Mayo Clinic Cancer Center

Phase I/II Study Of Lenalidomide (Revlimid), Rituximab, Cyclophosphamide, Doxorubicin, Vincristine And Prednisone (R2CHOP) Chemoimmunotherapy In Patients With Newly Diagnosed Diffuse Large Cell And Follicular Grade IIIA/B B Cell Lymphoma

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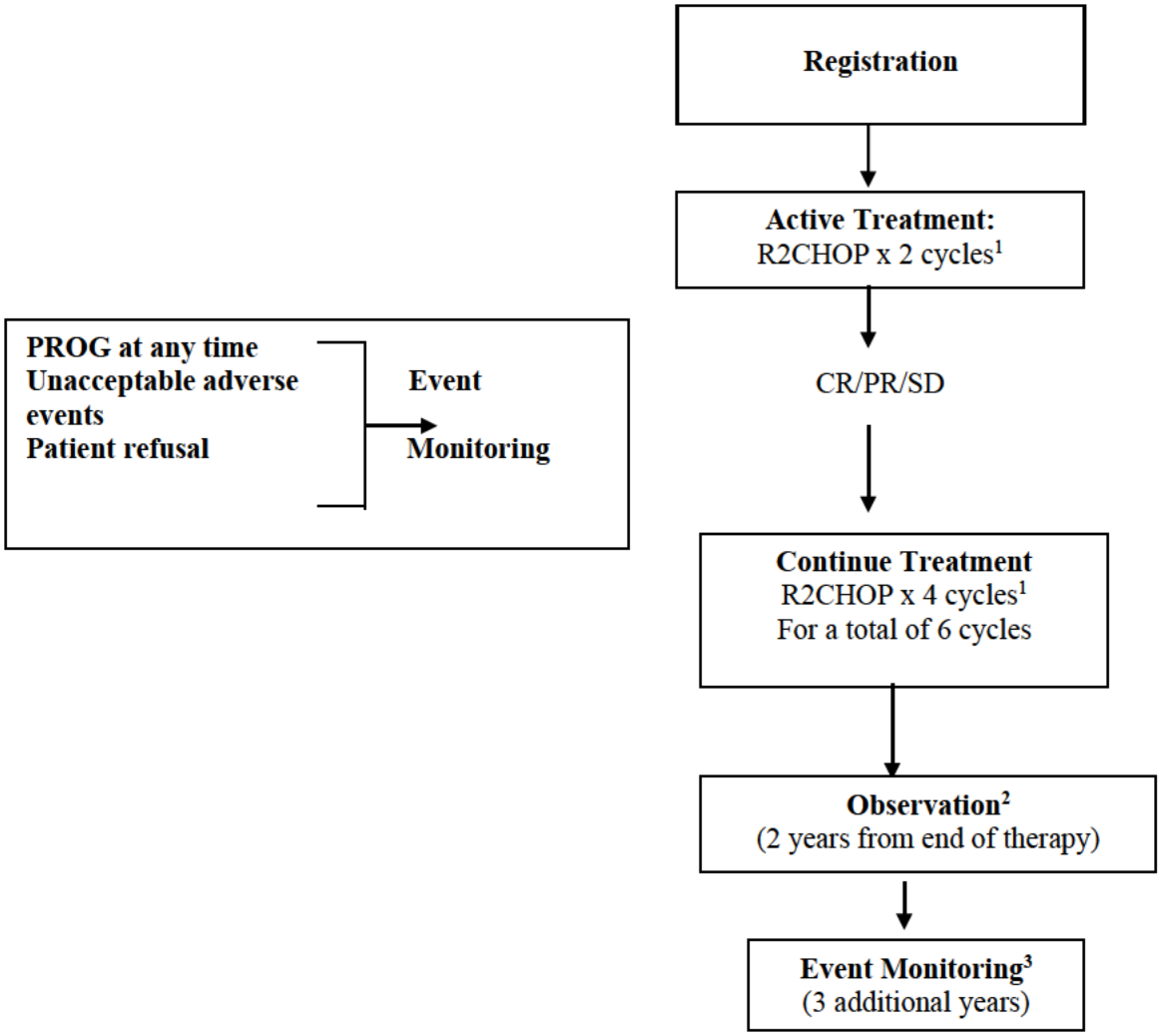
Schema

<u>Phase I only:</u> Prior to checking eligibility, contact the Registration Office ([redacted]) for study status and dose level.



If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

[1] Cycle length = 21 days

[2] Q 3 months for year 1 then Q 4 mos. for year 2. Patients continue in observation to 2 years then go to event monitoring. If patients experience disease progression before the end of the 2 year observation phase, then they will go to event monitoring.

[3] Q6 months until 5 years from registration.

Generic name: Lenalidomide	Generic name: Rituximab

Brand name(s): Revlimid® Mayo abbreviation: CC5013 Availability: Provided by Celgene	Brand name: Rituxan Mayo abbreviation: RITUX Availability: Commercial
Generic name: Cyclophosphamide Brand name: Cytoxan Mayo abbreviation: CTX Availability: Commercial	Generic name: Doxorubicin Brand name: Adriamycin Mayo abbreviation: ADR Availability: Commercial
Generic name: Vincristine Brand name: Mayo abbreviation: VCR Availability: Commercial	Generic name: Prednisone Brand name: Mayo abbreviation: PRED Availability: Commercial

1.0 Background

1.1 Diffuse large cell lymphoma and follicular grade III B cell lymphoma.

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of malignancies of the lymphatic system, with a clinical course ranging from very indolent to highly aggressive(Armitage and Weisenburger 1998). Aggressive NHLs constitute approximately 60% of NHL, with diffuse large B-cell lymphoma (DLCL) being the most common (approximately half of all aggressive NHL cases). Follicular grade III NHL is thought to have similar biology and outcome to DLCL(Rodriguez*, et al* 1999) and traditionally the treatment approach to follicular grade III A and B lymphoma has been the same as to DLCL (Anderson*, et al* 1993, Bierman 2007). The following protocol treatment options will use the term DLCL broadly, with the inclusion of follicular grade III lymphoma unless specified otherwise.

1.2 Current treatment of diffuse large cell lymphoma.

Anthracycline-containing combination chemotherapy remains the standard of care for the initial therapy of patients with advanced DLCL (Cooper*, et al* 1994, Gordon*, et al* 1992); of available combinations, a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is the widely accepted choice due to its efficacy and favorable toxicity profile. Recent studies have shown an improvement in response rate (RR), event free survival (EFS) and overall survival (OS) rates with the addition of rituximab to the CHOP regimen (R-CHOP)(Coiffier*, et al* 2002, Habermann*, et al* 2006, Pfreundschuh*, et al* 2004). The results of representative studies are summarized in Table 1.

Table 1. Results of Phase 3 Studies in First-Line Treatment of Diffuse Large B-Cell Lymphoma

Regiment	N	CR/CRu	OS	EFS/PFS	Reference
CHOP vs. RCHOP[1]	197 202	63% 75%	45% at 5 yrs 58% at 5 yrs	EFS 29% at 5 yrs EFS 47% at 5 yrs	Coiffier et al. 2002, Feugier et al. 2005
CHOP-like vs. RCHOP like[2]	411 413	67% 81%	84% at 3 yrs 93% at 3 yrs	EFS 59% at 3 yrs EFS 79% at 3 yrs	Pfreundschuh et al. 2006
CHOP vs. RCHOP	140 152	NR NR	52% at 2 yrs 78% at 2 yrs	PFS 51% at 2 yrs PFS 69% at 2 yrs	Sehn et al. 2005
CHOP RCHOP[3]	314 318	NR NR	NS[4]	EFS 46% at 3 yrs EFS 56% at 3 yrs	Habermann et al. 2006

1. Patients age 60 yrs and older.
2. Patients age 18-60 yrs.
3. RCHOP plus CHOP with R maintenance.
4. Difference not significant, however, secondary randomization to maintenance was performed.

As evident from the above cited studies, despite the improvements observed with the addition of rituximab, a significant proportion of patients will relapse, especially the elderly, those with bulky disease and high IPI score at diagnosis. Although some of the relapsed patients will be salvaged with second line chemotherapy (usually followed by

high dose chemotherapy with autologous stem cell transplantation for transplant eligible patients), the majority will succumb to the disease (Seyfarth, *et al* 2006, Singer and Goldstone 1986). ***Improvements in initial therapy leading to decreased relapse rates are clearly needed.***

1.3 Lenalidomide in hematological malignancies.

Lenalidomide (REVLIMID, Celgene Corp., NJ, USA) is a proprietary IMiD® compound. The mechanism of action of lenalidomide is complex and involves immune modulation(Haslett, *et al* 2003), antiangiogenetic potential(Zhang, *et al* 2005) and impact on the microenvironment and tumor itself(Pellagatti, *et al* 2007). Lenalidomide is marketed in the United States for the treatment of subjects with transfusion dependent anemia due to low- or intermediate-1 risk myelodysplastic syndrome (MDS) associated with a deletion 5-q cytogenetic abnormality with or without additional cytogenetic abnormalities based on the improvement of anemia(List, *et al* 2005). It is also used in combination with dexamethasone for subjects with previously treated multiple myeloma based on significant antitumor activity(Rajkumar, *et al* 2005, Richardson, *et al* 2002).

Lenalidomide has also shown activity in refractory/relapsed chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) (Chanan-Khan, *et al* 2006). Of forty-five enrolled patients, the majority of which were fludarabine refractory, 47% had evidence of a response, with 9% of the patients attaining complete remission. Fatigue, thrombocytopenia, and neutropenia were the most common adverse effects noted in 83%, 78%, and 78% of the patients respectively. “Flare reaction” – inflamed and often enlarged lymph nodes, was seen in 58% of patients, usually during the first cycle of therapy. The onset was usually seen within 24 hours of the first dose, with a median duration of 14 days. The initial 29 patients did not receive any prophylaxis, and on development of the flare reaction, ibuprofen was used for treatment. However, a few patients required additional oral morphine for pain control. Prednisone prophylaxis was used for the subsequent 16 patients, preventing flare. None of the patients (with or without the prophylaxis) required interruption, discontinuation, or dose reduction of therapy because of flare reaction. It appears that presence of flare reaction correlated with a high NK cell numbers prior to therapy and with clinical benefit (prolonged progression free survival) (Asher Chanan-Khan, personal communication, August 2007).

1.4 Lenalidomide in diffuse large cell lymphoma

The phase II study of lenalidomide (Celgene 002) in patients with relapsed/refractory aggressive non-Hodgkin's lymphoma has been conducted and the initial results reported by Wiernik and Habermann et al document single-agent activity of lenalidomide in relapsed large cell NHL (Wiernik, 2007). Patients received 25 mg of lenalidomide orally once daily on days 1-21 every 28 days and continued therapy for 52 weeks as tolerated or until disease progression. As of enrollment cut-off, 50 patients were enrolled and 49 received the drug. Forty-one patients were evaluable for response. The median age was 65 (46-84) and 18 were female. Histology was DLBCL (n=21), follicular center lymphoma grade 3 [FL] (n=3), mantle cell lymphoma [MCL] (n=14) and transformed [TSF] (n=3). Fourteen patients (34%) exhibited an objective response (5 complete responses unconfirmed (CRu) and 9 partial responses (PR)), 12 had stable disease (SD)

for a tumor control rate (TCR) of 63% and 15 progressive disease (PD). Responses were seen in each of the aggressive histologic subtypes studied: DLBCL (5/21), MCL (6/14), FL (2/3), and TSF (1/3). Progression-free survival (PFS), although ongoing, is currently > 239 (>191 - >373) days in patients experiencing CRu and > 160 (>54 - >251) days in patients with PR. The drug was well-tolerated with the most common Grade 4 adverse events were neutropenia (8.2%) and thrombocytopenia (8.2%), while most common Grade 3 adverse events were neutropenia (22%), leukopenia (14%) and thrombocytopenia (12%). In contrast to CLL, tumor flare reaction was not seen. Preliminary data from the Celgene 003 trial of lenalidomide in relapsed aggressive NHL suggest that the absolute lymphocyte count is a factor in response (Submitted ASH 2007).

