study Auditing

9.3.1 Investigator Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

The investigator will permit study-related monitoring, audits, and inspections by the IRB, ACC DOCM, the supporter (Celgene), government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

The Investigator will permit study-related audits by Celgene or its representatives providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Celgene representative so that the accuracy and completeness may be checked.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Statistical Considerations

10.1 Design

This is a single arm phase I/II trial of lenalidomide maintenance for patients with high risk relapsed/refractory lymphomas who underwent high dose chemotherapy and ASCT. At 28-100 days post-ASCT, eligible patients will begin lenalidomide maintenance. The trial will be conducted in two stages. Phase I will evaluate the safety of lenalidomide implemented after ASCT by a 3+3 cohort design. Once the safety of a specific dose after ASCT is established, additional patients will be enrolled in phase II to evaluate the progression-free survival. PFS is a relevant endpoint for lenalidomide maintenance since it is expected to delay progression of disease post-ASCT. A monitoring rule for unacceptable toxicity due to lenalidomide will be followed during phase II.

10.2 Objectives

The primary objective:
-Dose-limiting toxicity due to lenalidomide

The secondary objective is to determine:
-Progression-free survival
-Overall survival

10.3 Endpoints

Dose-limiting toxicity (DLT) is defined as any grade 3 toxicity or higher that occurs during the first 28 days of therapy and is possibly, probably or definitely related to lenalidomide maintenance. Because certain levels of toxicity are considered acceptable in lymphoma therapy, the definition of DLT is limited to the following:

-Any grade 3 or higher non-hematologic toxicity possibly, probably or definitely related to lenalidomide.

-Grade 4 hematologic toxicity not attributable to progressive disease and that does not decrease to a grade 3 or less within 7 days of drug cessation.

-Lymphopenia of any grade and anemia of any grade are not considered a DLT.

-Nausea and vomiting are not considered DLTs unless they cannot be controlled with standard antiemetic therapy.

-Diarrhea is not considered a DLT unless it cannot be controlled with standard anti-diarrheal therapy.

-Nausea, vomiting, heartburn, anorexia, diarrhea, or constipation that improved to grade 1 or better within 2 days with the addition of symptom directed treatment will not be considered a DLT.

NCI Common toxicity criteria (CTC Version 4.0) grades will be employed. Toxicity unrelated to lenalidomide (i.e. clearly related to ASCT) will be scored separately.

Progression-free survival (PFS) is defined from date of ASCT (day 0) to first documented progression of disease, death due to any cause or last patient contact. Progression-free survival rate at 12 months (PFS12) is also of interest and is defined as the percentage of patients that are alive and progression-free at 12 months. Overall survival (OS) is defined as days from date of ASCT to death due to any cause or last patient contact.

Patients are enrolled 28 to 100 days after ASCT (day 0). Patients who complete one full cycle of lenalidomide maintenance or who experience DLT during the first cycle will be considered evaluable for DLT determination. Patients who withdraw from the study prior to initiation of lenalidomide maintenance, or who initiate and discontinue lenalidomide maintenance before completing one full cycle and do not experience DLT, remain in the study population and are followed for PFS and OS but do not contribute to the determination of DLT. These patients will be included in the estimation of PFS and OS, according to an intent-to-treat analysis plan. A secondary analysis of PFS and OS will include only patients who complete at least one full cycle of lenalidomide or who experience DLT at any point during cycle 1 ("evaluable population"). Patients who did not progress will be censored at the time of last contact. Evaluable patients contribute to determination of DLT, PFS and OS. Evaluable patient outcomes will be compared to historical rates for PFS12.

10.4 Phase I Design

A 3+3 design will be employed to determine the tolerability of lenalidomide maintenance at the dose of 10 mg daily in this setting. The dose will not be escalated, but in the event of 2 or more DLTs at 10 mg, the dose will be de-escalated to 5 mg.

Dose Level 1: Three evaluable patients will be treated at 10 mg lenalidomide.

If 2 or more of 3 evaluable patients have DLT, then the dose will be de-escalated to 5 mg.

If 0 or 1 of 3 evaluable patients has DLT, then 3 more evaluable patients will be treated at 10 mg daily.

If 0 or 1 of 6 evaluable patients has DLT, then 10 mg will be declared the appropriate dose for phase II part of the trial. 18 additional evaluable patients will then be enrolled in phase II.

If 2 or more of 6 evaluable patients have DLT, then the dose will be de-escalated to 5 mg daily.