The significant activity of single agent lenalidomide in relapsed diffuse large cell lymphoma, the novel mechanism of action with lenalidomide compared with traditional cytotoxic therapy, and the need to further improve the RCHOP regimen provides a strong rationale for bringing lenalidomide to upfront therapy in DLCL.

1.5 Rationale for Expansion Cohort

Gene expression profiling revealed 3 molecular subsets of DLBCL: germinal-center B-cell-like (GCB) vs. activated B-cell-like (ABC) vs. unclassified lymphoma subtype (UCL). The ABC DLBCL constitutes approximately 40% of all DLBCL and is associated with inferior outcome despite introduction of rituximab to therapy. The 2 year progression free survival for ABC DLBCL treated with RCHOP is 40% in contrast to 82% for GCB type (Lenz et al, 2008).

Therefore, there is a critical need to evaluate impact of therapy on outcomes of patients with DLBCL based on molecular subtype. Recent data indicate that there are significant differences in response rates and progression free survival for patients treated with lenalidomide based on molecular DLBCL subtype in a setting of refractory/relapsed disease (Czuczman et al., ASCO Annual Meeting, 2010 Abstract 8038). In this study of 40 patients with relapsed DLBCL, lenalidomide treatment is associated with higher response rates and progression free survival in ABC-like DLBCL versus GCB-like DLBCL (50% vs. 11% and median PFS of 336 vs. 42 days). Importantly, lenalidomide was associated with meaningful clinical benefit in patients with both molecular subtypes of DLBCL. Indeed responding patients with GCB –like subtype enjoyed progression free survival similar to ABC group (median over 200 days). It is unknown if degree of the clinical benefit of lenalidomide in combination with chemotherapy is dependent on molecular DLBCL subtype in patients with newly diagnosed DLBCL. The expansion cohort allows analysis of outcomes of patients treated with R2CHOP based on DLBCL molecular subtype.

2.0 Goals

2.1 Primary goals

2.11 To assess the safety and efficacy of lenalidomide in combination with standard induction therapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone - RCHOP) in patients with newly diagnosed diffuse large cell and follicular grade IIIA/B B-cell lymphoma.

2.12 **Phase I trial:** To establish the maximum tolerated dose of lenalidomide in combination with RCHOP chemotherapy.

2.13 **Phase II trial:** To assess the efficacy (event-free survival and response rate) and safety of this combination.

2.2 Secondary goals

2.21 To assess the host immune function at baseline and after treatment and how these parameters relate to tumor response and event-free survival.

2.22 To assess the efficacy of this combination in DLBCL patients with activated B-cell-like lymphoma.

2.23 To assess the safety and efficacy of R2CHOP in patients with transformed or composite follicular lymphoma.

3.0 Patient Eligibility

Phase I only: Prior to checking eligibility contact the Registration Office [redacted]) for study status and dose level.

3.1 Inclusion Criteria

3.11 ≥18 years of age.

3.12 One of the following untreated, histological confirmed lymphoma expressing CD20 antigen. Criteria for diagnosis can be found in the following reference: J Clin Oncol 17(4):1244-53, 1999:

- DLBCL with disconcordant and/or composite pathology e.g. low grade follicular lymphoma within bone marrow or lymph node are eligible
- DLBCL transformation FL – untreated with anthracyclines or high dose chemotherapy/autologous stem cell transplantation; patients treated with rituximab alone, non-anthracycline containing regiments and previously observed only are eligible

3.13 Stages II, III, or IV (Ann Arbor Staging: see Appendix I).

3.14 Measurable disease (at least 1 lesion of ≥ 1.5 cm in one diameter) as detected by CT or the CT images of the PET/CT (PET/CT fusion). Skins lesions can be used if the area is greater than or equal to 2cm in at least one diameter and

photographed with a ruler.

3.15 ECOG Performance Status (PS) 0, 1, or 2 (see Appendix II).

3.16 The following laboratory values obtained ≤ 14 days prior to registration:

- ANC ≥ 1500
- PLT ≥ 100,000
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) or if total bilirubin is >1.5 x ULN, the direct bilirubin must be normal
- Alk. phosphatase ≤ 3 x ULN unless evidence of the direct liver involvement by lymphoma – then ≤ 5xULN
- AST ≤ 3 x ULN unless evidence of the direct liver involvement by lymphoma – then ≤ 5xULN
- Creatinine ≤ 2 x ULN

3.17 Females of reproductive potential must be willing to adhere to the scheduled pregnancy testing as required in the REVLIMID REMS™ program.

3.18 Willingness to provide informed written consent.

3.19a Willingness to return to enrolling institution for follow-up.

3.19b Patient willing to provide blood samples for research purposes (see Sections 6.2 and 14.0).

3.19c Patients who are not already on anticoagulation should be able to take low-dose aspirin (81 mg) daily. NOTE: If aspirin is contraindicated for other reasons, the patient may be considered for the study after consultation with the study chair regarding other alternatives including the possible use of warfarin or low molecular weight heparin. Patients unable to take any form of prophylaxis are not eligible.

3.19d Willing to be registered into the mandatory REVLIMID REMS™ program, and willing and able to comply with the requirements of the REVLIMID REMS™ program.

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women (lactating females are eligible provided that they agree not to breast feed while taking lenalidomide)
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.22 CNS lymphoma or cerebrospinal fluid involvement with malignant lymphoma cells.

3.23 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.24 Known to be HIV positive or immunocompromised with posttransplant lymphoproliferative disorder (PTLD).

3.25 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.26 Receiving any other agent which would be considered as a treatment for the lymphoma.

3.27 Another active malignancy requiring therapy such as radiation, chemotherapy, or immunotherapy. Exceptions to this are as follows: localized nonmelanotic skin cancer and any cancer that in the judgment of the investigator has been treated with curative intent and will not interfere with the study treatment plan and response assessment. Patients with ≥ 25% of the bone marrow radiated for other diseases are not eligible.

3.28 History of myocardial infarction ≤ 6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.29a Ejection fraction of <45% by either MUGA or ECHO.

3.29b History of life threatening or recurrent thrombosis/embolism. Patients may participate if they are on anticoagulation during the treatment.

3.29c Receiving erythroid stimulating agents (EPO: Procrit, Aranesp).

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase					
		Active treatment			Observation	
	≤ 14 days prior to registration	≤ 2 days (±2 days) prior to subsequent treatment (cycles 2-6)	During interval between cycles	After completion of therapy (4-6 weeks after day 1 of cycle 6)	Every 3 months for year 1	Every 4 months for year 2
History and exam, weight,	X	X		X	X	X
Adverse event assessment	X	X		X	X	X
Height, ECOG PS	X					
Registered in the REVLIMID REMS™ program	X[16]	X[16]	X[16]	X[16]		
Serum or urine pregnancy test[1]	X[1]	X[1]	X[1]	X[1]		
Tumor tissue sample for confirmation of diagnosis	X[2]					
Hematology group CBC (HgB, WBC, Differential, PLT)	X	X	Weekly	X	X	X
Chemistry group Total bilirubin, AST, Alk. Phosphatase, LDH, Creatinine, Sodium, Potassium, Calcium	X	X		X	X	X
Direct bilirubin[4]	X					
Hepatitis B and C screen[3]	X					
HIV screen	X					
Tumor Measurement/Evaluation of indicator lesion (CT chest, abdomen, pelvis; other CT and/or MRI when indicated)[12]	X[14]	Before cycle 3		X	X	X
PET scan	X[17]	Before cycle 3[13]		X[5]		
Bone marrow aspirate and biopsy (unilateral or bilateral)	X[15]			X[6]		

Tests and procedures	Active Monitoring Phase					
		Active treatment			Observation	
	≤ 14 days prior to registration	≤ 2 days prior to subsequent treatment (cycles 2-6)	During interval between cycles	After completion of therapy (4-6 weeks after day 1 of cycle 6)	Every 3 months for year 1	Every 4 months for year 2
Electrocardiogram	X[17]					
Left ventricular function measurement	X[7, 17]					
Cerebrospinal fluid analysis	X[8]					
Research blood samples [R]	X	Before cycle 3[R]		X[R]		
Research tissue samples [R9]	X	X[10,11]				

1. Pregnancy tests for females of childbearing potential. Patient must follow pregnancy testing requirements as outlined in the REVLIMID REMS™ program.
2. Central review of pathology is required for confirmation of diagnosis and CD20 positivity. Completion of central pathology review is not required prior to registration for patients requiring urgent treatment in opinion of investigator (see Section 17.0), however materials for central review must be submitted within 42 days after registration.
3. Hepatitis B surface antigen (HbsAg) and antibody to Hepatitis B core (anti-HBc); Hepatitis C antibody
4. To be done only if the total bilirubin is abnormal.
5. If positive after the completion of cycle 6, a biopsy of PET positive area may be done at MD discretion.
6. Repeat BM only required if initial BM was positive.
7. MUGA or Echo.
8. A lumbar puncture and cytologic examination of the cerebrospinal fluid is not required, but should be performed if clinically indicated.
9. Paraffin blocks of tumor tissue from initial diagnosis will be requested for research, Section 17. Patients undergoing excisional biopsies should have excess tissue frozen as part of Mayo IRB118-01 (SPORE Cell Bank).
10. Prior to cycle 2 a core needle biopsy will be performed for research purposes in consenting patients with easily accessible tumor; the biopsy is not mandatory for study treatment.
11. For patients who have a repeat biopsy for any reason while on study, excess tissue will be submitted for research purposes.
12. Measurements should preferably be done by dedicated CT or MRI; however, they can be done off the CT images of a PET/CT if that demonstrates the lesion more clearly. The image number should be included with the measurements. If patient has had PET/CT that can satisfy the PET and CT requirement. If questions, call the study chair.

13. PET is mandatory pre- and post-treatment. It is optional after 2 cycles; however, if PET/CT being used for the measureable lesion then it will be required before cycle 3.
14. CT must be done ≤ 28 days prior to study registration.
15. Bone marrow must be done ≤ 6 weeks prior to study registration.
16. All unused lenalidomide must be returned as instructed through the REVLIMID REMS™ program.
17. Must be done ≤ 28 days prior to study registration.

R. Research funded study.

5.0 Grouping Factors:

5.1 Phase I vs. Phase II.

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 Phase I Dose Escalation – Prior to discussing protocol entry with the patient, call the Registration Office to insure that a place on the protocol is open to the patient.

6.111 To register a patient, call [redacted]) a completed eligibility checklist to the Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.12 Phase II

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the remote system can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Translational Research

A mandatory translational research component for blood specimens is part of this study; the patient will be automatically registered onto this component (Sections 3.19 and 14.0).

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 17.0).

- Patient has/has not given permission to allow previously collected tumor tissue biopsy to be used for research studies.

6.3 A signed HHS 310 form must be on file in the Registration Office before an investigator may register any patients. Ongoing approval documentation must be submitted (no less than annually) to the Registration Office.

6.4 Prior to the patient being registered, the following will be verified:
- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

At the time of registration/randomization, the following will also be recorded:
- Patient has/has not given permission to store sample(s) for present and future research of lymphoma or other health problems at Mayo and to give his/her sample to other researchers at other institutions for research.
- Patient has/has not given permission to participate in the optional lymphoma research tissue biopsy before treatment, prior to cycle two, and to allow any excess tissue collected while on this study to be used for research studies.

6.5 Treatment on this protocol must commence at a Mayo Clinic Institution under the supervision of a hematologist/oncologist.

6.6 Treatment cannot begin prior to registration and must begin ≤ 7 days after registration.

6.7 Pretreatment tests must be completed within the guidelines specified on the test schedule.

6.8 All required baseline symptoms must be documented and graded.

6.9 Study drug availability checked.

7.0 Protocol Treatment

7.1 Treatment Schedule.

7.11 Pretreatment medications. Standard antiemetic prophylaxis will be given per RCHOP guidelines.

7.12 Phase I Cohort: Lenalidomide RCHOP regimen

Agent	Dose	Route	Day	Cycle Length
Rituximab[1]	375 mg/m2	IV	Day 1	Every 21 days
Cyclophosphamide[2]	750 mg/m2	IV	Day 1	Every 21 days
Doxorubicin[3]	50 mg/m2	IV	Day 1	Every 21 days
Vincristine	1.4 mg/m2 (max 2 mg)	IV	Day 1	Every 21 days
Prednisone[4]	100 mg/m2	po	Day 1-5	Every 21 days
Lenalidomide[5]	As assigned by Randomization Center	po	Day 1-10	Every 21 days
Pegfilgrastim	6 mg	SC	Day 2	Every 21 days

1. Rituximab may be rounded to nearest 50 mg.
2. Cyclophosphamide dose may be rounded to nearest 50 mg
3. Doxorubicin dose may be rounded to nearest 5 mg
4. Prednisone dose rounding to nearest 10 mg
5. See Ancillary Treatment section 9.1 regarding anticoagulation recommendations.

7.13 Phase 2 Cohort: Lenalidomide RCHOP regimen (at MTD from phase I)

Agent	Dose	Route	Day	Cycle Length
Rituximab[1]	375 mg/m2	IV	Day 1	Every 21 days
Cyclophosphamide[2]	750 mg/m2	IV	Day 1	Every 21 days
Doxorubicin[3]	50 mg/m2	IV	Day 1	Every 21 days
Vincristine	1.4 mg/m2 (max 2 mg)	IV	Day 1	Every 21 days
Prednisone[4]	100 mg/m2	po	Day 1-5	Every 21 days
Lenalidomide[5]	25 mg	po	Day 1-10	Every 21 days
Pegfilgrastim	6 mg	SC	Day 2	Every 21 days

1. Rituximab may be rounded to nearest 50 mg.
2. Cyclophosphamide dose may be rounded to nearest 50 mg
3. Doxorubicin dose may be rounded to nearest 5 mg
4. Prednisone dose rounding to nearest 10 mg
5. See Ancillary Treatment section 9.1 regarding anticoagulation recommendations.

7.2 Phase I dose escalation and determination of MTD.

7.21 Dose escalation of lenalidomide

Dose level		Dose	Day	Route
-2	Lenalidomide	5 mg	Day 1-10	orally
-1	Lenalidomide	10 mg	Day 1-10	orally
***1**	Lenalidomide	15 mg	Day 1-10	orally
2	Lenalidomide	20 mg	Day 1-10	orally
3	Lenalidomide	25 mg	Day 1-10	orally

***starting dose level**

7.211 Three patients will be treated at each dose level and observed for a minimum of 3 weeks (1 cycle), to assess toxicities, before new patients are treated. **Doses will not be escalated in any individual patient because of the risk of cumulative toxicity.**

7.212 Investigators are to contact the Study Chair as soon as any dose-limiting toxicity occurs.

7.22 Definitions of Dose Limiting Toxicity (DLT)

7.221 For this protocol, dose-limiting toxicity (DLT) will be defined as follows: an adverse event attributed (definitely, probably or possibly related) to the study treatment and meeting following criteria with the first cycle:

Toxicity	**Definition**
Hematologic	Either: 1. PLT <25,000 for ≥7days **or** platelet nadir <10,000 at anytime 2. Failure to recover counts to PLT ≥ 75,000 and/or ANC ≥1500 by day 28 after initiation of cycle 1 treatment.
Infection	Grade 4
Non-hematologic	Either: 1. ≥ grade 3 as per NCI Common Terminology Criteria for Adverse Events v3.0* 2. Any toxicities that caused dose delay of > 1 week of the intended next dose

*Grade 3 nausea, vomiting, or diarrhea with maximal supportive treatment(s) will be considered dose-limiting. Fatigue and mouth sores that are considered Grade 3 and are considered to be due to treatment (definitely, probably, or possibly related) will be considered as dose-limiting.

7.23 Maximal Tolerated Dose (MTD) Determination

The MTD in this study will be defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients). This will be defined on cycle 1 data; however,

toxicity data will be collected during all cycles and monitored for cumulative toxicity.

7.24 Dose Escalation

7.241 Three patients will be treated at a given dose level combination and observed for at least 3 weeks to assess toxicity.

7.242 If dose-limiting toxicity (DLT) is not seen in any of the 3 patients, up to 3 new patients will be accrued and treated at the next higher dose level (as specified in 7.21). If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

7.243 If a DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded, and further accrual will cease to this cohort. If potentially dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

7.245 If DLT is observed in at least 2 of 6 patients after enrolling 6 patients on a specific dose level, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

7.25 Dose De-escalation from Dose Level 1

7.251 If 2 treatment-related DLTs are observed at the starting dose level, patients will be accrued to level -1. The accrual rules based on observed DLT will be as outlined in 7.24 with deceleration to dose -2 if necessary.

7.26 If a patient in phase I part fails to complete cycle 1 for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced. In each instance, however, a specific notification needs to be made for review by the Oncology Research Executive Committee.

8.0 Dosage Modification Based on Adverse Events - Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

Omit = The current dose(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
Hold = Refers to decision made at the beginning of the cycle to delay the start of the cycle until the patient meets the protocol criteria to restart drug.

NOTE: Patients in whom one or more R2CHOP study treatment agents have been discontinued will remain on study unless all R2CHOP study treatment agents are discontinued. Patients in whom all the R2CHOP study treatment agents were discontinued will proceed to event monitoring (see Section 18.0).

Table 8.1 Dose Levels (Based on Adverse Events in Table 8.2)

Dose level		Dose	Day	Route
-2	Lenalidomide	5 mg	Day 1-10	orally
-1	Lenalidomide	10 mg	Day 1-10	orally
1	Lenalidomide	15 mg	Day 1-10	orally
2	Lenalidomide	20 mg	Day 1-10	orally
3	Lenalidomide	25 mg	Day 1-10	orally

Table 8.2 Adverse Events and Dose Modifications.

Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Blood/Bone marrow	Hematologic nadirs: ANC<500 for ≥7 days or PLT<25,000 for ≥7 days or <10,000 at any time	Lenalidomide/ CTX/ADR	Decrease lenalidomide to the next lowest dose level. If AE reoccurs with subsequent cycles, decrease lenalidomide to the next lowest dose level etc. If the lowest dose level is reached and AE occurs, discontinue lenalidomide. If AE occurs after lenalidomide discontinued, decrease CTX and ADR by 25% and follow standard dosing guidelines.
Cardiac General	Left ventricular systolic dysfunction ≥ grade 3	ADR	Discontinue ADR.
Renal/Genitourinary	Cystitis ≥ grade 2	CTX	Omit CTX until resolution of cystitis. Decrease CTX 50% of preceding dose for next cycle of treatment. If subsequent cycle is well tolerated and there is no grade ≥2 renal/GU adverse events, increase CTX to 100% of the original dose.
Neurology	Neuropathy – motor Grade 2	VCR	Omit VCR until neuropathy < grade 2 and resume at 50% dose reduction.
	Neuropathy – motor Grade ≥ 3		Discontinue VCR.
	Neuropathy – sensory Grade 3		Omit VCR until neuropathy <grade 2 and resume at 50% dose reduction.
	Neuropathy – sensory Grade 4		Discontinue VCR
Allergy/Immunology	Allergic reaction or hypersensitivity: Grade 2	Lenalidomide	Omit treatment until ≤ grade 1 and restart with prophylaxis. If questions, call study chair.
	Allergic reaction or hypersensitivity: Grade 3		Omit therapy; treat the reaction and restart at MD discretion.
	Allergic reaction or hypersensitivity: Grade 4		If attributable to lenalidomide, discontinue treatment with lenalidomide.
Vascular	Venous thrombosis/embolism Grade 3 or 4		Discontinue lenalidomide.

Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Gastrointestinal	Nausea/Vomiting ≥ Grade 3	Lenalidomide/ RCHOP	Maximize antiemetic therapy; if maximized antiemetic treatment ineffective, take off treatment at physician discretion.
	Mucositis/Stomatitis ≥ Grade 2	ADR	Decrease ADR by 25% of preceding dose for next cycle. If no grade ≥3 GI toxicities in subsequent cycle, increase ADR to 100% of original dose.
	Constipation grade 2 Constipation ≥ grade 3	Lenalidomide	Initiate bowel regimen and continue lenalidomide. Omit lenalidomide until grade 2, initiate bowel regimen and restart lenalidomide.
Dermatology/ Skin	Desquamating (blistering rash) grade 3	Lenalidomide	Omit lenalidomide until ≤ grade 2 and restart at next lower dose level. If Lenalidomide held for more that 21 days, call study chair.
	Desquamating (blistering rash) grade 4		Discontinue lenalidomide.
	Non desquamating rash grade 4		Discontinue lenalidomide.
Infection	Infection with ANC ≥ 1,000/μL	Lenalidomide/ RCHOP	Hold drugs in case of an infection requiring IV antibiotics or hospitalization and restart when infection is controlled. If dosing is held ≥ 21 days call study chair. If adverse event reoccurs on subsequent cycles, decrease lenalidomide to next lower dose level and consider prophylactic antibiotics. If AE re-occurs at this dose level call study chair.
	Infection with ANC < 1,000/μL		Hold drugs in case of an infection requiring IV antibiotics or hospitalization and restart when infection is controlled, decrease lenalidomide to the next lowest dose level. If dosing is held ≥ 21 days call study chair. If adverse event reoccurs despite discontinuation of lenalidomide, then on subsequent cycle reduce CTX by 25% and ADR by 25%, consider prophylactic antibiotics. If dosing is held ≥ 21 days, call study chair.
	New or reactivation of viral hepatitis		Discontinue treatment, treat hepatitis.

Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Other non-hematologic	Grade 3 or 4*	Lenalidomide/ RCHOP	Hold drugs until toxicity has resolved to grade 2 or baseline grade then restart drugs. If questions, contact the study chair.

*Nausea and vomiting of grade 3 or 4 after full anti-emetic therapy will then follow dose reduction guidelines.

Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
AT TIME OF RETREATMENT			
Blood/Bone marrow	ANC<1500 PLT< 75,000	Lenalidomide/ RCHOP	Hold drugs. Repeat CBC/diff and if counts recover anytime before or on d28 to ANC ≥1500 and PLT ≥75,000 proceed with full dose.
	Between days 29-35: ANC ≥1500, PLT ≥75,000		Decrease lenalidomide to the next lowest dose level, continue 100% RCHOP. If lenalidomide at the lowest dose level, discontinue. If not recovered continue to hold.
	Day 36 and beyond: ANC ≥1500, PLT ≥75,000		Discontinue lenalidomide, resume RCHOP with 25% ADR and 25% CTX dose reduction. Future dose modifications of RCHOP should follow standard RCHOP guidelines.
Other non-hematologic	Grade ≥ 3*		Hold drugs until toxicity has resolved to grade 2 or baseline grade then restart lenalidomide at next lower dose level. If lenalidomide is at lowest level, discontinue. If next cycle is delayed by ≥ 2 weeks, contact study chair.

*Nausea and vomiting of grade 3 or 4 after full anti-emetic therapy will then follow dose reduction guidelines.