Dose Level -1: Three evaluable patients will be treated at 5 mg lenalidomide.

If 2 or more of 3 evaluable patients have DLT, then the appropriate dose is not defined and the trial will be terminated.

If 0 or 1 of 3 evaluable patients has DLT, then 3 more evaluable patients will be treated at 5 mg daily.

If 0 or 1 of 6 evaluable patients has DLT, then 5 mg will be declared the appropriate dose.

18 additional evaluable patients will then be enrolled in phase II.

If 2 or more of 6 evaluable patients have DLT, then the appropriate dose is not defined and the trial will be terminated.

10.5 Rules for Early Termination for Dose Limiting Toxicity during Phase II

Bayesian probability calculations will be employed to define rules for early termination. The table below indicates termination rules after groups of 6 evaluable patients have been treated. We will assume prior information equivalent to that of 6 treated patients which is commonly required to establish safety in a standard 3+3 phase I design. We will assume a beta(1,5) prior, which is information equivalent to DLT observed in 1 of 6 treated patients. A DLT rate <33% is considered acceptable. If the number of patients with DLT is greater than or equal to the number in the table below then termination will be considered as it is likely that the DLT rate is >33%, as noted by the Bayesian posterior probabilities.

BAYESIAN TERMINATION RULE FOR DOSE LIMITING TOXICITY			
PATIENTS TREATED WITH LENALIDOMIDE	12	18	24
PATIENTS WHO EXPERIENCE DLT	7	9	11
POSTERIOR PROB [DLT RATE >33%]	0.84	0.80	0.78
ACTION	TERMINATE ENROLLMENT		

10.6 Plans for Data Analysis

All observed toxicities will be graded and tabled. The toxicities may be stratified as either related to lenalidomide or other medications (i.e. high dose chemotherapy and ASCT). Progression-free survival and overall survival will be estimated by the method of Kaplan and Meier. A minimum of 12 months of observation time is required on all patients (or less if patient has failed), in order to estimate PFS12. The PFS12 rate and 95% confidence interval will be computed. In addition to the observed rate and 95% CI, evidence for success of lenalidomide will be assumed if >4 of 24 evaluable patients are alive and progression-free at 12 months, based on operating characteristics defined by binomial probabilities. The probability of observing >4 patients alive and progression-free in 24 patients when true rate is 10%, is 0.09 (false positive rate). The probability of observing $\leq$4 patients alive and progression-free when true rate is 30%, is 0.11 (false negative rate).

10.7 Sample Size

Twenty-four evaluable patients will be enrolled. If the rate of enrolled patients who underwent ASCT and do not receive lenalidomide is about 15% then at least 28 patients may need to be enrolled. Regimens of high dose chemotherapy and ASCT for high risk (PET positive) lymphomas have historically produced a PFS12 of <10%. Single agent lenalidomide in relapsed/refractory lymphomas has been shown to produce a PFS12 of approximately 30%. The use of lenalidomide after high dose chemotherapy and ASCT will be considered worthy of further development if the PFS12 is 30% and will be considered not worthy of further development if the PFS12 is 10%. A total of 24 evaluable patients will provide 89% power for an exact test for a single proportion, with null rate of no interest (π_0) of 10%, alternative rate of interest (π_A) of 30%, at one-sided type I error (α) = 10%. A one-sided test is appropriate for early phase trials seeking to detect an improvement over historical rates.

10.8 Study Duration

Assuming that lenalidomide at 10 mg will be feasible and an accrual rate of 8-10 patients per year, accrual will continue for initial 36 months. PFS12 will be evaluated 12 months after end of accrual. Lenalidomide maintenance will continue for up to 24 months after the end accrual. The total duration of the study will be up to 60 months.

11 Regulatory Considerations

11.1 Institutional Review Board/Clinical Trials Scientific Review and Monitoring Committee Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/CTSRMC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/CTSRMC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval and version date.

Any amendments to the protocol after receipt of IRB/CTSRMC approval must be submitted by the Investigator to the IRB/CTSRMC for approval.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/CTSRMC prior to use.

11.2 Informed Consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

11.3 Subject Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit representatives of Celgene Corporation and, when necessary, representatives of the FDA or other 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 subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

11.4 Study Records Requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

11.5 Premature Discontinuation of Study

The Principal Investigator, institution and Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

Appendices

Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. 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. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

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 patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before Starting Lenalidomide

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:
Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During Study Participation and for 28 days Following Lenalidomide Discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests every 28 days throughout the duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly every 14 days throughout the duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions:

- Patients should be instructed never to give lenalidomide to another person.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

Appendix B: ECOG Performance Status Scale

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 house work, 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.