9.0 Ancillary Treatment

9.1 Patients who are not already on anticoagulation should receive low-dose aspirin (81 mg) daily. This should be discontinued if platelets are <50,000 or if the patient is intolerant of aspirin or develops bleeding complications irrespective of the platelet count. If aspirin is contraindicated for other reasons – call study chair.

9.2 Patients should be given a proton pump inhibitor while on aspirin or other prophylaxis per MD discretion.

9.3 Antiemetics may be used at the discretion of the attending physician.

9.4 Tumor lysis syndrome prophylaxis will be used at the discretion of the treating physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. Pegfilgrastim support will be given with each cycle. Treat as needed.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with anti-diarrheal agents such as loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Use of statin drugs (i.e. Lipitor, Zocor, etc.) is strongly discouraged while on study treatment. If statins are strongly indicated patients may continue at discretion of treating MD. If questions contact the study chair.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTC v3.0 can be accessed via the CTEP home page: http://ctep.cancer.gov/. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (refer to Sections 10.12 and 15.0) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2) in addition to the routinely reported clinical data (see Sections 10.31 and 18.0).

Expedited adverse event reporting requires submission of a written report, but may also involve telephone notifications. Telephone and written reports are to be completed within the timeframes specified in Section 10.2. All expedited adverse event reports should also be submitted to the local Institutional Review Board (IRB).

10.12 Expected vs. Unexpected

- The determination of whether an AE is expected is based on agent-specific adverse event information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific adverse event information provided in Section 15.0 of the protocol.

10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the investigational agent(s).
Probable - The adverse event *is likely related* to the investigational agent(s).
Possible - The adverse event *may be related* to the investigational agent(s).
Unlikely - The adverse event *is doubtfully related* to the investigational agent(s).
Unrelated - The adverse event *is clearly NOT related* to the investigational agent(s)

10.14 When a study includes both investigational and commercial agents, the following apply:

- When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered investigational. Expedited reporting of adverse events follows the guidelines for investigational agents.

10.2 Expedited Adverse Event Reporting Requirements

	Grade 4 or 5[1] Unexpected with Attribution of Possible, Probable, or Definite	Other Grade 4 or 5 or Any hospitalization during treatment[4]	Secondary AML/MDS[2]
Submit written report within 5 working days[3, 5]	X		
submit written report within 15 working days[3]			X
Submit Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days.[4]		X[4]	

1. Includes all deaths within 30 days of the last dose of investigational agent regardless of attribution or any death attributed to the agent(s) (possible, probable, or definite) regardless of timeframe.
2. Reporting for this AE required during or after treatment.
3. Use *Adverse Event Expedited Report – Single Agent* or *Multiple Agents* report form. Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.
4. Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the MCCC Remote Data Entry System within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an expedited written report has been submitted, this form does not need to be submitted. See exceptions to the submission of this notification form in section 10.21.
5. See Section 10.21 for Celgene specific reporting requirements.

10.21 Special Situations for Expedited Reporting and Submission of Notification Form

Exceptions to Expedited Reporting and Submission of Notification Form: EXPECTED Serious Adverse Events

An expedited report or notification form may not be required for specific Grade 1, 2, 3, and 4 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supercede the standard Expedited Adverse Event Reporting Requirements:

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Investigations	Leukocyte count decreased	≤4
	Neutrophil count decreased	≤4
	Platelet count decreased	≤4
	Lymphocyte count decreased	≤4

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event. These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

10.22 Celgene Reporting Requirements:

10.221 Serious Adverse Event (SAE) Reporting

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]
- Suspected positive 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.

10.222 Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing 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). 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 MEDWATCH. A final report to document resolution of the SAE is required. The Celgene protocol number (RV-NHL-PI-325) and 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.

10.223 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 subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately of 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 study drug 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.

Male Subjects
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.

Celgene Drug Safety Contact Information:

[redacted]

10.224 Investigator Reporting Responsibilities
The conduct of the study will comply with all FDA safety reporting requirements. The investigator will also provide Celgene as a supporter of the study a copy of the Investigator IND annual report at the time of the investigators submission to the FDA, if applicable, as follows.

Celgene Corporation

[redacted]

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described above.

10.225 Report of Adverse Events to the Institutional Review Board

The principal investigator is required to notify his/her Institutional Review Board (IRB) of a serious and unexpected adverse event according to Cancer Center and IRB policies and procedures.

10.226 Investigator Reporting to the FDA

For this study, the Mayo Clinic Cancer Center (MCCC) IND Coordinator will facilitate the investigator-sponsor's reporting to the FDA The MCCC IND Coordinator can be notified by telephone [redacted]

Serious, unlisted/unexpected event at least possibly associated to the drug should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator-sponsor (or designee) engaged in clinical research if the type of effect has not previously been reported in the Investigators brochure or literature. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The investigator-sponsor (or designee) must also call the FDA as soon as a serious, unlisted/unexpected event at least possibly associated to the drug occurs. The phone number is [redacted]. A recorder is available after hours. Report these reactions to the FDA within ten (10) working days both verbal and written.

The address of the Food and Drug Administration is:
FDA
Division of Oncology
[redacted]

The phone number of the FDA is [redacted]
Please ask to speak with the Division of Oncology.

10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated:

Category	Adverse Event/Symptoms	Baseline	Each evaluation
Blood/Bone marrow	Neutrophils/granulocytes (ANC/AGC)	X	X
	Platelets	X	X
Infection	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC $\leq$1.0 x 10^9/L, fever $\geq$ 38.5°C)	X	X

10.31 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.3:

10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

10.313 Grade 5 AEs (Deaths)

10.3131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.3132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation

11.1 Definition for clinical response for patients with lymphoma are from the Cheson et al. Revised Response Criteria for Malignant Lymphoma (Cheson*, et al* 2007), aggressive PET positive lymphomas section. Lymph node measurements should be taken from CT, CT portion of the PET/CT, or MRI scans where applicable. Measurement of lymphadenopathy will be determined by adding the **s**um of the products of the maximal perpendicular diameters of measured lesions (SDP). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative

Response is based on CT alone or the CT component of PET/CT or MRI where applicable and the PET.

Response criteria, modified from Cheson et al. 2007. DLCL and follicular grade III lymphoma are considered FDG avid.

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

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

11.2 Complete Response (CR)

11.21 Complete disappearance of all detectable clinical evidence of disease and definitely disease-related symptoms if present before therapy.

11.22 DLCL and follicular lymphoma are FDG-avid lymphomas: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

11.23 The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

11.24 If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

11.3 Criteria for Partial Response (PR). The designation of PR requires all of the following:

11.31 At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following:

- they should be clearly measurable in at least 2 perpendicular dimensions
- if possible they should be from disparate regions of the body
- they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

11.32 No increase should be observed in the size of other nodes, liver, or spleen.

11.33 Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

11.34 With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

11.35 Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow

involvement will be considered partial responders.
When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

11.36 No new sites of disease should be observed.

11.37 For patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

11.4 Criteria for Stable Disease (STAB)

11.41 A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR (see above), but does not fulfill those for progressive disease (see below).

11.42 The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

11.5 **Relapsed Disease (after CR)/Progressive Disease (after PR, SD):** Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

11.51 Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

11.52 At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

11.53 At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

11.54 Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

12.0 Descriptive Factors

12.1 Dose Level (to be assigned by Randomization Center): -2 vs. -1 vs. 1 vs. 2 vs. 3.

12.2 International Prognostic Index (IPI): Low (1-2) vs. high (≥3).

12.3 Subgroup (DLBCL patients only): germinal center B-cell-like subtype (GCB) vs. non-germinal center B-cell-like subtype (non-GCB).

12.4 Disease group: DLBCL or FLIII (Group 1) vs. transformed or composite follicular lymphoma (Group 2).

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or STAB will continue treatment per protocol until a maximum of 6 cycles have been received.

13.2 Patients who develop progressive disease while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for unacceptable adverse events or patient refusal will go to the event-monitoring phase per Section 18.0.

13.4 Observation: If the patient has achieved CR, PR, or STAB, at the post-treatment evaluation, the patient will be observed every 3 months for the first year then every 4 months for the second year or until PROG and then they will go to event monitoring.

13.5 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.51 Patients who are determined to have a histology other than diffuse large cell or follicular grade III A/B B-cell lymphoma on central pathology review but started on study (urgency to initiate treatment, see section 17.0) may continue on R2CHOP per discretion of treating MD; however, for the purpose of analysis will be deemed ineligible and will go to the event-monitoring phase of the study.

13.6 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring

will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission

NOTE: Patients must have consented to submission of the following biospecimen(s).

14.11 Summary Table of Body Fluid Biospecimens for this Protocol

Type of biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission**	**Where to find specific details for specimen submission**
Blood/blood products (EDTA whole blood)	Mandatory	Multiple draws (see Section 14.24 for schedule)	Immunology studies (Section 14.32)	Section 14.2
Blood/blood products (EDTA whole blood)	Mandatory	Multiple draws (see Section 14.24 for schedule)	Banking (Section 14.31)	Section 14.2

14.2 Blood/Blood Products Handling

14.21 Blood samples prior to treatment, prior to cycle 3 and after treatment will be collected at treating centers.

14.22 All samples must be collected **Monday-Friday ONLY for specimens collected at Mayo Clinic Rochester and Monday-Thursday for all other locations.**

14.23 Label specimen tube(s) with protocol number, patient study ID number, and time and date blood drawn.

14.24 Collect and process all blood/blood products according to instructions and table below

14.241 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed	Component being harvested	Before tx	Before Cycle 3	After completion of therapy (4-6 weeks after day 1 of cycle 6)	Process at site?	Storage/ shipping conditions[1]
Mandatory	ACD (yellow)	10 mL (1)	Whole blood	Plasma Cells for DNA/RNA, Protein	X	X	X	No	Refrigerate /cold pack (DO NOT FREEZE)
Mandatory	EDTA (purple)	10 mL (1)	Whole Blood	Plasma Cells for DNA/RNA, Protein	X	X	X	No	Refrigerate /cold pack (DO NOT FREEZE)
Mandatory	Red top	10 mL (1)	Whole Blood	Serum	X	X	X	No	Refrigerate /cold pack (DO NOT FREEZE)

1. All specimens should be sent to [redacted].

14.3 Background/Methodology Information

14.31 Immunology Studies: Blood/blood product samples (serum, plasma, and mononuclear cells) will be collected for assessment of immune function and cytokine analysis. These assays will be performed in the Lymphoma SPORE Research lab on [redacted] under grant CA97274. Excess samples will be stored for future assays that are within the realm of immune function and tumor biology and host immune response. These research test results will not be placed into the patient's clinical record.

14.32 T and B quantitative lymphocyte analysis will be performed in the clinical laboratory and will not be sent to [redacted]

14.33 Genetic polymorphisms: Mononuclear cells (as a source of host germline DNA) will be banked or processed for DNA extraction for single nucleotide polymorphisms (SNPs) analysis, since genetic polymorphism may be responsible for differences in response to therapy. These results will not be placed into the clinical record. If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 Lenalidomide (Revlimid®, CC-5013, CDC-501)

Please consult the most current Investigator's Brochure and package insert for complete drug information.

15.11 **Background**: Lenalidomide has a wide range of effects, including the inhibition of hematopoietic tumor cell proliferation, the enhancement of T cells and natural killer (NK) cell activity, the modulation of stem cell differentiation, the inhibition of angiogenesis, and the inhibition of inflammation.

15.12 **Formulation**: For clinical study, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Placebo capsules for the 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg lenalidomide capsules are available for use in blinded studies. Each placebo capsule visually matches the drug product.

The lenalidomide and placebo capsules are supplied in push-through blister foil or tamper-evident, child-resistant, opaque, high-density polyethylene (HDPE) containers with HDPE caps.

15.13 **Preparation and storage**: Lenalidomide should be stored at room temperature, between 59 and 86ºF (15-30ºC). Store drug away from direct sunlight.

15.14 **Administration:** Capsules are administered by mouth daily with water. Patients should not break, chew or open the capsules.

15.15 **Pharmacokinetic information**:
a) Absorption – Lenalidomide is rapidly absorbed following oral administration to subjects with multiple myeloma or MDS, with maximum plasma concentrations occurring between 0.5 and 1.5 hours post-dose. Co-administration with a high-fat and high-calorie meal in healthy subjects reduced the extent of absorption, resulting in an approximately 20% decrease in AUC and 50% decrease in C_{max} in plasma.

In the pivotal MM and MDS registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Multiple dosing (up to 100 mg BID) did not cause marked drug accumulation.

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

c) Metabolism – Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

d) Excretion – Elimination is primarily renal. Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The half-life of elimination is approximately 3 to 4 hours (2 to 3 hours in patients 5 to 21 years) at the clinically relevant doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days.

15.16 **Potential Drug Interactions**: In vitro studies demonstrate that lenalidomide is not a substrate of CYP enzymes. In addition, lenalidomide shows little inhibitory or induction potential towards the CYP enzymes in vitro. Hence, coadministration of CYP substrates, inhibitors, or inducers with lenalidomide is not likely to result in clinically relevant drug-drug interactions in humans.

In vitro, lenalidomide is not a substrate of BCRP, MRP1, MRP2, MRP3, OAT1, OAT3, OATP1B1, OCT1, OCT2, MATE1, OCTN1, or OCTN2. Thus, it is unlikely that substrates or inhibitors of these transporters would affect lenalidomide disposition in humans.

Lenalidomide is not an inhibitor of BSEP, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. Thus, lenalidomide is not anticipated to cause any significant drug-drug interactions due to inhibition of these transporters.

Lenalidomide is not an inhibitor of UGT1A1 and is not anticipated to cause any significant drug-drug interactions due to UGT1A1 inhibition.

In vitro, lenalidomide is a weak substrate, but not an inhibitor of P-glycoprotein (P-gp).

Erythropoietic agents or other agents that may increase the risk of thrombosis, such as hormone replacement therapy and oral contraceptives, should be used with caution in patients with multiple myeloma receiving lenalidomide with dexamethasone.

Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant lenalidomide therapy. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

15.17 **Known potential toxicities**:

Pregnancy Warning: Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, a teratogenic effect of Lenalidomide in humans cannot be ruled out. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Very Common AEs (≥ 10%): anemia, febrile neutropenia, leukopenia, neutropenia, thrombocytopenia, cataracts, blurred vision, abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, asthenia, chills, edema including peripheral, fatigue, pyrexia, abnormal liver function tests, bronchitis, gastroenteritis, influenza, nasopharyngitis, sinusitis, pneumonia, rhinitis, upper respiratory tract infection, urinary tract infection, weight decreased, decreased appetite, hyperglycemia, hypocalcemia, hypokalemia, arthralgia, back pain, bone pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity, dizziness, dysgeusia, headache, hypoesthesia, neuropathy peripheral, neuropathy, tremor, depression, insomnia, renal failure, cough, dyspnea, epistaxis, pharyngitis, pulmonary embolism, dry skin, pruritus, rash, and deep vein thrombosis.

Common (≥ 1% and < 10%):, granulocytopenia, hemolytic anemia, lymphopenia, pancytopenia, acute myocardial infarction, atrial fibrillation, cardiac failure, congestive heart failure, myocardial ischemia, tachycardia, vertigo, upper abdominal pain dry mouth, toothache, chest pain, fall, cholestasis, arthritis infective, bacteremia, cellulitis, erysipelas, herpes simplex, herpes zoster, infection, lower respiratory infection, respiratory infection, lung infection, meningitis, ophthalmic herpes zoster, sepsis, contusion, alanine aminotransferase increased, c-reactive protein increased, gamma-glutamyltransferase increased, dehydration, diabetes mellitus, gout, hypercalcemia, hyperuricemia, hypophosphatemia, hypomagnesemia, hyponatremia, iron overload, muscular weakness, acute myeloid leukemia, basal cell carcinoma, Myelodysplastic syndrome, squamous cell carcinoma of skin, T-cell type acute leukemia, tumor flare, tumor lysis syndrome, cerebrovascular accident, lethargy, paresthesia, peripheral sensory neuropathy, syncope, mood altered, respiratory distress, erythema, hyperhidrosis, night sweats, hematoma, hypertension, hypotension, peripheral ischemia, thrombosis, and vasculitis.

Uncommon, limited to important or life-threatening (< 1%): appendicitis, bursitis infective, airways disease, pyelonephritis, hypersensitivity, Graft vs. Host Disease, viral reactivation (such as hepatitis B virus or herpes zoster), DRESS.

The following additional adverse reactions have been reported in Celgene-sponsored clinical studies and are considered by the company to be at least possibly related to the administration of lenalidomide: pneumonitis, transient abnormal liver laboratory tests, hyperthyroidism, , TLS, TFR, rhabdomyolysis, and allergic conditions, including angioedema, SJS, and toxic epidermal

necrolysis. These reactions are reported voluntarily from a population of uncertain size, so it is not possible to reliably estimate their frequency.

Lenalidomide may have minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

Please refer to the Investigator Brochure for a more comprehensive list of treatment-emergent adverse events.

15.18 **Drug procurement:** Lenalidomide (Revlimid®) will be provided directly to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers in accordance with the REVLIMID REMS™ program. Per standard 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 Celgene REVLIMID REMS™ program. Prescriptions must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Any unused lenalidomide should be returned for disposition in accordance with the REVLIMID REMS™ program.

15.19 **Nursing Guidelines:**

15.191 Myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction. Monitor CBC w/diff regularly. Instruct patient to report any unusual bruising or bleeding (thrombocytopenia); signs and symptoms of infection (neutropenia); and energy conserving lifestyle (anemia).

15.192 Lenalidomide can have thrombotic adverse events (i.e DVT and PE). Instruct patient to report any limb swelling or pain, and to seek medical attention for shortness of breath or chest pain.

15.193 Because of the potential for birth defects patients should be instructed in effective methods of birth control. Female patients should use 2 forms of birth control during treatment and for 4 weeks after discontinuing therapy. Males must be instructed to use a latex condom during any sexual contact with a woman of child bearing potential (even if they have had a vasectomy), because it is unknown if lenalidomide is present in semen.

15.194 Patents may experience pruritus, rash and dry skin. Because of the rare risk of Steven's Johnson Syndrome, patients should immediately report any rash to their provider.

15.195 Drug may cause hyperglycemia. Patients with diabetes or impaired fasting glucose may need to have their glucose levels monitored more closely.

15.196 Gastrointestinal side effects (diarrhea, constipation, nausea, dyspepsia, anorexia, etc) are commonly seen. Manage patent symptomatically and monitor for effectiveness.

15.197 Patients may experience myalgias, arthralgias, and other generalized pain. Administer analgesics as ordered and monitor for their effectiveness.

15.198 Upper respiratory symptoms (nasopharyngitis, cough, epistaxis, etc.) can be seen. Manage symptomatically and monitor for effectiveness.

15.199a Agent may cause fatigue, dizziness, vertigo or blurred vision. Instruct patients to use caution when driving or operating machines.

15.199b Monitor LFT's and report any elevations to the study team. Instruct patient to report abdominal pain and/or jaundice to the study team.

15.199c All prescribers and patients must be enrolled into the REVLIMID REMS program. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

15.199d Rarely secondary malignancies have been seen after lenolidamide therapy, including MDS, squamous/basal cell carcinomas of the skin, T-cell type acute leukemia.

15.2 Cyclophosphamide (Cytoxan, CTX, Neosar®)

15.21 Preparation and storage: Injectable powder is stored at room temperature. The temperature is not to exceed 90°F. Reconstituted parenteral solutions are stable for 24 hours at room temperature or six days if refrigerated. Dissolve the 100 mg, 200 mg, 500 mg, 1 gm, and 2 gm vials in 5, 10, 25, 50, and 100 mL of sterile water, respectively, resulting in a solution of 20 mg/mL. Shake vials vigorously and warm slightly in lukewarm water to facilitate the dissolving of crystals. The lyophilized form is more easily solubilized. Cyclophosphamide should be administered according to standard R-CHOP regimen.

15.22 Known potential toxicities: Myelosuppression, hemorrhagic cystitis, alopecia, nausea, and vomiting are all common, SIADH is dose–related (more common with single doses > 2 gm/m^2), cardiac (if dose level ≥2 gm/m^2). Secondary

leukemia, liver dysfunction, headaches, dizziness, interstitial pulmonary fibrosis, cardiac necrosis may occur. Anaphylaxis is rare.

15.23 Drug procurement: Commercially available for injection in 100 mg, 200 mg, 500 mg, 1 gm and 2 gm vials.

15.24 Nursing guidelines

15.241 Leukopenia nadir occurs 8-14 days after administration and recovery is usually 18-25 days. Monitor CBC.

15.242 Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate emptying the bladder of drug.

15.243 Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria.

15.244 Advise patient of possible strong metallic taste associated with Cytoxan and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.

15.245 Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration.

15.246 Report and record any complaint of lightheadedness, facial “heat sensation”, or diaphoresis during administration.

15.247 Corticosteroids, phenothiazine, imipramine, and allopurinol may inhibit Cytoxan metabolism and modify its effect. They may also increase bone marrow suppression.

15.3 **Rituximab (Rituxan®, C2B8)**

15.31 **Background**: Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. CD20 regulates cell cycle initiation; and, possibly, functions as a calcium channel. Rituximab binds to the antigen on the cell surface, activating complement-dependent cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity.

15.32 **Formulation**: Commercially available for injection, solution [preservative free]: 10 mg/mL (10 mL, 50 mL) [contains Polysorbate 80].

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store vials at refrigeration temperature, do not freeze or shake. Protect vials from direct sunlight. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1-4 mg/mL with 0.9% NaCL or D_5W. Gently invert the bag to mix the solution; do not shake. Solutions

for infusion are stable at 2ºC to 8ºC for 24 hours and at room temperature for an additional 24 hours.

15.34 **Administration:** Do not administer I.V. push or bolus. Refer to treatment section for specific infusion instructions. Suggested administration guidelines are:
Initial infusion: Start rate of 50 mg/hour; if there is no reaction, increase the rate by 50 mg/hr every 30 minutes, to a maximum of 400 mg/hour.
Subsequent infusions: If patient did not tolerate initial infusion follow initial infusion guidelines. If patient tolerated initial infusion, start at 100 mg/hour; if there is no reaction; increase the rate by 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour.
Note: If a reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate.

Accelerated infusion rate (90 minutes): For patients with previously untreated follicular NHL and diffuse large B-cell NHL who are receiving a corticosteroid as part of their combination chemotherapy regimen, have a circulating lymphocyte count <5000/mm^3, or have no significant cardiovascular disease. After tolerance has been established (no grade 3 or 4 infusion-related event) at the recommended infusion rate in cycle 1, a rapid infusion rate may be used beginning with cycle 2. The daily corticosteroid, acetaminophen, and diphenhydramine are administered prior to treatment, then the rituximab dose is administered over 90 minutes, with 20% of the dose administered over the first 30 minutes and the remaining 80% is given over 60 minutes. If the 90-minute infusion in cycle 2 is tolerated, the same rate may be used for the remainder of the treatment regimen (through cycles 6 or 8).