Appendix C: International Workshop Response Criteria (IWRC) for Non-Hodgkin Lymphoma

Complete Response (CR)

Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all-disease related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., lactate dehydrogenase [LDH] definitely assignable to NHL.

All lymph nodes and nodal masses must have regressed to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to < 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan is cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (>20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time.

Complete Response/Unconfirmed (Cru)

CR/unconfirmed (CRu) includes those subjects who fulfill criteria 1 and 3 above, but with one or more of the following features:

A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

Indeterminate bone marrow (increased number or size of aggregates without cytological or architectural atypia).

Partial Response (PR)

>50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should also include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

No increase in the size of the other nodes, liver, or spleen.

Splenic and hepatic nodules must regress by at least 50% in the SPD.

With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.

Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, e.g., large-cell lymphoma or low-grade lymphoma (i.e., small, lymphocytic small cleaved, or mixed small and large cells.)

No new sites of disease.

Stable Disease (SD)

Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed Disease (RD)

Appearance of any new lesion or increase by >50% in the size of previously involved sites (only applies to subjects that achieve a CR).

>50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive Disease (PD)

>50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.
Appearance of any new lesion during or at the end of therapy which is >1.5 cm by radiologic evaluation or greater than 1 cm by physical examination

Bibliography

Ahmadi, Tahamtan, Elise A. Chong, Amanda Gordon, Nicole A. Aqui, Lisa H. Downs, Leah Leinbach, Steven C. Goldstein, et al. 2009. "Phase II Trial of Lenalidomide - Dexamethasone - Rituximab in Relapsed Or Refractory Indolent B-Cell Or Mantle Cell Lymphomas Resistant to Rituximab." *ASH Annual Meeting Abstracts* 114 (22): 1700.

Al-Sugair, A. and R. E. Coleman. 1998. "Applications of PET in Lung Cancer." *Seminars in Nuclear Medicine* 28 (4): 303-319.

Andritsos, L. A., A. J. Johnson, G. Lozanski, W. Blum, C. Kefauver, F. Awan, L. L. Smith, et al. 2008. "Higher Doses of Lenalidomide are Associated with Unacceptable Toxicity Including Life-Threatening Tumor Flare in Patients with Chronic Lymphocytic Leukemia." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 26 (15): 2519-2525.

Attal, M., V. Lauwers, G. Marit, D. Caillot, T. Facon, C. Hulin, P. Moreau, and C. Mathiot. 2010. "Maintenance Treatment with Lenalidomide After Transplantation for MYELOMA : Final Analysis of the IFM 2005-02." *Blood*.

Boll, B., P. Borchmann, M. S. Topp, M. Hanel, K. S. Reiners, A. Engert, and R. Naumann. 2010. "Lenalidomide in Patients with Refractory Or Multiple Relapsed Hodgkin Lymphoma." *British Journal of Haematology* 148 (3): 480-482.

Corral, L. G., P. A. Haslett, G. W. Muller, R. Chen, L. M. Wong, C. J. Ocampo, R. T. Patterson, D. I. Stirling, and G. Kaplan. 1999. "Differential Cytokine Modulation and T Cell Activation by Two Distinct Classes of Thalidomide Analogues that are Potent Inhibitors of TNF-Alpha." *Journal of Immunology (Baltimore, Md.: 1950)* 163 (1): 380-386.

Davies, F. E., N. Raje, T. Hideshima, S. Lentzsch, G. Young, Y. T. Tai, B. Lin, et al. 2001. "Thalidomide and Immunomodulatory Derivatives Augment Natural Killer Cell Cytotoxicity in Multiple Myeloma." *Blood* 98 (1): 210-216.

Dredge, K., R. Horsfall, S. P. Robinson, L. H. Zhang, L. Lu, Y. Tang, M. A. Shirley, et al. 2005. "Orally Administered Lenalidomide (CC-5013) is Anti-Angiogenic in Vivo and Inhibits Endothelial Cell Migration and Akt Phosphorylation in Vitro." *Microvascular Research* 69 (1-2): 56-63.

Elstrom, R., L. Guan, G. Baker, K. Nakhoda, J. A. Vergilio, H. Zhuang, S. Pitsilos, et al. 2003. "Utility of FDG-PET Scanning in Lymphoma by WHO Classification." *Blood* 101 (10): 3875-3876.