15.35 **Pharmacokinetic information**:
Duration: Detectable in serum 3-6 months after completion of treatment; B-cell recover begins ~6 months following completion of treatment; median B-cell levels return to normal by 12 months following completion of treatment
Distribution: RA: 3.1 L; GPA/MPA: 4.5 L
Absorption: Immediate and results in a rapid and sustained depletion of circulating and tissue-based B cells
4.3 L
Half-life elimination: Proportional to dose; wide ranges reflect variable tumor burden and changes in CD20 positive B-cell populations with repeated doses:
Following first dose: Mean half-life: 3.2 days
Following fourth dose: Mean half-life: 8.6 days
CLL: Median terminal half-life: 32 days
NHL: Median terminal half-life: 22 days
RA: Mean terminal half-life: 18 days
GPA/MPA: 23 days

Excretion: Uncertain; may undergo phagocytosis and catabolism in the reticuloendothelial system

15.36 **Potential Drug Interactions**:
Increased Effect/Toxicity: Monoclonal antibodies may increase the risk for allergic reactions to rituximab due to the presence of HAC antibody. Antihypertensive medications may exacerbate hypotension.
Decreased Effect: Currently recommended not to administer live vaccines during rituximab treatment.

Herb/Nutraceutical Interactions: Avoid hypoglycemic herbs, including alfalfa, bilberry, bitter melon, burdock, celery, domain, fenugreek, grainier, garlic, ginger, ginseng, gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effect of rituximab). Monitor.

Immunosuppressants: Rituximab may enhance the adverse/toxic effects of pimecrolimus, tacrolimus and to a lesser extent of denosumab.

Rituximab may enhance the adverse/toxic effects of abatacept, belimumab, clozapine, dipyrone and tofacitinib.

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: Severe infusion reactions; Progressive multifocal leukoencephalopathy (PML); Tumor lysis syndrome leading to acute renal failure; and severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis).
Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema, hypertension
Central nervous system: Fever, fatigue, chills, headache, insomnia, pain
Dermatologic: Skin rash, pruritus, night sweats
Endocrine & metabolic: Weight gain
Gastrointestinal: Nausea, diarrhea, abdominal pain
Hematologic: Lymphopenia, anemia, leukopenia, neutropenia, thrombocytopenia, cytopenia, febrile neutropenia
Hepatic: ALT increased
Hypersensitivity: Angioedema
Immunologic: Antibody development
Infection: Infection, bacterial infection
Neuromuscular & skeletal: Weakness, muscle spasm, arthralgia
Respiratory: Cough, rhinitis, epistaxis
Miscellaneous: Infusion-related reaction: fever

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Hypotension, flushing
Central nervous system: Dizziness, anxiety, migraine, paresthesia
Dermatologic: Urticaria
Endocrine & metabolic: Hyperglycemia, increased lactate dehydrogenase
Gastrointestinal: Vomiting, dyspepsia
Neuromuscular & skeletal: Back pain, myalgia
Respiratory: Dyspnea, throat irritation, bronchospasm, upper respiratory tract infection, sinusitis

Rare known potential toxicities, <1% (Postmarketing and/or case reports):
Acute mucocutaneous toxicity, acute renal failure (associated with tumor lysis syndrome), acute respiratory distress, anaphylactoid reaction/anaphylaxis, angina pectoris, aplastic anemia, arthritis (polyarticular), bone marrow depression, bronchiolitis obliterans, cardiac arrhythmia, cardiac failure, cardiogenic shock, encephalitis, fulminant hepatitis, gastrointestinal perforation, hemolytic anemia, hepatic failure, hepatitis, hypogammaglobulinemia (prolonged), hypoxia, increased serum immunoglobulins (hyperciscosity syndrome in Waldenstrom's macroglobulinemia, interstitial pneumonitis, intestinal obstruction, Kaposi's sarcoma (progression), laryngeal edema, lichenoid dermatitis, lupus-like syndrome, mucositis, myelitis, MI, nephrotoxicity, optic neuritis, pancytopenia, paraneoplastic pemphigus, pleurisy, pneumonia, pneumonitis, polymyositis, progressive multifocal leukoencephalopathy, pure red cell aplasia, reactivated pure red cell aplasia, reactivated tuberculosis, reaction of HBV, reversible posterior leukoencephalopathy syndrome, serum sickness, Stevens-Johnson syndrome, supraventricular arrhythmia, toxic epidermal necrolysis, uveitis, vasculitis with rash, ventricular fibrillation, ventricular tachycardia, vesiculobullous dermatitis, viral reactivation (includes JC virus [PML], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C), wheezing

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 Nursing guidelines:

15.391 Do not administer as an IV push or bolus since it increases the risk of a hypersensitivity reaction.

15.392 Hypotension, bronchospasm, and angioedema have occurred in association with Rituxan infusion. Stop infusion for severe reaction. Infusion may be restarted at 50% rate after resolution of symptoms. It is recommended that diphenhydramine, acetaminophen, epinephrine, bronchodilators, IV saline, and corticosteroids be available for immediate use in the event of a hypersensitivity reaction during administration.

15.393 Patients should be cautioned to withhold their anti-hypertensive medication for 12 hours prior to drug administration.

15.394 Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during Rituxan therapy and should be monitored throughout the infusion and immediate post-infusion period.

15.395 It has been found that patients with bulky disease (lesion >10 cm in diameter) have an increased incidence of adverse events.

15.396 An infusion-related symptom complex consisting of fever and chills/rigors occurs in the majority of patients during the first infusion. These reactions generally occur within 30 minutes to 2 hours of beginning the first infusion and resolve with slowing or stopping the infusion and giving supportive care. The incidence of adverse reactions decreased from 80% to 40% with subsequent infusions.

15.397 Cytopenias are common and can be long term. Monitor CBC. Instruct patient to report signs and symptoms of infection, excessive bruising and/or bleeding to the health care team.

15.398 GI disturbances (Nausea, abdominal pain and less commonly diarrhea, vomiting, dyspepsia) headache, and weakness are common side effects. Treat as necessary. Monitor for effectiveness.

15.399a Adequate birth control measures should be used during therapy and for 12 months following therapy. Women should not breastfeed while drug is detectable in serum.

15.399b Endocrine and metabolic disturbances can be seen (hyper/hypoglycemia, hypocalcemia, hypocholesterolemia, hyperphosphatemia, hyperuricemia. Monitor labs and for signs or symptoms of these conditions. Treat accordingly.

15.399c There is the possibility of reactivation of Hepatitis B (HBV). Paitents who are at high risk of hepatitis B virus should be screened prior to initiation of therapy, carriers of hepatitis B should be closely monitored.

15.4 Doxorubicin (ADR)

15.41 Preparation and storage: Doxorubicin RDF intact vials are stable protected from light at room temperature. Doxorubicin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The doxorubicin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperatures or 15 days if refrigerated and protected from sunlight. It is not necessary to further dilute. This avoids long infusion times and the risk of extravasation. Dilution takes place when administered through a rapidly flowing IV line. Doxorubicin should be administered according to standard R-CHOP regimen.

15.42 Known potential toxicities:

15.421 Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.

15.422 Dermatologic: Alopecia, usually complete, hyperpigmentation of nailbeds and dermal creases, radiation recall.

15.423 Gastrointestinal: Nausea and vomiting, sometimes severe, anorexia, diarrhea, mucositis.

15.424 Cardiovascular: Arrhythmias, thrombosis/embolism, ECG changes, rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose, risk is greater with doses greater than 550 mg/m^2, mediastinal irradiation, preexisting cardiac disease, advanced age, risk is reduced with weekly or continuous infusion regimens.

15.425 Other: Red discoloration of urine, fever, anaphylactoid reaction, may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity, secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an alkylating agent, especially if one or both are given at higher than standard doses.

15.426 Local effects: Vesicant if extravasated; flush along vein, facial flush.

15.43 Availability: Commercially available as powder for injection in 10, 20, 50, 100, 150 mg vials, and as 2 mg/ml solution for injection in 10, 20, 50, and 200 mg vials.

15.43 Nursing guidelines:

15.441 Check CBC and platelet counts. Monitor for signs of infection, bleeding, and anemia.

15.442 Advise patient that their urine may turn pink in color for approximately 24 hours after administration of the drug.

15.443 Doxorubicin is a vesicant. Check IV potency before and frequently during administration. If extravasation occurs, refer to institutional extravasation policy.

15.444 Hair loss occurs 2-4 weeks after initial injection and can be complete. Regrowth begins 2-3 months after discontinuation.

15.445 Beware of doxorubicin "flare" that can occur during administration. The reaction consists of an erythematous streak up the vein receiving the infusion. Adjacent veins may also demonstrate red streaks. Urticaria and pruritus can be associated with the reaction. The use of corticosteroids and/or antihistamines has been helpful.

15.446 Administer antiemetics to minimize nausea and vomiting.

15.447 Assess for alterations in mucous membranes. Stomatitis occurs within 7-10 days after injection. It begins with burning sensation and can progress to ulceration, which can last 3 days. Carafate slurry may be useful. Adequate nutritional counseling is important. Topical anesthetics such as viscous Xylocaine can be used symptomatically.

15.448 Advise patient that there is often significant malaise and fatigue 1-2 weeks after injection.

15.449a Doxorubicin may potentiate toxicity of other antineoplastic therapies. It has reportedly exacerbated Cyclophosphamide- (Cytoxan, CTX) induced hemorrhagic cystitis.

15.449b Assess heart and lung sounds. Monitor vital signs (resting pulse). Be alert to early signs of cardiotoxicity, i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales.

15.449c Document cumulative dose, which should not exceed maximum cumulative dose.

15.449d Advise patient of probable facial flushing for several hours after drug administration, especially if given quickly.

15.5 Vincristine (VCR)

15.51 Preparation and storage: Vincristine is stored in the refrigerator. No preparation is required. Vincristine should be administered according to standard R-CHOP regimen.

15.52 Known potential toxicities:

15.521 Hematologic: Rarely leukopenia (mild), rarely thrombocytopenia, and anemia.

15.522 Dermatologic: Alopecia, skin and soft tissue damage if extravasated (the manufacturer recommends subcutaneous injection of hyaluronidase and application of heat to help disperse the drug), rash.

15.523 Gastrointestinal: Nausea, rarely vomiting, constipation, abdominal cramps, anorexia, and diarrhea. Fatal ascending paralysis follows intrathecal administration.

15.524 Hepatic: Elevation of AST and ALT (mild and transient).

15.525 Neurologic: Peripheral neuropathy (loss of deep tendon reflexes, paresthesias, paralysis), autonomic neuropathy (constipation, paralytic ileus, urinary retention, orthostasis), ataxia, myalgias, cortical blindness, headache, seizures.

15.526 Pulmonary: Bronchospasm (acute shortness of breath), more common when administered with mitomycin.

15.527 Ocular: Diplopia, ptosis, photophobia, cortical blindness (see neurologic), and optic atrophy.

15.528 Other: Severe pain in the jaw, pharynx, bones, back, and limbs following injection, syndrome of inappropriate antidiuretic hormone (SIADH), fever, rarely pancreatitis.

15.529 Cardiovascular: Thrombosis/embolism.

15.53 Availability: Commercially available in a concentration of 1 mg/ml in 1, 2, and 5 mg vials and 1 mg and 2 mg syringes.

15.54 Nursing guidelines:

15.541 Check IV patency before and frequently during administration. Vincristine is a vesicant. If extravasation occurs, refer to agency extravasation policy.

15.542 Evaluate the patient for numbness and tingling in fingertips and toes, clumsiness of hands, and difficulty walking.

15.543 Monitor bowel function and encourage use of stool softeners.

15.544 Symptoms of cranial nerve neuropathy may develop several weeks after drug administration and take 10–12 months to resolve.

15.6 Name of drug: Prednisone (PRED)

15.61 Preparation and storage: The drug is stored at room temperature in a dry place.

15.62 Known potential toxicities:

15.621 Hematologic: Leukocytosis.

15.622 Gastrointestinal: Nausea, vomiting, anorexia, increased appetite and weight gain, peptic ulcer.

15.623 Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, and ecchymoses.

15.624 Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities)

15.625 Neurologic: Insomnia, muscle weakness, euphoria, psychosis, depression, headache, vertigo, and seizures.

15.626 Cardiovascular: Fluid retention and edema, hypertension, hyperkalemia.

15.627 Ocular: Cataracts, increased intraocular pressure, and exophthalmos.

15.628 Metabolic: Hyperglycemia decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression, and cushingoid syndrome.

15.629 Other: Osteoporosis (and resulting back pain), serious infections including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis, muscle wasting.

15.63 Availability: Commercially available in 1, 2.5, 5, 10, 20, 25, and 50 mg tablets. Also available as 1 mg/ml oral solution and syrup, and as a 5 mg/ml oral solution.

15.64 Nursing guidelines:

15.641 Instruct patient to report any abdominal pain, GI bleeding (i.e., tarry stools, vomiting coffee-ground material, etc.) to health care team immediately since active peptic ulceration is a toxicity that requires dose modification. Antacid therapy may be employed.

15.642 Instruct patient to take prednisone after and close to meals. To prevent sleep disruption and restlessness, avoid taking prednisone at bedtime. A mild sedative may be needed.

15.643 Monitor CBC and glucose levels.

15.644 Educate patient concerning potential mood changes.

15.645 Gradual tapering of doses should be employed after long-term use.

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a phase I/II study in newly diagnosed diffuse large cell and follicular grade III A/B B-cell lymphoma patients treated with a combination of lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R2CHOP). The phase I portion of this study is designed to determine the maximum tolerated dose (MTD) of R2CHOP in this patient population. The phase II portion of this study will use a one-stage design to assess the efficacy of R2CHOP in this patient population.

16.11 Primary Endpoint: The primary endpoint of the phase I portion of this trial is toxicity. For the phase II portion of this trial, the primary endpoint is event-free survival at 12 months (EFS12). An event will be defined as death due to any cause, tumor progression or relapse (by CT scan), or initiation of subsequent anti-lymphoma therapy following R2CHOP study therapy. A patient will be considered a success if they are event-free at 12 months.

16.12 Sample Size: This phase I portion of this study is expected to require a minimum of 9 and a maximum of 18 patients. The 6 patients treated at the MTD in the phase I portion will also be included in the phase II portion. An additional 26 evaluable patients will be accrued at the MTD dose level for a maximum of 32 evaluable patients in the phase II portion of this study. If a patient is found to be ineligible after enrollment due to central pathology review, they will be replaced. We anticipate accruing maximum of 3 additional patients during the phase II portion of the trial to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the phase II portion is expected to accrue a maximum of 35 patients and the overall sample size will be a maximum of 47 patients.

As of Addendum 6, it is estimated that approximately 60% of DLBCL patients accrued to this study will have non-GCB lymphoma. Approximately 18 patients with non-GCB lymphoma have been accrued to date. Therefore, 32 additional evaluable DLBCL patients will need to be accrued to have 37 evaluable patients with this subtype. We anticipate accruing 5 additional patients (overaccrual of 15%) to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of 37 additional DLBCL patients. With 65 patients already accrued to the phase II portion of this study, there will be a total of 102 patients in the phase II portion and 108 patients overall.

As of Addendum 8, ECOG will open a study for DLBCL patients that will be a replacement for this study for patients with DLBCL. DLBCL patients will no longer be accrued to this study. To further explore the R2CHOP regimen, this study will now focus on other subtypes of lymphoma to evaluate efficacy and toxicity. We anticipate accruing 35 evaluable patients with transformed or

composite follicular lymphoma. We anticipate accruing 4 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of 39 additional patients. As of July 10, 2013, 98 patients have been accrued to this study and a maximum of 7 additional patients with DLBCL may be accrued before activation of Addendum 8. Therefore, a maximum of 144 may be accrued overall.

16.13 Accrual Rate and Study Duration: The anticipated accrual rate is 2-3 evaluable patients per month. At this rate, it will likely take about 2 months to enroll, treat, and evaluate each set of 3 patients in the phase I portion of this study. The phase I portion is expected to take between 6 and 12 months. The phase II portion of this study will accrue in the subsequent 12 months.

As of Addendum 6, we expect the additional DLBCL patients will be accrued in approximately 2 years. The total study duration is expected to be approximately 8 years, or until the last patient accrued has been observed for at least 3 years.

As of Addendum 8, we expect the additional patients will be accrued in approximately 1.5 years. The study is expected to be completed 3.5 years after Addendum 8 is implemented, or until the last patient accrued has been observed for 2 years.

Phase I Portion (Cohort I):

This portion of the study is designed to determine the MTD and toxicity of R2CHOP in patients with newly diagnosed diffuse large cell and follicular grade III A/B B-cell lymphoma.

16.2 Study Design: This portion of the study will consist of a single-arm, phase I trial to determine the MTD of R2CHOP.

16.21 MTD Determination: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients). See section 7.2 for the MTD determination algorithm and DLT definitions.

16.22 Primary Outcome Analyses:

16.221 Adverse Events Profile: The number and severity of all adverse events will be tabulated and summarized in this patient population. The grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

16.222 Toxicity Profile: As per NCI CTCAE v3.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures

(primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level and patient will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

Phase II Portion (Cohort II)

16.3 Statistical Design:

16.31 Decision Rule: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 80%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 95%. The following one-stage design uses 32 patients to test the null hypothesis that the true success proportion in a given patient population is at most 80%. Success is defined as being event-free at 12 months.

16.311 Final Decision Rule: If 28 or fewer successes are observed in the first 32 evaluable patients, we will consider this regimen ineffective in this patient population. If 29 or more successes are observed in the first 32 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population.

16.312 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients is discussed in Section 16.44.

16.32 Power and Signficance Level: Assuming that the number of successes is binomially distributed, the significance level is .09, i.e. there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	.80	.85	.90	.95
Then the probability of declaring that the regimen warrants further study is…	.09	.27	.60	.93

16.33 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.4 Analysis Plan

16.41 Primary Outcome Analyses (Group 1):

16.411 Definition: The primary endpoint for the phase II portion of this trial is event-free survival at 12 months. An event will be defined as death due to any cause, tumor progression or relapse (by CT scan), or initiation of subsequent anti-lymphoma therapy following R2CHOP study therapy. A patient will be considered a success if they are event-free at 12 months. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for event-free survival.

16.412 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true rate of event-free survival at 12 months will be calculated.

16.413 As of March 2012, the Kaplan-Meier estimate for event-free survival at 12 months is 75% (95% CI: 61-92%) in the first 32 evaluable patients included in the phase II portion. Although this estimate is lower than we anticipated, there are several factors that warrant continuation of the expanded cohort:

- There were 4/32 patients (13%) with primary mediastinal large B-cell lymphoma, a subtype known to have shorter time to progression. In the 8 patients who experienced an event during the first year after registration, 2 of these occurred in patients with primary mediastinal disease. Comparisons to RCHOP studies that did not include patients with primary mediastinal disease may be misleading. Of note, primary mediastinal large cell lymphoma patients are excluded from study extension and no longer eligible.
- Significant percentage (35%) of patients accrued to study was over 60 years old with high or high-intermediate risk score according to International prognostic index (IPI). Advanced age and high IPI is associated with inferior outcome in patients with DLBCL largely due to more aggressive disease in this group with reported one-year EFS of 60% (Fuegier et al. J. of Clin. Oncol. 2005.23;18 pp-4117-4126).
- Due to developments in imaging technology and the more frequent response evaluations that occur during observation (every 3 months for year 1 and every 4 months for year 2), it is possible that progressive disease is being discovered earlier than in studies where monitoring is done every 6 months or annually. This notion is further supported by earlier plateau in EFS curves in current study than observed in older studies. It is important to point out that as outlined in background section, that 2 year EFS is reported in previous studies of RCHOP is reported to be to be 55-60%.
- RCHOP is the standard of care for DLBCL. The addition of lenalidomide to RCHOP has not added significant toxicities so there are no safety concerns in giving more patients this combination
- Molecular classification of DLBCL by immunohistochemistry is a potential prognostic factor that is emerging. There is preliminary

evidence that the addition of lenalidomide to RCHOP may increase event-free survival in patients with the non-GCB subtype. The expanded cohort will be used to investigate molecular classification.

16.42 Secondary Outcome Analyses (to be evaluated in each group independently, unless specified otherwise)

16.421 Overall response rate: The overall response rate will be estimated by the number of patients with an objective status of CR or PR divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true overall response rate will be calculated.

16.422 Overall CR rate: The proportion of patients who achieve a CR will be estimated. The overall CR rate will be estimated by the number of patients who achieve a CR divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true overall CR rate will be calculated.

16.423 Event-free survival: The event-free survival (EFS) time is defined as the time from registration to progression, subsequent anti-lymphoma treatment, or death due to any cause. The distribution of EFS time will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958).

16.424 Overall survival: Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958).

16.425 Progression-free survival: The progression-free survival (PFS) time is defined as the time from registration to progression or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958).

16.426 Duration of response is defined for all evaluable patients who have achieved an objective response as the date at which the patient's objective status is first noted to be either a CR or PR to the earliest date progression is documented. The distribution of duration of response will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958).

16.427 Analyses of translational endpoints: Immune function will be evaluated before and after treatment by assessing T, B, and NK cell quantification. Changes in these values will be both graphically and quanitatively summarized and explored. In addition, these values

will be explored in relation to clinical outcomes such as EFS and response (responder vs non-responder as well as by quality of response, i.e. CR vs PR).

16.428 R2CHOP in non-germinal center B-cell-like lymphoma (Group 1 only)

DLBCL patients will be profiled for gene expression using pretreatment samples. Patients will be categorized as germinal-center B-cell-like (GCB) vs. non-germinal center B-cell-like (non-GCB).

In a previous study of large B-cell lymphoma treated with R-CHOP, patients with the non-GCB subtype had significantly worse overall survival and lower event-free survival than patients with the germinal-center B-cell-like subtype (Fu et al, 2008). The 3-year event-free survival for the 63 patients with the non-GCB subtype was approximately 52%. Although event-free survival also includes initiation of subsequent anti-lymphoma therapy as an event for this study, it is rare to see a patient receive subsequent treatment before tumor progression or relapse. A 3-year event-free survival of 50% would be a reasonable historical estimate for non-GCB subtype lymphoma treated with R-CHOP even where subsequent treatment is considered an event. We are interesting in testing the null hypothesis that the 3-year event-free survival for R2CHOP is 50% for DLBCL patients with the activated B-cell-like subtype.

Decision Rule for DLBCL patients with activated B-cell-like lymphoma: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 50%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 70%. The following one-stage three-outcome design (Sargent et al, 2001) uses 37 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 50%. Success is defined as being event-free at 3 years, where an event is defined as death due to any cause, tumor progression or relapse (by CT scan), or initiation of subsequent anti-lymphoma therapy following R2CHOP study therapy. Assuming the number of successes is binomially distributed, the significance level is 0.05.

Final Decision Rule: The following decision criteria will be used in the evaluation of all 37 evaluable patients:
• “Not promising”: This regimen will be classified as not promising with respect to the success rate in this patient population if at most 21 successes are observed in 37 evaluable patients.

• "Inconclusive": The results of this study will be classified as inconclusive with respect to this regimen demonstrating an improved success rate if 22 or 23 successes are observed in 37 evaluable patients. In this case, overall survival will be used in addition to event-free survival at 3 years to make the final decision as to whether or not this treatment is considered promising and worthy of further study in this patient population.
• "Promising": This regimen will be classified as promising with respect to increasing the success rate in this patient population if at least 24 successes are observed in 37 evaluable patients. Subsequent studies may be recommended.