Habermann, T. M., I. S. Lossos, G. Justice, J. M. Vose, P. H. Wiernik, K. McBride, K. Wride, et al. 2009. "Lenalidomide Oral Monotherapy Produces a High Response Rate in Patients with Relapsed Or Refractory Mantle Cell Lymphoma." *British Journal of Haematology* 145 (3): 344-349.

Ivanov, V., E. Tabouret, G. Chuto, B. Chetaille, H. Fezoui, D. Coso, J. Rey, et al. 2010. "Rituximab-Lenalidomide-Dexamethasone Induces Complete and Durable Remission in Relapsed Refractory Diffuse Large B-Cell Non-Hodgkin Lymphoma." *Leukemia & Lymphoma* 51 (9): 1758-1760.

Juweid, M. E., S. Stroobants, O. S. Hoekstra, F. M. Mottaghy, M. Dietlein, A. Guermazi, G. A. Wiseman, et al. 2007. "Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 25 (5): 571-578.

McCarthy, P. L., K. Owzar, K. C. Anderson, C. C. Hofmeister, D. D. Hurd, H. :. Giralt Hassoun S., and E. A. Stadtmauer. 2010. "Phase III Intergroup Study of Lenalidomide Versus Placebo Maintenance Therapy Following Single Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Multiple Myeloma: CALGB 100104." *Blood*.

Musuraca, G., P. P. Fattori, M. Ceccolini, D. Cangini, M. B. Giannini, S. Ronconi, F. Matteucci, S. Asioli, and D. Amadori. 2010. "Prolonged (18)FDG-PET Negative Complete Remission in a Heavily Pretreated, Elderly Patient with Diffuse Large B Cell Lymphoma Treated with Lenalidomide, Low Dose Dexamethasone, and Colony Stimulating Factor (Rd-G)." *American Journal of Hematology*.

Philip, T., J. O. Armitage, G. Spitzer, F. Chauvin, S. Jagannath, J. Y. Cahn, P. Colombat, A. H. Goldstone, N. C. Gorin, and M. Flesh. 1987. "High-Dose Therapy and Autologous Bone Marrow Transplantation After Failure of Conventional Chemotherapy in Adults with Intermediate-Grade Or High-Grade Non-Hodgkin's Lymphoma." *The New England Journal of Medicine* 316 (24): 1493-1498.

Schafer, P. H., A. K. Gandhi, M. A. Loveland, R. S. Chen, H. W. Man, P. P. Schnetkamp, G. Wolbring, et al. 2003. "Enhancement of Cytokine Production and AP-1 Transcriptional Activity in T Cells by Thalidomide-Related Immunomodulatory Drugs." *The Journal of Pharmacology and Experimental Therapeutics* 305 (3): 1222-1232.

Spaepen, K., S. Stroobants, P. Dupont, P. Vandenberghe, J. Maertens, G. Bormans, J. Thomas, et al. 2003. "Prognostic Value of Pretransplantation Positron Emission Tomography using Fluorine 18-Fluorodeoxyglucose in Patients with Aggressive Lymphoma Treated with High-Dose Chemotherapy and Stem Cell Transplantation." *Blood* 102 (1): 53-59.

Svoboda, J., C. Andreadis, R. Elstrom, E. A. Chong, L. H. Downs, A. Berkowitz, S. M. Luger, et al. 2006. "Prognostic Value of FDG-PET Scan Imaging in Lymphoma Patients Undergoing Autologous Stem Cell Transplantation." *Bone Marrow Transplantation* 38 (3): 211-216.

Wiernik, P. H., I. S. Lossos, J. M. Tuscano, G. Justice, J. M. Vose, C. E. Cole, W. Lam, et al. 2008. "Lenalidomide Monotherapy in Relapsed Or Refractory Aggressive Non-Hodgkin's Lymphoma." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 26 (30): 4952-4957.

Witzig, T. E., P. H. Wiernik, T. Moore, C. Reeder, C. Cole, G. Justice, H. Kaplan, et al. 2009. "Lenalidomide Oral Monotherapy Produces Durable Responses in Relapsed Or Refractory Indolent Non-Hodgkin's Lymphoma." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 27 (32): 5404-5409.

Wu A., Scheffler M. R. 2004. "Multiple-Dose Pharmacokinetics and Safety of Lenalidomide in 15 Multiple Myeloma Patients." Abstract. *Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition).* 22, no. No 14S (July 15 Supplement): 2056.