16.429 R2CHOP in transformed and composite follicular lymphoma (Group 2)

In a previous study including 53 patients with transformed follicular lymphoma treated with a ritixumab-containing chemotherapy, the 2-year progression-free survival estimate was approximately 60% (Villa et al, 2013). We expect the addition of lenalidomide will increase the 2-year progression-free survival. However, due to the heterogeneous nature of this patient population, the patients on this study may have a worse prognosis. Therefore, we are interesting in testing the null hypothesis that the 2-year progression-free survival for R2CHOP is 50% for patients with transformed or composite lymphoma.

Decision rule for patients with transformed and composite lymphoma: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 50%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 70%. The following one-stage binomial design uses 35 patients to test the null hypothesis that the true success proportion in a given patient population is at most 50%. Success is defined as being alive and progression-free at 24 months.

Final Decision Rule: If 21 or fewer successes are observed in the first 35 evaluable patients, we will consider this regimen ineffective in this patient population. If 22 or more successes are observed in the first 35 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population.

Assuming the number of successes is binomially distributed, this one-stage binomial design will have 87% power, with a 9% Type I error rate.

16.43 Adverse Events: All eligible patients that have intitiated treatment will be considered evaluable for assessing adverse event rates. The maximum grade for

each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse events to the study treatment will be taken into consideration.

16.44 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.45 Data & Safety Monitoring:

16.451 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.452 Adverse Event Stopping Rules (These rules apply to all patients in this study treated at the MTD): The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe adverse events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy either of the following:

If in the first 18 treated patients any of the following occur:

- 3 or more patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment with lenalidomide.
- 3 or more patients experience a grade 3 or higher thrombosis/embolism at least possibly related to treatment with lenalidomide.
- 3 or more patients experience a dose reduction or delay of over 7 days of RCHOP at least possibly related to the addition of lenalidomide to RCHOP. The dose modifications of RCHOP based on known toxicity of RCHOP agents and thought to be unrelated or unlikely related to the addition of lenalidomide to study treatment will not be considered.

If after the first 18 patients have been treated any of the following occur:

- 20% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment with lenalidomide.
- 20% of all patients experience a grade 3 or higher thrombosis/embolism at least possibly related to treatment with lenalidomide.
- 20% of all patients experience a dose reduction or delay of over 7 days of RCHOP at least possibly related to the addition of lenalidomide to RCHOP. The dose modifications of RCHOP based on known toxicity of RCHOP agents and thought to be unrelated or unlikely related to the addition of lenalidomide to study treatment will be not considered.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Inclusion of Women and Minorities

16.51 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.52 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.53 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 7% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	1	1	0	2
Not Hispanic or Latino	57	85	0	142
Unknown	0	0	0	0
Ethnic Category: Total of all subjects	58	86	0	**144**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	1	1	0	2
Black or African American	1	2	0	3
Native Hawaiian or other Pacific Islander	0	0	0	0
White	56	83	0	139
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects	58	86	0	**144**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission.

NOTE: Patients must have consented to submission of the optional tissue(s) listed in the following table.

17.11 Summary Table of Tissue Biospecimens for this Protocol

Type of tissue to submit	Mandatory or optional	When to submit	Reason for submission	Where to find specific details for submission
Formalin-fixed paraffin-embedded (FFPE) tissue blocks/slides	Mandatory	≤ 42 days following registration	Pathology review Immunohistochemistry for non-GCB vs. GCB subtype (DLBCL patients only)	Section 17.2
Formalin-fixed paraffin-embedded (FFPE) tissue blocks/slides**	Optional	≤ 42 days following registration	Correlative studies	Section 17.3
Frozen recurrent/refractory tumor tissue**	Mandatory	Anytime during study	Correlative studies	Section 17.4
Frozen recurrent/refractory tumor tissue**	Optional	Anytime during study	Correlative studies	Section 17.4
Tumor biopsy specimen	Optional	After registration, before treatment and prior to cycle 2	Banking (Section 17.54-17.55)	Section 17.5
Tumor biopsy specimen	Optional	After treatment – refractory/relapsed disease.	Banking (Section 17.56)	Section 17.5

***If an institution is not able to provide the tissue, it does not cause the patient to be ineligible; however, the collection of these tissues is **strongly recommended**.*

17. 2 Central pathology review including and CD20 positivity will be performed for all patients participating in the study to confirm patient eligibility. Immunohistochemistry will be performed for DLBCL patients to determine the molecular subtype (non-GCB vs. GCB) using the Hans method (Hans et al, 2004). Completion of central pathology review is not required prior to registration; however materials for central review must be reviewed within 42 days <u>after registration.</u>

17.3 Tumor tissue from original diagnosis remaining after diagnostic studies and mandated archiving will be banked for future tissue microarray studies in order to identify tumor specific predictors of response and prolonged progression free survival (See section 17.5).

17.4 Tumor tissue from re-biopsied accessible tumor (selected patients, not mandatory) and from relapsed/refractory tumors remaining after diagnostic studies will be banked for correlative studies in order to identify tumor specific predictors of response and prolonged progression free survival in Lymphoma SPORE tissue bank (Section 17.53 and 17.56).

17.5 Study Methodology and Storage Information

Central pathology review will be conducted for confirmation of diagnosis by [redacted] and colleagues at Mayo Clinic Rochester.

For Mayo Clinic Arizona and Mayo Clinic Florida:
Within 21 days after registration, submit the following materials t [redacted]. Phone for [redacted]

Required materials:

- Lymphoma Pathology Reporting Form (Complete Section I only)
- Baseline Tissue Specimen Submission Form
- Bone marrow biopsy report
- Tumor tissue pathology report
- CD20 stained slide, if available
- Paraffin block containing tumor tissue from the most recent tumor tissue biopsy is preferred, not bone marrow or peripheral blood. If the institution is unwilling to release a block, 20 unstained, charged slides cut at 5µ should be submitted. Slides should be placed in appropriate slide container.
- Tumor tissue diagnostic H&E stained slide
- Tumor tissue immunochemistry or immunophenotyping by flow cytometry report (if available)

Submitted tissue samples will be analyzed as follows:

17.51 FFPE tumor tissue blocks/slides will be collected in order to assess correlation of responses to treatment with R2CHOP by immunohistochemistry (IHC) and/or fluorescence *in situ* hybridization (FISH). For tissue blocks received, tissue microarrays (TMAs) will be constructed and analyzed. For TMA constructions, the donor block remains intact except for 6 small (0.6mm) holes where the cores were taken. This process has minimal impact on the utility of the block for future clinical diagnostic needs.

17.52 At the completion of the study, any unused/remaining FFPE and frozen pieces of material will be stored in Hematopathology for future research according to the patient consent permission (see Section 6.2). Potential future research may include immunohistochemistry (IHC) analyses, DNA extraction, and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse

events. For TMAs, the donor block remains intact except for 6 small (0.6mm) holes where the cores were taken. This process has minimal impact on the utility of the block for future clinical diagnostic needs.

17.53 Fresh tissue obtained pre-treatment and at other timepoints in the study that were made into cell suspensions will be banked on [redacted] in the SPORE Biospecimens repository and be available for future research.

17.54 Paraffin-embedded primary biopsy material. This material will be archived in hematopathology and will be available for future unspecified research at Mayo such as immunohistochemistry of new markers under the direction of the Mayo Hematopathology Group (Dr. W. Macon), see 17.5.

17.55 Frozen pieces of primary biopsy material will be retained within Hematopathology or the diagnosis site and will be requested if needed for future unspecified research.

17.56 Excess fresh tissue obtained at the time of the on-study biopsy (most likely consented under SPORE IRB 118-01) or if the patient consents to re-biopsy on this study per test schedule will be retained in the SPORE lab on [redacted] Depending on size of tissue, some may be cryopreserved in the SPORE Biospecimens bank on [redacted] for future unspecified research.

17.6 Return of Genetic Testing Research Results. For this study, DNA and/or RNA specimens are only being banked and no specific genetic testing is being performed. If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

18.1 Submission Timelines

Forms	Active-Monitoring Phase (Compliance with Test Schedule)			Event-Monitoring Phase[1] (Completion of Active-Monitoring Phase)				At Each Occurrence			
	Initial Material	Follow-up material									
	≤2 weeks after registration	At each evaluation	At end of treatment	q.6 months until PROG	At PROG	After PROG q.6 mos.	Death	ADR/ AER	New Primary	Grade 4 or 5 Non-AER Reportable Events/ Hospitalization	Late Adverse Event
On-Study Form	X										
Baseline Adverse Events Form	X										
Measurement Form	X	X	X								
Blood Specimen Submission Form (Section 14.0)	X	X[6]	X								
Tissue Specimen Submission Form (Section 17.0)	X	X[6]									
Evaluation/Treatment Form		X[3]	X								
Nadir/Adverse Event Form		X	X								
End of Active Treatment/Cancel Notification Form	X[4]		X								
Event Monitoring Form				X	X	X	X		X		X
Evaluation/Observation Form		X[2]									
ADR/AER (See Section 10.0)								X			
NCI/CTEP Secondary AML/MDS Report Form (See Section 10.0)									X[5]		
Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form										X	
Tumor Tissue Pathology Report	X										
Pathology Reporting Form	X[7]										
CT, PET, MRI reports	X	X									
Bone Marrow Biopsy Report	X	X[6]									
Quantitative Flow Cytometry Form	X	X[6]									

Footnotes on following page.

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. Complete at each evaluation during Observation (see Section 4.0).
3. Complete at each evaluation during Active Treatment (see Section 4.0)
4. Submit if withdrawal/refusal prior to beginning protocol therapy occurs.
5. Only applicable to new AML/MDS primaries, not for all new primaries.
6. At timepoints required by Section 4.0.
7. After the central review has been completed and materials have been returned, forward a copy of the Pathology Reporting Form to the QAS for documentation. Send to: QAS for MC078E, RO_FF_03_24-CC/NW Clinic.

19.0 Budget

19.1 Costs charged to patient: All routine clinical care. Lenalidomide will be provided by Celgene at no cost to the participant; however, standard charges will be assessed for all commercially available agents (RCHOP) and their administration. The participant will be billed for pharmacy charges and other ancillary expenses such as any oral medications prescribed at the time of discharge.

19.2 Tests to be research funded: Lymphocyte panel by flow cytometry, tumor biopsy not required for clinical evaluation will be research funded. Specimen banking will be funded by Lymphoma SPORE CA97274.

19.3 Protocol administration, data management and statistical analysis efforts will be by funded by a grant from Celgene, according to the terms of the contract.

20.0 References

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Appendix I

Ann Arbor NHL Staging System

Stage I - disease in single lymph node or lymph node region.

Stage II - disease in two or more lymph node regions on same side of diaphragm.

Stage III - disease in lymph node regions on both sides of the diaphragm are affected.

Stage IV - disease is wide spread, including multiple involvement at one or more extranodal (beyond the lymph node) sites, such as the bone marrow.

Appendix II

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 housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix III

MEDICATION DIARY

Name _____ Study No. _____
Mayo Clinic No. _____

Please complete this diary on a daily basis. Write in the amount of the dose of Lenalidomide and aspirin that you took in the appropriate "Day" box. Lenalidomide should be taken before eating. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. 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. If you take more than the prescribed dose of lenalidomide, seek emergency medical care if needed and contact study staff immediately.

If the capsules are thrown up, this should be noted on your diary but you should not take another capsule until your next scheduled dose.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

Week of:

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Lenalidomide							
Prednisone							
Aspirin							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Lenalidomide							
Aspirin							

Week of:

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Lenalidomide							
Aspirin							

My next scheduled visit is: _____
If you have any questions, please call: _____

_____ _____
(Date) (Participant's Signature)